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FRONTIER

Long-term survival outcome of laparoscopic liver resection for hepatocellular carcinoma

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Abstract

Long-term survival is the most important outcome measurement of a curative oncological treatment. For hepatocellular carcinoma (HCC), the long-term disease-free and overall survival of laparoscopic liver resection (LLR) is shown to be non-inferior to the current standard of open liver resection (OLR). Some studies have reported a superior long-term oncological outcome in LLR when compared to OLR. It has been argued that improvement of visualization and instrumentation and reduced operative blood loss and perioperative blood transfusion may contribute to reduced risk of postoperative tumor recurrence. On the other hand, since most of the comparative studies of the oncological outcomes of LLR and OLR for HCC are non-randomized, it remained inconclusive as to whether LLR confers additional survival benefit compared to OLR. Despite the paucity of level 1 evidence, the practice of LLR for HCC has gained wide-spread acceptance due to the reproducible improvements in the perioperative outcomes and non-inferior oncological outcomes demonstrated by large-scaled, matched comparative studies. Meta-analyses of the outcomes of these studies by multiple systematic reviews have also returned noncontradictory conclusions. On the basis of a theoretical advantage of LLR over OLR in preventing tumor recurrence, the current review aims to dissect from the current meta-analyses and comparative studies any evidence of such superiority.

Key Words: Hepatocellular carcinoma; Laparoscopic hepatectomy; Liver resection; Long-term outcome; Overall survival; Disease-free survival

Core Tip: Laparoscopic liver resection (LLR) resulted in better perioperative outcomes when compared with open liver resection. However, for long-term outcomes, the

quality classification
Grade A (Excellent): 0
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reported ranges of disease-free survival rate and overall survival rate at 5 years after LLR of hepatocellular carcinoma (HCC) can be as wide as 20%-64% and 47%-95%, respectively. This reflects the heterogeneity of clinical practice and outcome reporting. The purpose of this review is to elucidate the true picture of the oncological efficacy of LLR in the treatment of HCC by critical appraisal of current evidence including meta-analyses and comparative studies.

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INTRODUCTION

Laparoscopic liver resection (LLR) is widely practiced nowadays for the treatment of hepatocellular carcinoma (HCC). The practice of LLR has propagated on the basis of recommendations by the three international consensus statements published in 2008, 2015 and 2018[1-3]. As of the latest recommendation from the 2018 Southampton consensus[3], LLR is preferred over open liver resection (OLR) in selected cases of HCC because of its better early postoperative outcomes and non-inferior oncological outcomes. This recommendation is supported by findings of meta-analyses and large propensity score-matched retrospective studies comparing LLR and OLR for HCC.

As a curative oncological treatment, disease-free and overall survival are the most important outcome measures of LLR. The reported ranges of disease-free survival rate and overall survival rate at 5 years after LLR of HCC can be as wide as 20%-64% and 47%-95%, respectively. This reflects the heterogeneity of clinical practice and outcome reporting. The purpose of this review is to elucidate the true picture of the oncological efficacy of LLR in the treatment of HCC by critical appraisal of current evidence including comparative studies and meta-analyses. Robotic surgeries and single-port surgeries were excluded because they involved different sets of skills and complexity of operations.

COMPARATIVE STUDIES

It appears to be true that LLR has a non-inferior oncological outcome compared to OLR for HCC – a finding supported by multiple comparative studies, despite the presence of heterogeneity of treatment effect among the studies.

In general terms, the survival outcome of a cancer treatment program is a function of the disease spectrum of patients included and the adequacy of treatment delivery. For HCC, predictors of long-term survival after resection of HCC include factors relating to tumor extent (size, number, macrovascular invasion), tumor biology (microvascular invasion, differentiation grading, serum alpha-fetoprotein level, *etc*.), ongoing liver damage and technical success of surgery (resection margin, perioperative transfusion, anatomical resection)[4].With accumulation of worldwide experience in LLR, reports to address such factors in the practice of LLR have also been published.

Prior to 2018, all studies comparing outcomes of LLR and OLR were non-randomized[5-14]. Selection bias has been a significant concern, especially in the earlier cohorts, in which patients included for LLR tended to have more favorable disease for oncologically adequate resections (tumor size, location, width of tumor-free margin)[5]. Later studies have attempted to ameliorate the impact of selection bias by matching of baseline patient characteristics such as demographic features, tumor status, degree of cirrhosis, American Society of Anesthesiologists (ASA) class, procedure types *etc*. in the LLR and OLR group. Nevertheless, a wider resection margin is often observed in the resected specimens from the LLR group. As acknowledged by Belli *et al*[5], this could be due to the selection of tumors with greater distance of tumor from the vital vasculature for LLR – an important preoperative consideration that is difficult to quantify for the performance of matching. Interestingly, such difference is less frequently observed in the more recent reports,

probably due to the more liberal inclusion of patients for LLR with accumulation of technical experience (Tables 1 and 2).

After 2018, 21 comparative studies of LLR *vs* OLR for HCC can be identified[15-35] (Tables 1-4). Only one was a randomized controlled trial[18], while the rest were non-randomized. Studies with special focus of patient population included major hepatectomy in six, minor hepatectomy in one, cirrhosis in four, small tumors in two, multiple tumors in one and elderly patients in one. All but three of the non-randomized studies adopt propensity score-matching (Table 3). Sporadic differences between the LLR and OLR group were still identifiable in some reports, including: Tumor size in the studies by Li *et al*[25] and Tsai *et al*[23]; prevalence of cirrhosis in the study by Guro *et al*[17]; ASA class in the study by Yoon *et al*[29] and procedure magnitude in the study by Tsai *et al*[23].

The only randomized controlled trial was performed in Egypt[18]. They included patients with Child's A solitary HCC equal to or less than 5 cm, located in the peripheral segments of the liver II-VI, at a distance from the line of transection, hepatic hilum, and the vena cava and treatable by limited resection (< 3 segments). Exclusion criteria were tumors close to the portal pedicle or hepatic veins, located in segments I, VII and VIII, an ASA score exceeding 3, a decompensated cirrhosis (Child B or C), esophageal varices grade > 2, and a platelet count < 80 × 10^9/L, and patients with previous upper abdominal surgeries. On sample size calculation, a total of 42 patients was required in the study to detect a change of mean hospital stay duration from 8.5 d among patients subjected to OLR to 4.0 d among patients subjected to LRR. The estimated sample size was made assuming 95% confidence interval (CI) and 80% power of study. Eventually, they recruited a total of 50 patients with 25 patients in each group. The LLR group achieved similar disease-free survival to the OLR group (P = 0.849). The 1- and 3-year disease-free survival was 88% and 59%, and 84% and 54% for the LLR and OLR groups, respectively. However, survival outcomes were secondary endpoints, with such a small sample size, these survival outcomes were subject to type II error.

Apart from two studies by Tsai *et al*[23] and Ho *et al*[35], all of the oncological outcomes at various time spans were not statistically different. For LLR, the reported ranges of 1-, 3- and 5-year overall survival and disease-free survival were 89.9%-100%, 68%-100% and 45.3%-94.5%, and 67%-93.8%, 36%-79.6% and 24%-67.4%, respectively. In the study by Tsai *et al*[23], the group categorization did have some bias because of the earlier stage of HCC (stage I + II: 85.0% *vs* 57.4%; P < 0.001) and lower rate of major resection (22.2% *vs* 45.6%; P < 0.001) in the LLR group compared with the OLR group. When long-term oncological outcomes of the LLR and OLR group were assessed in terms of stage-specific overall survival and disease-free survival, the result did not differ significantly. On the other hand, in the study by Ho *et al*[35], the 5-year overall survival for LLR was better than OLR (84.9% *vs* 61.1%; P = 0.036), but disease-free survival was similar (20.0% *vs* 22.2%; P = 0.613). The survival advantage of LLR could be contributed by the five perioperative mortalities in the OLR group, which occurred all in the first half of the hepatectomy experience. In other words, better perioperative outcome of LLR may contribute to better long-term survival outcome.

No qualitative association between the baseline or operative factors and oncological outcomes is immediately appreciable. Of note, transfusion requirement and margin involvement are rare events for both LLR and OLR nowadays in most of the reported series.

META-ANALYSES

Due to the paucity of randomized controlled trial, meta-analyses of non-randomized comparative studies with low risk of bias represented the highest level of evidence until recently. The majority of meta-analyses were published after the Morioka consensus, although evidence of four meta-analyses have been adopted by the consensus[2]. A summary of the findings of these four meta-analyses is provided in the systematic review of Morise *et al*[36] – there is no difference in disease-free and overall survival with LLR or OLR for HCC, a result with low impact of statistical heterogeneity. This is probably because the studies included four meta-analysis of oncological outcome published between the release of Louisville and Morioka consensus statements, when LLRs were mainly performed for resection of lesions in the antero-lateral segments[37-41].

Following the Morioka consensus meeting in 2014, there was a bloom of publications reporting experience worldwide on the practice of LLR for the treatment of

Table 1 Summary of comparative studies: Operative outcomes

Ref.	Blood loss in mL /transfused %			Resection margin in mm			R0 resection rate %		
	LLR	OLR	*P*	LLR	OLR	*P*	LLR	OLR	*P*
Belli *et al*[5]	297	580	< 0.001				100	93.6	0.057
Tranchart *et al*[6]	364.3	723.7	< 0.0001	10.4	10.6	NS			
Lee *et al*[7]	150	240	NS	1.8	1.05	0.016	97	98	NS
Ahn *et al*[8]	350	355	NS	17	13	NS			
Memeo *et al*[9]	200	200	NS	10	6	0.02			
Lee *et al*[10]	300	700	0.004	13	10	0.25			
Yoon *et al*[11]	3.4%	7.5%	0.04	2.03	1.12	0.01			
Xiao *et al*[12]	272	450	0.001				100	98	NS
Sposito *et al*[13]			NS	6	5	NS	98	98	NS
Cheung *et al*[14]	100	300	< 0.001				100	93.1	NS
Ryu *et al*[15]							95	83	NS
Rhu *et al*[16]	13%	2%	NS	13	12	NS			
Guro *et al*[17]	1543	1248					97.6	94.6	NS
El-Gendi *et al*[18]	230	250	NS				100	100	NS
Inoue *et al*[19]	100	380	< 0.0001	7	5	NS			
Kim *et al*[20]	300	250	NS	13	15	NS			
Deng *et al*[21]	150	380	< 0.001				98	90	NS
Wu *et al*[22]	150	250	NS						
Tsai *et al*[23]	363	839	< 0.001	5	5.2	NS			
Di Sandro *et al*[24]	150	200	0.007	5	5	NS			
Li *et al*[25]	328	396	NS						
Kim *et al*[26]	152	245		8.5	8.4	NS			
Chen *et al*[27]	300	500	< 0.1				97	100	NS
Untereiner *et al*[28]	150	250	NS				91	85	NS
Yoon *et al*[29]	226	251					98	98	
Peng *et al*[30]	200	300	NS				100	100	NS
Yamamoto *et al*[31]	87	223		3	3	NS			
Lee *et al*[32]	19%	28%	NS	9	16.5	NS			
Navarro *et al*[33]	234	454	0.021				100	100	NS
Delvecchio *et al*[34]	13%	25%	NS				95	87	NS
Ho *et al*[35]	500	725	NS	5	3	0.043	91	91	NS

LLR: Laparoscopic liver resection; NS: Statistically not significant; OLR: Open liver resection.

HCC. While level 1 evidence was lacking at that time, strong recommendations were made regarding the non-inferiority of both minor and major LLR in short-term postoperative and long-term outcomes, as the relative benefits of LLR over OLR had appeared to be reproducible in the larger-scaled, propensity score-matched non-randomized comparative studies conducted worldwide[2]. Yet in 2018, the very "concern of selection bias" that is inherent to non-randomized studies was then resolved with the publication of the OSLO-COMET trial, which convincingly showed that LLR has superior perioperative outcomes, non-inferior oncological safety, similar cost and better gain of life quality to OLR for the treatment of colorectal cancer liver metastases[42].

Table 2 Summary of comparative studies: Baseline clinical-pathological features of both treatment groups

Ref.	Difference between study groups	ICG, %		Child A/B/C, %		Tumor size in cm				Microvascular invasion, %	
		LLR	OLR	LLR	OLR	LLR	+/- SD/95%CI	OLR	+/- SD/95%CI	LLR	OLR
Belli *et al*[5]	Tumor size, AFP level, margin width			91/9/0	93.6/6.4/0	3.8	+/-1.3	6	+/-2.3	37	39.2
Tranchart *et al*[6]						3.6	+/-1.75	3.7	+/-2.1	33.3	35.7
Lee *et al*[7]	Cirrhosis, previous abdominal surgery, margin width					2.5	1.5-9	2.9	1.2-9		
Ahn *et al*[8]		14.5	13.1			2.6	+/-1.5	2.8	+/-1.2	15.7	19.6
Memeo *et al*[9]	Margin width			98/2/0	96/4/0	3.2	0.9-11	3.7	0.1-15		
Lee *et al*[10]	Margin width			97.6/2.4/0	97.6/2.4/0	5.4	2-16	4.4	2-14	52.5	43.5
Yoon *et al*[11]	Margin width	12.1	12.4			2.87	0.7-4.9	3.04	0.2-4.9		
Xiao *et al*[12]				95/5/0	96.5/3.5/0	4.22	+/-2.05	4.3	+/-1.49		
Sposito *et al*[13]		15	15	98/2/0	95/5/0	2.6	1-6.5	2.2	1-8.5	56	37
Cheung *et al*[14]	Age			100/0/0	96.6/3.4/0	3	1.2-5	3.5	1.5-8.5		
Ryu *et al*[15]		11.9	14			3.9	1.1-17	4.9	1-14.5	30	40
Rhu *et al*[16]				37.7/0/0	37.1/0/0	3.1	+/-5.7	3.1	+/-1.7	56.6	58.8
Guro *et al*[17]	Cirrhosis, tumor size			95/2.4/2.4	88/9.9/7.2	4.1	+/-2.4	6.3	+/-3.8		
El-Gendi *et al*[18]				100/0/0	100/0/0	3.3	+/-0.57	3.4	0.59	60	68
Inoue *et al*[19]				89/11/0	100/0/0	2.5		2.6		12	13
Kim *et al*[20]		9.3	8			2.8		2.8		25	23
Deng *et al*[21]	Procedure type			100/0/0	100/0/0	2.5		2.8		10.2	16.6
Wu *et al*[22]						3.5	0.9-12.5	3.5	0.8-11.3	38.4	41.9
Tsai *et al*[23]	Procedure magnitude, tumor size			93/7/0	98/2/0	3.9	+/-2.6	7.2	+/-5.3		
Di Sandro *et al*[24]				87/13/0	84/16/0	2.5	2-3.0	2.5	1.8-3.3	29.3	29.3
Li *et al*[25]	Tumor size					4	+/-2	5.7	+/-3	17	30
Kim *et al*[26]		10.4	12.8			3	+/-2.1	3.2	+/-3.14	22.2	27.8
Chen *et al*[27]		6.9	6.9			7.3	+/-3.4	7.6	+/-4.2	37	32
Untereiner *et al*[28]				64/0/0	73/0/0	3	2.1-4.9	3	2.3-5		
Yoon *et al*[29]	ASA class, medical disease	13.6	14	66.8/0/0	65.4/0/0	2.83	1.28	2.9	1.31	14.3	15.7
Peng *et al*[30]				94/6/0	91/9/0	4.8	2-8.5	5.5	2-8.5	30	30
Yamamoto *et al*[31]				88/22/0	84/16/0	1.7	1.2-4.2	2	0.7-9.9		
Lee *et al*[32]				90/10/0	91/9/0	2.5	7-14.5	2.6	1.1-14.5	8.6	8.6
Navarro *et al*[33]						3.5	8.5	3.3	8.1	51.2	51.2
Delvecchio *et al*[34]				97/3/0	98/2/0	4	3.0-16	7	1.5-14		
Ho *et al*[35]	Hepatitis C carrier status			100/0/0	92/8/0	3.5	2-5	4	3-5	28.9	30

	margin width

AFP: Alpha-fetoprotein; ASA: American Society of Anesthesiologists; CI: Confidence interval; ICG: Indocyanine green retention at 15 min; LLR: Laparoscopic liver resection; OLR: Open liver resection; SD: Standard deviation.

The question is now left with HCC though, as obvious difference exists between patients with HCC and colorectal liver metastases. As a majority of HCC patients have underlying cirrhosis, liver decompensation and oncological outcomes are HCC-specific outcomes to consider for LLR. Since the first published meta-analysis on the long-term outcomes of LLR for HCC in 2011[43], there have been about 20 meta-analyses on the topic published, 15 of which were published after 2017. Ciria *et al*[44] published a meta-analysis in 2018 that included 28 non-randomized comparative studies with low risk of bias. In contrast to those included by meta-analyses in the "pre-Morioka era", the studies reviewed by Ciria *et al*[44] encompassed a much wider spectrum of disease in clinical practice: Three were on major liver resection, twenty-two on minor liver resection, five on Child-Pugh class A cirrhosis, sixteen on solitary tumors and three on unstratified operable patients. For the disease-free and overall survival, meta-analyses could only be performed for studies featuring cirrhotic patients, minor hepatectomy and solitary tumors but not for major hepatectomy. The pooled relative effect of LLR to OLR showed an odds ratio (OR) in favor of LLR for 1-year disease-free survival in patients with minor hepatectomy (I^2 = 66%; OR = 0.133; 95%CI: 0.001–0.265; P < 0.048). For patients with Child's A cirrhosis and solitary tumor, no significant relative benefit or harm were found for the 1-, 3- and 5-year disease-free and overall survivals. For patients with major hepatectomy, meta-analysis was not performed due to lack of data. Moderate to high heterogeneity (I^2 = 17%-66%) was noted among the studies of laparoscopic minor hepatectomy. The highest heterogeneity is among the five studies for compilation of 1-year disease-free survival (I^2 = 66%), and the biggest discrepancy of mean relative effect lies between the study by Cheung *et al*[14] and Kobayashi *et al*[45]. This is probably related to the inclusion of recurrent HCC and hybrid or hand-assisted laparoscopic procedures in the study population in the study by Kobayashi *et al*[45]. Moreover, two studies with the greatest tendency to favor LLR came from the same center[14,46] with overlapping study period and study population (left lateral sectionectomy in 25% and 100% of studied population), giving rise to the concern of overestimation of the relative benefit of LLR.

The lack of long-term survival data specifically for laparoscopic major hepatectomies in the above meta-analysis was addressed by a recent meta-analysis by Wang *et al*[47] that included nine studies of the patient population. Interestingly, a favorable result for LLR was again noted in 1-year disease-free survival (I^2 = 0%; OR = 1.55; 95%CI: 1.04-2.31; P = 0.03), but not in disease-free or overall survival in another analyzed timespan. Again, one of the constituent studies for the pooled analysis of 1-year disease-free survival is notably out-standing with regard to the tumor recurrence rate in the OLR group, and an apparent reason that is also acknowledged by the author was the significantly bigger tumor size (6.3 ± 3.8 *vs* 4.1 ± 2.4 cm; P = 0.000) included in the OLR arm[17].

In contrast to most of the meta-analyses showing non-significant difference in overall survival, Jiang *et al*[48] meta-analyzed studies of cirrhotic patients and found significant relative benefit of LLR in 1-, 3- and 5-year overall survival and 1-year disease-free survival, with only moderate issue of heterogeneity (I^2 = 36%-39%). The apparent reason for the discrepancy between that study and Ciria *et al*[44]'s sub-group analyses for cirrhotic patients is that the two reviews included different sets of studies for analyses. The rationale behind study selection is difficult to judge, but Jiang *et al*[48] excluded the study because the data were not retrievable, which could potentially lead to bias. On the other hand, Ciria *et al*[44] only included three studies for the analyses of long-term outcome of cirrhotic patients, which may not be powerful enough to detect small effects.

DISCUSSION

Theoretically, LLR has a few advantages over OLR that may potentially give rise to a superior oncological outcome; these include reduced perioperative transfusion and reduced tumor manipulation. Practically, such an effect has not been convincingly demonstrated in the currently available evidence. An overall improvement in the pre-

Table 3 Summary of comparative studies: Study design

Ref.	Year	Number of patients		Matching	Study population			
		LLR	OLR		Demographic	Tumor	Cirrhosis	Procedure
Belli *et al*[5]	2009	54	125	No		< 5 cm, anterolaterally located		
Tranchart *et al*[6]	2010	42	42	Yes				
Lee *et al*[7]	2011	33	50	Yes				Minor resection
Ahn *et al*[8]	2014	51	51	Yes		Solitary		
Memeo *et al*[9]	2014	45	45	Yes			Cirrhosis	
Lee *et al*[10]	2015	43	86	Yes				
Yoon *et al*[11]	2015	58	174	Yes		< 5 cm		
Xiao *et al*[12]	2015	41	86	No		Posterosuperior		
Sposito *et al*[13]	2016	43	43	Yes			Cirrhosis	Minor resection
Cheung *et al*[14]	2016	24	29	Yes				Left lateral sectionectomy
Ryu *et al*[15]	2018	40	30	No				Anatomical resection
Rhu *et al*[16]	2018	58	133	Yes				Right posterior sectionectomy
Guro *et al*[17]	2018	67	110	No				Major hepatectomy
El-Gendi *et al*[18]	2018	25	25	Randomized		< 5 cm	Child A	
Inoue *et al*[19]	2018	61	175	Yes		< 5 cm		Parenchymal sparing hepatectomy
Kim *et al*[20]	2018	37	37	Yes				Left hepatectomy
Deng *et al*[21]	2018	157	157	Yes				
Wu *et al*[22]	2019	86	86	Yes			Cirrhosis	
Tsai *et al*[23]	2019	153	160	Yes				
Di Sandro *et al*[24]	2018	75	75	Yes			Cirrhosis	Minor hepatectomy
Li *et al*[25]	2019	41	307	Yes				Mesohepatectomy
Kim *et al*[26]	2018	18	36	Yes		Central		
Chen *et al*[27]	2019	38	38	Yes				Right hepatectomy
Untereiner *et al*[28]	2019	33	33	Yes				
Yoon *et al*[29]	2020	217	434	Yes				
Peng *et al*[30]	2019	33	33	Yes		Multiple		
Yamamoto *et al*[31]	2020	58	197	Yes			Cirrhosis	
Lee *et al*[32]	2021	58	110	Yes				
Navarro *et al*[33]	2021	106	299	Yes				Major hepatectomy
Delvecchio *et al*[34]	2021	38	84	Yes	Elderly			Major hepatectomy
Ho *et al*[35]	2021	45	90	Yes				

LLR: Laparoscopic liver resection; OLR: Open liver resection.

operative stratification, diverting away of selected patient population to liver transplantation, improved surgical techniques to minimize blood transfusion requirement even in the OLR group, a better medical control of background liver disease activity, *etc*., might all be possible to ameliorate any marginal survival advantage of LLR over OLR.

Table 4 Summary of comparative studies: Long-term oncological outcomes

Ref.	1-year OS, %			3-year OS, %			5-year OS, %			1-year DFS, %			3-year DFS, %			5-year DFS, %		
	LLR	OLR	*P*	LLR	OLR	*P*	LLR	OLR	*P*	LLR	OLR	*P*	LLR	OLR	*P*	LLR	OLR	*P*
Belli *et al*[5]	94	85	NS	67	53	NS				78	79	NS	52	52	NS			
Tranchart *et al*[6]	93.1	81.8	NS	74.4	73	NS	59.5	47.4	NS	81.6	70.2	NS	60.9	54.3	NS	45.6	37.2	NS
Lee *et al*[7]	86.9	98	NS	81.8	80.6	NS	76	76.1	NS	78.8	69.2	NS	51	55.9	NS	45.3	55.9	NS
Ahn *et al*[8]							80.1	85.7	NS							67.8	54.8	NS
Memeo *et al*[9]	88	63	NS				59	44	NS	80	60	NS				19	23	NS
Lee *et al*[10]	95.3	93.9	NS	89.7	89.5	NS	89.7	87.3	NS	60.5	81.5	NS	60.3	66.7	NS	60.3	58.6	NS
Yoon *et al*[11]	95	98	NS	86	84	NS				82	88	NS	63	62	NS			
Xiao *et al*[12]	95.1	89.5	NS	78	76.7	NS				87.8	82.6	NS	70.7	68.6	NS			
Sposito *et al*[13]				75	79	NS	38	46	NS				41	44	NS	25	11	NS
Cheung *et al*[14]	100	93	NS	85.6	84.1	NS	69.1	77.6	NS	95	69.2	NS	72.8	61.5	NS	51.8	61.5	NS
Ryu *et al*[15]	89.9	89.9	NS	84.7	68	NS	70.9	63.1	NS	79.5	72.4	NS	58	56.1	NS	42.5	50.4	NS
Rhu *et al*[16]	96.8	96.8	NS	94.5	94.5	NS	94.5	94.5	NS	77.8	77.8	NS	68.3	68.3	NS	62.5	62.5	NS
Guro *et al*[17]							77.3	60.2	NS							50.8	40.1	NS
El-Gendi *et al*[18]										88	84	NS	58.7	54	NS			
Inoue *et al*[19]	97.8	87.9	NS	78.8	70.6	NS				83.8	75	NS	57.5	54.8	NS			
Kim *et al*[20]				93.9	93.8								79.6	91.1	NS			
Deng *et al*[21]	96.2	96.8	NS	72.6	73.4	NS	45.3	46.9	NS	90.5	91.7	NS	53.7	54.4	NS	24.6	19.9	NS
Wu *et al*[22]	93	81.4	NS	81.4	75.5	NS	69.8	62.8	NS	75.6	69.8	NS	60.5	53.5	NS	44.2	38.4	NS
Tsai *et al*[23]	90.3	85	0.002	82.9	63.6	0.002	78.1	57.6	0.002	72.9	60.8	NS	49.2	43	NS	37.9	31	NS
Di Sandro *et al*[24]				68	76								44	44	NS			
Li *et al*[25]	96.3	95.3	NS	68.4	90.5	NS				84	87.2	NS	36	59.7	NS			
Kim *et al*[26]	94.4	100	NS	94.4	92.9	NS				93.8	76.5	NS	56.3	41.3	NS			
Chen *et al*[27]				69.8	74	NS							51.6	57.8	NS			
Untereiner *et al*[28]				78	79	NS							72	58.6	NS			
Yoon *et al*[29]	98.1	93.8	NS	87	90.8	NS	78.6	84.3	NS	81	85.3	NS	62	64.7	NS	49.1	56.2	NS

Peng *et al*[30]	95.8	92.8		77	77	NS				71.9	79.1	NS	51.4	46.2	NS			
Yamamoto *et al*[31]				82	78.4	NS	58.9	62.3	NS				52.6	40.3	NS	24	24.1	NS
Lee *et al*[32]	96.6	92.8	NS	73.3	93.1	NS	88.8	76.1	NS	84.4	64	NS	60.2	93.1	NS	67.4	63.9	NS
Navarro *et al*[33]							90	90	NS							58	40	NS
Delvecchio *et al*[34]	100	95	NS	100	88	NS	77	75	NS	67	79	NS	44	54	NS	29	46	NS
Ho *et al*[35]	95.6	87.5	0.036	84.9	70.3	0.036	84.9	61.1	0.036	80.0	73.3	NS	40.0	41.1	NS	20.0	22.2	NS

DFS: Disease-free survival; LLR: Laparoscopic liver resection; NS: Statistically not significant; OLR: Open liver resection; OS: Overall survival.

Two observations were made from the current review of meta-analyses and recent comparative studies. Firstly, the non-inferiority in long-term oncological outcome of LLR *vs* OLR has been repeatedly shown by pooling of various combinations of studies, patient populations and LLR procedures. This should partially address the concern of selection bias, as such outcomes are now widely reproducible worldwide. Secondly, while the studies on LLR for HCC are increasingly heterogenous in terms of disease spectrum included and type of procedure performed, the study methodologies adopted are more and more standardized. Thus, future publications are likely to reflect the advanced practice of difficult procedures of high-volume centers, while the diffusion of the technique among lower-volume centers may be underrepresented in the medical literature. This echoes the need of a broad-based prospectively collected registry database for the purpose of ongoing consolidation of evidence and monitoring of the development of LLR.

CONCLUSION

The current review has updated the findings on long-term oncological outcomes of LLR for HCC. Depicted is also a phenomenal development of LLR, in which there is a widespread adoption of an innovative invasive technique long before the availability of level 1 evidence. Complicated surgical procedures, heterogenous diseases presentation and a long learning curve are the main hurdles of conducting a widely generalizable randomized controlled trial. Given the heterogeneity of the data and the lack of randomized controlled trial, it may still be too bold to prioritize LLR in long-term survival, its advantage being more evident in the perioperative period. A broad-based prospective LLR registry keeping safety and oncological outcomes in check may be a better solution to the need of stronger evidence in the field.

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OPINION REVIEW

Review of minimally invasive pancreas surgery and opinion on its incorporation into low volume and resource poor centres

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Abstract

Pancreatic surgery has been one of the last areas for the application of minimally invasive surgery (MIS) because there are many factors that make laparoscopic pancreas resections difficult. The concept of service centralization has also limited expertise to a small cadre of high-volume centres in resource rich countries. However, this is not the environment that many surgeons in developing countries work in. These patients often do not have the opportunity to travel to high volume centres for care. Therefore, we sought to review the existing data on MIS for the pancreas and to discuss. In this paper, we review the evolution of MIS on the pancreas and discuss the incorporation of this service into low-volume and

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resource-poor countries, such as those in the Caribbean. This paper has two parts. First, we performed a literature review evaluating all studies published on laparoscopic and robotic surgery of the pancreas. The data in the Caribbean is examined and we discuss tips for incorporating this operation into resource poor hospital practice. Low pancreatic case volume in the Caribbean, and financial barriers to MIS in general, laparoscopic distal pancreatectomy, enucleation and cystogastrostomy are feasible operations to integrate in to a resource-limited healthcare environment. This is because they can be performed with minimal to no consumables and require an intermediate MIS skillset to complement an open pancreatic surgeon's peri-operative experience.

Key Words: Pancreas; Surgery; Laparoscopic; Minimally invasive; Pancreatectomy; Whipple's; Pancreaticoduidenectomy

Core Tip: The published data generally support the use of the minimally invasive approach for surgery on the pancreas. However, it has been under-utilized in the Caribbean because both minimally invasive surgery and service centralization for pancreatic surgery are in their infancy in the Caribbean. Only 3.25 Laparoscopic distal pancreatectomies are performed per annum across the entire region. In this paper we explore the obstacles to incorporating a minimally invasive service for pancreatic surgery.

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INTRODUCTION

Surgeons across the globe embraced minimally invasive surgery (MIS) by the end of the 20th century, but pancreatic surgery was one of the last frontiers for its application. Many factors make laparoscopic pancreatic surgery difficult: The organ is deep in the retroperitoneum, attached to the duodenum, intimately related to large mesenteric vessels and draped by viscera. In addition, its soft glandular consistency and its ability to fibrose surrounding tissues in the setting of pathology make it a treacherous contender for laparoscopy.

An additional consideration is the fact that multiple studies demonstrated that patient safety and outcomes are better when pancreatic operations are performed in high volume centers by specialized surgical teams[1,2]. This limits the experience with laparoscopic pancreatic surgery to a small cadre of institutions, mostly in high-income, resource-rich countries. In this paper, we review the evolution of minimally invasive pancreatic surgery and discuss our experience incorporating this into low-volume, resource-poor countries such as those in the Caribbean.

LITERATURE REVIEW

The first report of a laparoscopic operation on the pancreas was published by Gagner *et al*[3] who completed a pancreaticoduodenectomy (PD) in 1994. Their operation was complicated by a jejunal ulcer, delayed gastric emptying and a prolonged 30-d post-operative hospitalization, forcing the authors to conclude that "*although technically feasible, the laparoscopic Whipple procedure did not improve the postoperative outcome or shorten the postoperative recovery*"[1]. It was interesting that Gagner and Pomp chose this operation for their initial attempt at laparoscopic pancreatic surgery, considering that a

PD is longer and technically more complex than left-sided resections.

Most of the subsequent reports in the 1990's focused on laparoscopic distal pancreatectomies (LDP), demonstrating that it was feasible for benign endocrine lesions and chronic pancreatitis[4-11]. By the end of the 20th century, it appeared that laparoscopy was being seriously entertained for benign pancreatic diseases. In 1998, Cuschieri *et al* [11] wrote "*laparoscopic distal pancreatic resections have been entirely favorable, with benefit to the patient in terms of postoperative recovery, minimal morbidity and short hospital stay*". And in 1999, Park *et al*[10] stated that "*patients appear to benefit from laparoscopic distal pancreatic resections*."

MINIMALLY INVASIVE DISTAL PANCREATECTOMY

In the first decade of the 21st century, more robust publications began to appear proving that LDP was feasible, technically reproducible and accompanied by encouraging short-term outcomes[12-18]. One decade later, sufficient data had accumulated to allow large metanalyses[19-21].

Venkat *et al*[19] published a metanalysis in 2012 that compared LDP and open distal pancreatectomy (ODP) in 1814 patients across 18 studies. They demonstrated that both techniques had similar operative times, margin positivity, postoperative pancreatic fistula and mortality, but LDP brought statistically significant reductions in blood loss, hospital stay, overall morbidity and surgical site infection. Venkat *et al*[19] wrote that the "*improved complication profile of LDP, taken together with the lack of compromise of margin status, suggests that this technique is a reasonable approach in selected cancer patients.*"

In 2013 Nakamura *et al*[20] published a meta-analysis of 2904 distal pancreatectomies across 24 studies. Compared with ODP, LDP showed statistically significant reductions in blood loss, transfusion requirements, wound infection rates, morbidity rates and hospitalization. Based on this, Nakamura *et al*[20] wrote "*LDP showed significantly better perioperative outcomes and is a reasonable operative method for benign tumors and some ductal carcinomas in the pancreas*".

Riviere *et al*[21] then published a 2016 Cochrane Database Systematic Review that compared ODP and LDP in 1576 patients. They noted that hospital stay was 2.43 d shorter in the laparoscopic group, but lamented that existing data were from observational and case-control studies with confounders that did not allow definitive conclusions. Riviere *et al*[21] called for prospective randomized trials to evaluate this further. The Dutch Pancreatic Cancer Group responded and published results of the LEOPARD trial in 2019 that randomized patients to LDP or ODP, blinding patients with a large abdominal dressing[22]. In this trial, patients who had LDP had statistically significant reductions in the time to functional recovery (4 d *vs* 6 d), operative blood less (150 mL *vs* 400 mL) and incidence of delayed gastric emptying (6% *vs* 20%). They also had better quality of life after LDP. Although the time to complete LDP was significantly longer (217 min *vs* 179 min), it did not increase the overall cost of care.

The data in support of LDP continued to accrue, but as laparoscopic surgeons pushed the boundaries of pancreatic surgery another development occurred simultaneously. The approval of Intuitive's DaVinci surgical robot by the United States Food and Drug Administration (FDA) in the year 2000[23] ushered in the robotic surgical revolution. In 2003, Melvin *et al*[24] published a report of the first robotic distal pancreatectomy (RDP) and this was followed by a publication from Guilianotti *et al*[25] in 2003 documenting 13 robotic pancreatic operations (among a series of 193 varied robotic operations) that included 5 RDPs and 8 robotic-assisted pancreaticoduodenectomy (RPDs). They reported good outcomes with RDP, with 270 min operating time, 20% overall morbidity and no mortality. Within a few years, the robotic approach became popular in resource-rich countries and small RDP series with good results were published[26-29].

Within a decade, sufficient data were accrued to allow meta-analyses to be performed[30-35]. The first was published by Gavriilidis *et al*[30] in 2016 and compared RDP *vs* LDP in 637 patients across 9 studies. They found no significant difference in operative time, conversions, grade B–C pancreatic fistula, morbidity, spleen preservation, perioperative mortality or R0 surgical margins. There was a reduction in hospitalization by one day when patients underwent RDP, but this was countered by significantly increased readmission rates. Therefore, Gavriilidis *et al*[30] concluded that both were reasonable techniques with similar feasibility, safety and oncological adequacy.

In 2017, Huang *et al*[31] compared LDP and RDP in more than 1100 patients across 9 studies and found no difference in operating time, conversions, pancreatic fistulae, spleen preservation, transfusion rates or post-operative hospitalization between the two approaches. Huang *et al*[31] also concluded that RDP was a "*safe and effective alternative*".

In 2017, Guerrini *et al*[32] compared RDP and LDP in a metanalysis of 813 patients across 10 studies. They were able to show definite advantages for RDP, with significantly greater spleen preservation, less conversions and shorter hospitalization. Although there was greater higher cost associated with RDP, Guerrini *et al*[32] concluded that RDP was "*safe and comparable to LDP*" and suggested that the increase in cost was balanced by the improved peri-operative profile.

In 2019, Gavriilidis *et al*[33] published an updated metanalysis comparing the oncological adequacy and efficacy between RDP, LDP and ODP in 6796 patients across 36 studies. Both RDP and LDP brought significantly less blood loss, shorter length of stay and better R0 margins compared to open surgery. When they compared LDP and RDP directly, RDP had lower conversion rates, reduced blood loss and shorter hospital stay. In their conclusion, however, they acknowledged that the data were "*underpowered and did not permit conclusions about oncological safety for pancreatic adenocarcinoma*."

Hu *et al*[34] published another metanalysis comparing RDP and LDP across 22 studies in 2020. In this study, robotic surgery significantly increased spleen preservation, reduced conversions and shortened hospitalization, at the expense of increased cost. There were no differences in blood loss, overall morbidity, node harvest, transfusions, grade B-C pancreatic fistula, margin positivity or mortality. Hu *et al*[34] concluded that "*both RDP and LDP are safe and feasible alternatives*" and suggested that the advantages of RDP balanced the increase in cost.

Finally, in 2020 Zhou *et al*[35] compared RDP and ODP in 2264 patients in a meta-analysis of 7 studies. They demonstrated that RDP significantly reduced blood loss, transfusion rates, postoperative mortality and length of hospital stay. There was no difference in operating time, node harvest, margin positivity, spleen preservation, severe morbidity or grade B-C pancreatic fistula between the groups. They concluded that RDP was a "*safe and feasible alternative in centers with expertise in robotic surgery*."

It appears that within the first two decades of the 21st century, there was a rapid swing of the pendulum, moving from open to laparoscopic to robotic distal pancreatectomy. Indeed, the conclusions of early authors seem to have been dismissed and many now propone LDP as standard of care, and RDP as a safe and feasible alternative. While the qualities of a surgical robot (better 3-dimentional visualization, tremor filtration, motion scaling, improved ergonomics and better freedom of motion) appear attractive compared to conventional laparoscopy, the exorbitant cost is prohibitive even in the health care systems of high-income economies. Many developing countries are not be able to afford the high cost, and in the English-speaking Caribbean there are no surgical robots available for use.

MINIMALLY INVASIVE WHIPPLE'S PD

Although LDP gained footing in the late 1990s, there was reluctance to embrace laparoscopy for PD. In 1998 Cuschieri *et al*[11] wrote "*the experience with laparoscopic PD has been unfavorable. With the current technology, the laparoscopic approach for this procedure is too prolonged and does not seem to offer any benefit to the patient.*" Similarly, in 1999 Parks *et al*[10] wrote that "*patients benefit from laparoscopic distal pancreatic resection but not from laparoscopic PD*". And in 2001, Gentileschi *et al*[12] wrote that laparoscopic PD "*is not associated with patient benefit and may be accompanied by increased morbidity.*" The general theme during the late 1990s was to dissuade the surgical community in its pursuit of minimally invasive PD.

The turn of the 21st century saw publication of small series demonstrating that LPD was technically feasible and associated with reasonable short-term outcomes[36,37]. And by the second decade of the 21st century there were increasing numbers of larger, more robust studies comparing LPD and open pancreaticoduodenectomy (OPD) being published[38-49]. Most publications reported significantly longer operating time[20,42,43] and increased cost[20,39,41-43]. But the data supported LPD by showing benefit with significantly reduced post-operative pain[42], quicker return of bowel function [42], reduced overall morbidity[43], shorter high dependency unit or intensive care unit (HDU/ICU) stay[38,40], shorter hospitalization[38,39,42,43] and lower blood loss [20,38,39,43]. It is clear that within 2 decades most authors adopted conclusions that

were opposite to those in the late 1990s[42-49].

Although there now seemed to be a general embrace of the minimally invasive approach, the Dutch LEOPARD trials[50] mounted a challenge. The Dutch LEOPARD trial was a multi-centre randomized blinded trial that randomized 99 patients to OPD or LPD[50]. The surgeons in this trial were highly skilled pancreatic surgeons who had to complete at least 20 LPDs in an approved training programme before they participated in the study. Patients who underwent LPD had a trend toward greater 90-d mortality (10% *vs* 2%; $P = 0.02$; RR 4.9; 95%CI: 0.59-40.4), but no difference in median time to functional recovery (10 d *vs* 8 d; 95%CI: 7-9), no difference in major morbidity (50% *vs* 39%; RR 1.29; 95%CI: 0.82-2.02; $P = 0.26$) and no difference in grade B/C pancreatic fistula (28% *vs* 24%; RR 1.14; 95%CI: 0.59-2.22; $P = 0.69$). Although there was no statistically significant difference between the two groups, the study was concluded early based on the rationale that the findings were "*unexpected and worrisome, especially in the setting of trained surgeons working in centres performing 20 or more pancreatoduodenectomies annually*."

But before consensus was achieved, the direction again shifted soon after the FDA approval of Intuitive's DaVinci surgical robot[23]. Guilianotti *et al*[25] in 2003 published the first series of 193 robotic operations that included 8 RPDs. Within a few years, RPD gained traction in resource-rich countries and their outcomes data were published[30,47,48,51]. Four authors attempted to collectively evaluate the existing data in meta-analyses to compare the robotic approach with OPD[52-55].

Peng *et al*[52] reported on a meta-analysis of 435 patients undergoing OPD *vs* 245 undergoing RPD across 9 non-randomized studies. Patients in the RPD group had significantly lower overall morbidity, significantly better R0 margin clearance, lower surgical site infections and a shorter duration of post-operative hospital stay. This was achieved without any difference in operation time, node harvest, pancreatic fistulae or mortality. Peng *et al*[52] concluded that RPD was safe and efficient, but noted that multi-centre randomized, controlled trials were lacking.

Zhao *et al*[53] published a meta-analysis that compared RPD (assisted) and OPD across 11 non-randomized controlled trials. The robotic approach had longer operative times, but was accompanied by statistically significant reductions in blood loss, surgical site infections, R1 margin involvement, overall morbidity and time to return of post-operative activity. Compared to OPD, there was equivalent lymph node harvest, post-operative pancreatic fistula, hospitalization and mortality rates. Zhao *et al*[53] concluded that RPD is a "*safe and feasible alternative to OPD with regard to perioperative outcomes. However, due to the lack of high-quality randomized controlled trials, the evidence is still limited*".

Shin *et al*[54] published a systematic review comparing RPD or LPD and OPD. Both techniques had similar oncologic outcomes, but the robotic approach had significantly longer operative times, less intraoperative blood loss and shorter hospital stay. Shin *et al*[54] concluded that RPD was "*feasible and oncologically safe*", but lamented the paucity of robust data.

Podda *et al*[55] published the most recent metanalysis to date compared 1593 patients who underwent RPD to 12046 patients who underwent OPD across 18 non-randomized studies. They found that both techniques had similar outcomes in mortality, overall morbidity, post-operative pancreatic fistula rates, haemorrhage, bile leaks, nodal harvest and positive margin status. While RPD did require significantly longer operating time (461 min *vs* 384 min), it did have the advantage of significantly lower operative blood loss (174 mL *vs* 352 mL). Based on this, Podda *et al*[55] concluded that RPD was a "*safe and feasible alternative*" to open surgery.

Simultaneously, two meta-analyses evaluated the existing data to compare the robotic and laparoscopic approaches to PD[47,56]. In 2014 Boggi *et al*[47] published a systematic review of 746 LPDs done across 25 published articles. These included pure laparoscopic (386), robot assisted (243), laparoscopic assisted (121) and hand-assisted (5) cases. Interestingly, they were able to show that pure LPD was associated with a significant reduction in operative time, blood loss and pancreatic fistulae *vs* cases completed with laparoscopic assistance and robotic assistance.

Kamarajah *et al*[56] published a metanalysis comparing outcomes in 2437 patients undergoing LPD and 1025 patients undergoing RPD across 44 studies. They noted that RPD was associated with significantly less conversions, lower transfusion requirements and shorter post-operative hospitalization (11 d *vs* 12 d). But there was no difference in blood loss, (220 mL *vs* 287 mL), operating time (405 min *vs* 418 min), overall morbidity, pancreatic fistula or margin involvement. Kamarajah *et al*[56] noted that RPD did have advantages, but the data was limited and so had to be considered to "*offerequivalent clinical outcomes*."

In summary, it appears that there was a similar swing of the pendulum for PD from open to laparoscopic and robotic approaches, although the movement took longer to gain momentum. Although some authors have documented good outcome data in select patients at experienced centres, most agree that minimally invasive PD, whether purely laparoscopic, hybrid (laparoscopic dissection with open or robotic reconstruction) or wholly robotic, remain in the hands of experienced pancreatic surgeons in high-volume centers.

CARIBBEAN EXPERIENCE

Although the first reports of laparoscopy in the Anglophone Caribbean date back to 1991 with a cholecystectomy in Trinidad & Tobago, MIS remained relatively dormant and did not gain traction in the Caribbean until 2005[57]. As it relates to service centralization, regional referral centers for pancreatic diseases in the Caribbean were only established in 2010 under the auspices of the Caribbean Chapter of the Americas Hepaticopancreaticobiliary Association (AHPBA)[58]. Therefore, a situation exists where both centralization for pancreatic surgery and the minimally invasive surgical revolution are in their infancy in the Caribbean.

The surgeons attached to the pancreatic referral centers all completed formal fellowship training at high-volume hospitals in Canada (4), the United Kingdom (1) and India (1). In these centers they gained sufficient experience to overcome learning curves for the full range of open pancreatic operations and select minimally invasive operations[58]. It is important to appreciate that these training centers all ran accredited fellowships in hepatopancreaticobiliary surgery, but they were high-volume hospitals that operated in different healthcare environments. Although the local surgeons generally surpassed their learning curves, they repatriated to the resource-poor settings with many challenges: scarce blood products, high competition for ICU/HDU beds, an undersupply of consumables and referral bias. Consequently, pancreatic operations are still performed at low volumes in the region. To illustrate this point, consider data from the largest Caribbean hepatopancreatobiliary referral center in Trinidad & Tobago, where only 12.8 pancreaticoduodenectomies were performed annually[58]. This falls short of the "high-volume" mark of 15-20 procedures generally quoted in the medical literature[1,2]. Pancreatic operations outside of these centers are performed in very small volumes by general surgeons with even less experience in pancreatic surgery and with varied MIS exposure.

Although the surgeons in regional referral centers received sufficient exposure during fellowship training to overcome the learning curve for LDP, LPD was not performed regularly during their training[58]. Consequently, LPD is not popular in the region. To date there have only been one published case report of totally LPD[59] and three (un-published) laparoscopic-assisted PDs performed in Trinidad & Tobago. Otherwise, the reports of minimally invasive pancreatic surgery in the Anglophone Caribbean have been limited to three small series of laparoscopic distal pancreatectomies[57,60,61] and two reports of laparoscopic cysto-gastrostomy[62,63]. Up to the year 2021, there were no surgical robots in any English-speaking Caribbean country.

Unpublished data from the registry maintained by the Caribbean Chapter of the AHPBA revealed that only 13 LDPs were performed over the four-year period between January 1, 2014 and December 30, 2017 for trauma (2), adenocarcinoma (2), neuroendocrine tumours (3) and Frantz tumours (3). Generally, the small numbers (3.25 distal pancreatectomies annually) are reflective of low case volumes in the Caribbean. It is hoped that the volumes will increase once the centralization concept is embraced and there is continued progress in MIS in the region. In the region, we experience obstacles that are similar to other developing countries that wish to commence minimally invasive pancreatic surgery: (1) scarce consumables for MIS surgery; (2) lack of universal health insurance for Caribbean populations; (3) paucity of operating list time; (4) limited ICU/HDU space; and (5) poor attitudes toward MIS[58].

Despite the existing challenges, we believe that LDP is an operation that can be done with minimal consumables and in similar time to the open approach. It is attractive to healthcare administrators because it can prevent lengthy hospitalizations, thereby saving limited resources. An intermediate MIS surgeon should have safe dissection skills (since there are no anastomoses) and sufficient familiarity with the instrumentation to make this is a feasible operation to integrate in to a resource-limited environment.

Therefore, for the remainder of this paper, we focus on LDP, cystogastrosomy and enucleations because we believe these are realistic operations to be learned and

practiced in developing countries. The authors advocate these as the initial operations to be introduced in expanding MIS programs because it does not require specialized instruments, does not require a keen grasp of intracorporal suturing and treats that part of the pancreas that is most maneuverable and easiest to control if hemorrhage were to occur.

TECHNICAL ASPECTS

Surgeons seeking to incorporate minimally invasive pancreatic surgery into their practice should be intimately familiar with pancreatic anatomy as well as common anatomic variants. Facility with laparoscopic foregut surgery is an advantage when beginning, including appreciation of optimal patient positioning, port placement, intracorporeal suturing skills and proficiency with laparoscopic ultrasonography. We advocate for a team-based approach, where an advanced laparoscopic surgeon is paired with an experienced pancreatic surgeon. The authors also suggest mastery of the operations in a step-wise fashion, starting with completing the simpler dissections initially and gradually rising to the most difficult step (Figure 1). Initial un-proctored exposure should aim for the most straightforward anatomy possible, and as the learning curve levels off, more challenging cases can be attempted. Finally, there should be no shame or bruised ego when conversion to an open procedure is required as patient welfare and oncologic principles must come first.

Patient selection

Because the pancreas is a retroperitoneal organ, patients with lower body mass index, less visceral fat and no previous abdominal operations are more straightforward laparoscopic candidates. At the same time, thin or short patients may present the surgeon with diminished working space. As skill and comfort develops, less ideal patients can be considered. Of course, a patient with compromised pulmonary mechanics or severe acid-base disorders may not be the best choice for a prolonged laparoscopic procedure, where CO_2 retention can be considerable.

Favorable lesions include those located toward the pancreatic tail, requiring less retroperitoneal dissection and laying comfortably away from major vascular structures (celiac trunk, superior mesenteric artery, inferior mesenteric vein, superior mesenteric and portal veins). Benign diseases tend to result in easier dissection planes, as do small neuroendocrine lesions. In contrast, "benign" acute or chronic pancreatitis may present obscure tissue planes and rock-hard fibrosis making dissection exceedingly challenging. Malignant lesions also can range in the spectrum from small tumors with minimal desmoplastic reaction to large immobile tumors which obscure a laparoscopic camera view.

Distal pancreatectomies are the most straightforward cases to integrate, especially where instrumentation, personnel and operative time may be limited. When the surgeon is prepared to tackle more complex cases, patient selection is again paramount. Even many experienced laparoscopic or robotic surgeons will not plan a minimally invasive approach for lesions that abut or invade major vascular structures.

Patient positioning and trocar placement

Careful patient positioning is a critical step for successful minimally invasive pancreatectomy. The first consideration is where the operating surgeon will stand. To perform a distal (left-sided) pancreatectomy, the surgeon may either stand to the patient's right side or between the legs in a modified lithotomy position. A surgeon performing midline (central) pancreatectomy or pancreaticoduodenectomy may be better served standing between split legs or on the patient's left side. Steep reverse Trendelenberg position is useful to allow viscera to fall, facilitating exposure of the lesser sac. To ensure patient safety, footboards should be in place and safety straps should be used to prevent slipping. An electric operating table is useful (but not essential) to provide lateral tilt for gravity-assisted retraction of viscera.

Optimal trocar placement relies on the principle of triangulation, where the visual access, operator and assistant are arranged in a triangle centered on the target pathology; the pathology should be considered the apex of a diamond with the instruments as the remaining three points. Thus, in a left upper quadrant procedure, one or two working trocars should be midline/right abdomen, the viewing port left mid-abdomen, and a retraction port left lateral abdomen. However, a large pannus often distorts anatomy, with the umbilicus far more caudad, so the trocars may be better positioned more cephalad than external landmarks indicate. Handedness of the

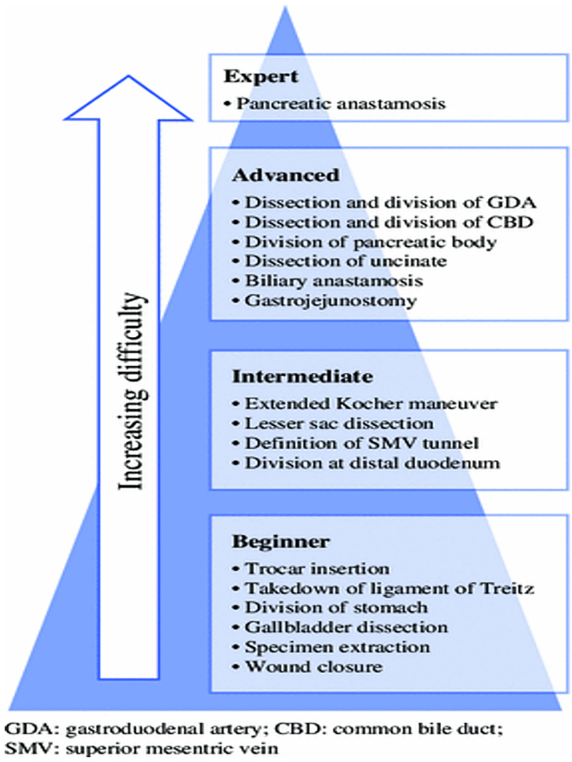

Figure 1 Learning curve pyramid illustrating the suggested mastery of pancreatic operations in a step-wise fashion, starting with simpler dissections initially and gradually rising to the most difficult operations. Citation: Speicher PJ, Nussbaum DP, White RR, Zani S, Mosca PJ, Blazer DG 3rd, Clary BM, Pappas TN, Tyler DS, Perez A. Defining the learning curve for team-based laparoscopic pancreaticoduodenectomy. *Ann Surg Oncol* 2014; 21(12): 4014-4019. Copyright © Speicher PJ *et al* 2014. Published by Springer Nature[74].

operating surgeon may also play a role in trocar position and size. The size of the trocars depends on the instruments used; often the authors will start with all 5 mm trocars and upsize when it is clear where the stapler, suturing device or extraction site will be best positioned. Most of the dissection can be done with 5 mm instruments and energy devices. All trocars are typically placed off midline for these cases; the umbilical trocar used for appendectomy or cholecystectomy is rarely needed.

Technical aspects of dissection including instrumentation

There are many types of laparoscopic instruments available, and surgeons should accumulate a representative selection for the task at hand. We typically use 30 angled laparoscopes and pneumoperitoneum pressures ranging from 12-15 mmHg, depending on body habitus and respiratory physiology.

Atraumatic graspers should be used to grasping bowel and stomach. Note that most pancreata are fragile and should not be grasped, but rather nudged or held by surrounding fatty tissue. Finer dissectors, either needle-nosed, round-nosed or curved, can be used for blunt dissection and one might consider a few bariatric length instruments for use on the proximal short gastric vascular bundles and around the spleen. Fine electrocautery tips or hooks are handy tools for rendering hemostasis on raw surfaces. Energy instruments are useful for hemostatic peripancreatic dissection and the surgeon should ultimately choose ones they are comfortable with, remaining aware of the capabilities and precautions of each.

As with the energy devices, the surgeon should choose the stapling device they wish to use based on: what is available in their setting, one that they are comfortable with, that is easy for them to handle and fire, and reasonable for the operating room staff to load. One prerequisite is that the stapler should be able to articulate and rotate, as the retroperitoneal space does not offer much flexibility for stapler positioning. Prolonged compression before slow firing may aid in hemostasis and has even been proposed as a maneuver to decrease the incidence of pancreatic leaks[64,65]. Buttress materials for staplers are also available, and there is data suggesting that they decrease the incidence of pancreatic fistula[66]. We advocate using different staple heights based on the types of tissues and texture of the pancreas, though we acknowledge that there is no data to guide this. For very thick pancreata, we prefer to transect with energy devices and suture the duct because a stapled closure may not be robust. In

fact, in some cases the stapler may not even close over the organ or it may fracture the gland[67,68]. This technique may be feasible for low resource centres where staplers are not readily available.

Intracorporeal suturing is one of the more challenging minimally invasive skills to acquire. Therefore, laparoscopically assisted dissection and resection can be considered followed by a mini-laparotomy for the reconstruction. Alternatively, there are several enabling devices are available to facilitate suturing such as Endo360 (Endoevolution, LLC, Raynam, MA, United States) or EndoStitch (Covidien Ltd, Minneapolis, MN, United States) devices. As a note, it also takes practice to master these instruments so the surgeon should make an individualized decision on their use, weighing the instrument capabilities and cost with free hand suturing.

Exposure of the pancreas

We were being by using an energy device to open the gastrocolic ligament in an avascular plane, preserving the gastroepiploic vessels along the greater curvature of stomach. If there is an option to preserve the spleen, the short gastric vascular bundles should be preserved as long as possible to allow a Warshaw-type spleen preservation if the main splenic artery and vein need to be sacrificed[69]. If splenectomy is planned or visualization is poor, the short gastric vascular bundles can be divided early. There are often adhesions between the pancreas and the posterior stomach to the pancreas that can be safely divided with energy. The stomach will then need to be retracted to expose the pancreas and this can be achieved either with laparoscopic self-retaining retractors or using a marionette technique to suspending it with sutures placed along the posterior gastric body and exiting through the abdominal wall[70]. This allows the surgeon and assistant to use both hands for the operation.

Dissection of the body and tail of the gland from the retroperitoneum

As the pancreas is often a soft and fragile organ, grasping it should be kept to a minimum, if at all. One may consider placing a small gauze sponge inside the abdomen, for quick access in case unexpected bleeding is encountered or as a gentle retractor held by another instrument. We usually start the pancreatic dissection 2 cm proximal to the intended resection margin, or at the superior mesenteric vein for formal distal pancreatectomy, by lifting the inferior edge using gentle, blunt dissection aided by energy devices as needed. The objective is to make a tunnel behind the pancreas from caudad to cephalad direction. The surgeon must heed the splenic vein, especially during the initial exposure, taking care to avoid direct application of energy to this large vein. The splenic artery is usually easy to separate from the gland, but the splenic vein is not and it is laden with many tiny branches all along the pancreas. Proper identification of the origin of the splenic artery as well as the common hepatic and left gastric branches is critical for dissections near the neck of the gland. We find an articulating instrument such as an esophageal dissector to be useful when creating the retro-pancreatic tunnel and then we routinely pass an umbilical tape through the tunnel to allow retraction and facilitate further dissection.

Division of the pancreas

There is no reconstruction required in LDP so the surgeon aims to divide with an intention to seal. This can be achieved by linear stapling, with or without buttress material, or by dividing with an energy device followed by suturing the cut edge. In a recent multi-institutional retrospective study of fistula after distal pancreatectomy, none of the following operative techniques independently affected the occurrence of fistulae: method of pancreas transection, suture ligation of the pancreatic duct, staple size, the use of staple line reinforcement, tissue patches, biologic sealants, or prophylactic octreotide[71]. Although the study was primarily (70%) comprised of open cases, there is no reason to expect differences for a minimally invasive approach.

Suturing

This is generally more straightforward when suturing mobile organs on mesenteries (stomach, bowel), but becomes increasingly difficult when mobility is limited. And that is compounded when suturing small, fragile pancreatic and bile ducts. To add an extra layer of complexity, many of the previously mentioned suture-assist devices are not well-suited for these anastomoses. The small, straight needles used in these devices are inappropriate for securing a thick pancreas margin, or for passing through fragile pancreatic tissue for a pancreatic anastomosis. Similarly, barbed sutures are generally too traumatic for soft pancreata. Realistically, minimally invasive surgeons intending to perform a pancreatic anastomosis must be practiced in intracorporeal

suturing and knot-tying with conventional curved needles. The choice of suture (monofilament *vs* braided, absorbable *vs* nonabsorbable) and technique (running *vs* interrupted) can mirror the surgeon's choice in open surgery.

PROCEDURES

Pancreatic tumor enucleation

Well-chosen tumor enucleations may be excellent cases to start with during the initial minimally invasive experience. Generally, these are small (< 2 cm), tumors with well-defined borders, in the body and tail of the pancreas. In addition, a reasonable distance from the pancreatic duct (at least 2 mm) is suggested to avoid duct disruption, either directly during dissection or postoperatively due to duct ischemia. The pancreas may not need to be mobilized much, if at all for anterior lesions. Visible lesions are simpler to extract; those requiring ultrasound guidance require a slightly greater degree of sophistication and comfort with the technology. After the tumor is removed the magnification afforded by laparoscopy is excellent to survey the pancreatic bed for evidence of ductal disruption and for hemostasis. In the absence of intra-operative ultrasound, these procedures should be avoided because determination of distance from the main pancreatic duct cannot be determined increasing the risk of pancreatic leak and complications, as in general, enucleations have the highest risk of fistula.

Distal pancreatectomy

Much of the technique for distal pancreatectomy without reconstruction has been reviewed in the previous sections. Splenic preservation should always be considered for benign lesions by either technique: splenic artery and vein preservation (Kimura technique) or maintenance of the short gastric vessels and transection of the splenic artery and vein (Warshaw technique)[69,72,73].

Drainage of symptomatic pancreatic pseudocysts–cystogastrostomy, cystenterostomy

Acute pancreatitis is common, and endoscopic drainage through a transoral route is rarely possible outside of dedicated centers. Large, well-formed pancreatic pseudocysts can interfere in recovery from acute pancreatitis, causing pain and poor oral intake. In these delicate patients, an open operation can cause considerable physiologic stress and delayed healing. A cyst posterior to the stomach can be an excellent opportunity to enlist laparoscopy. The abdomen is explored laparoscopically and an anterior gastrostomy created with diathermy, attending to hemostasis as varices may be present if the splenic vein is thrombosed. If ultrasonography is available, an optimal location for cystogastrostomy can be determined by placing the probe on the posterior gastric wall anterior to the cyst. Otherwise, the cyst is punctured at a point of bulging through the posterior gastric wall to confirm cyst location. Again, attending to hemostasis as varices may be present, the posterior gastric wall is incised with diathermy approximately 2-4 cm until the inside of the cyst can be visualized. Then using endovascular staplers with staple height depending on wall thickness, a stapled, hemostatic anastomosis is created between the posterior gastric and anterior cyst walls. Any debris should be aspirated. The anterior wall of the stomach is stapled closed. In the absence of staplers, the cysto-gastrostomy anastomosis and anterior gastrotomy can be sewn. For large symptomatic cysts not aligned with the stomach, a Roux-en-Y cyst-enterostomy can be created by anastomosing the drainage limb to the pseudocyst. This can be done with staplers or suture, but clearly requires more advanced laparoscopic skills than that for cysto-gastrostomy.

Drainage procedures for chronic pancreatitis–Frey, Puestow

Similarly, the drainage procedures involve a pancreatic anastomosis to a Roux limb of jejunum. The conditions necessitating such procedures often render the gland very firm and fibrotic–delightful to manipulate, but challenging for suture placement with the laparoscopic needle drivers. The length of the instrument is mechanically not favorable to grab on to the needle if too much force is required to pass it through tissue. Little experience is reported on these cases.

CONCLUSION

With minimally invasive pancreatic surgery, one should aim for a better operation that results in less morbidity and improved survival with lesser importance to the abdominal access method or shortening the hospital stay. That being said, more and broader experience with minimally invasive techniques in pancreatic surgery will determine the future of this modality. Despite low pancreatic case volume in the Caribbean, and financial barriers to MIS in general, laparoscopic distal pancreatectomy, enucleation and cystogastrostomy are feasible operations to integrate in to a resource-limited healthcare environment. This is because they can be performed with minimal to no consumables and require an intermediate MIS skillset to complement an open pancreatic surgeon's peri-operative experience.

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MINIREVIEWS

Research progress regarding programmed cell death 1/programmed cell death ligand 1 inhibitors combined with targeted therapy for treating hepatocellular carcinoma

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Abstract

In recent years, a number of targeted therapeutic agents have achieved success in phase III trials in patients with advanced hepatocellular carcinoma (HCC), including sorafenib, lenvatinib, and regorafenib. Immunotherapy is considered to be an effective treatment for advanced HCC. Immune checkpoint inhibitors targeting programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) are important antitumor immunotherapy agents that represent breakthroughs in the treatment of advanced HCC. However, treating advanced HCC is still a great challenge, and the need for new treatments remains urgent. This review briefly summarizes the research progress in the use of PD-1/PD-L1 inhibitors combined with targeted therapy for treating HCC.

Key Words: Programmed cell death 1/programmed cell death ligand 1 inhibitors; Targeted therapy; Hepatocellular carcinoma; Programmed cell death 1; Programmed cell death ligand 1

Core Tip: The incidence of liver cancer is high. Because the disease can develop rapidly, most patients progress to the intermediate or advanced stages and lose the

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opportunity to undergo radical hepatectomy. Targeted therapy brings a glimmer of hope for patients with advanced hepatocellular carcinoma. Immunotherapy is a major focus in the field of tumor therapy, and it represents a breakthrough in the treatment of advanced hepatocellular carcinoma. The combination of programmed cell death 1/programmed cell death ligand 1 inhibitors and targeted therapy, to potentially achieve the superposition of 1 + 1 > 2 effects, is a promising strategy for treating cancer.

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INTRODUCTION

Worldwide, liver cancer is the sixth most common cancer and the second leading cause of cancer-related deaths[1]. According to the global statistics of the International Agency for Research on Cancer, there were approximately 841000 new cases of liver cancer worldwide in 2018, the standardized incidence of liver cancer was 9.3/100000, there were approximately 782000 liver cancer deaths, and the average mortality rate of liver cancer was 8.5/100000, a figure that is on the rise[2]. The vast majority of primary liver cancers are hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and HCC-ICC. Among them, HCC accounts for more than 90% of cases[3]. HCC rarely shows specific or obvious symptoms in the early stage. Nearly 80% of patients with HCC have progressed to an advanced stage by the time of diagnosis and have lost the opportunity to undergo radical hepatectomy, which results in a poor prognosis and high mortality rate. Although progress has been made in early detection, most HCC patients are still diagnosed with advanced cancer[4].

The mainstay of systemic treatment for advanced HCC includes immunotherapy, chemotherapy, and targeted therapy. In recent years, a number of targeted therapeutic agents including sorafenib, lenvatinib, and regorafenib have achieved success in phase III trials of advanced HCC. Immunotherapy is considered to be an effective treatment for advanced HCC. Immune checkpoint inhibitors that target programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) are important antitumor immunotherapeutics that represent a major breakthrough in the treatment of advanced HCC. Nivolumab and pembrolizumab have been approved by the United States Food and Drug Administration (FDA) as second-line treatments for HCC. This review briefly summarizes the research progress in the use of PD-1/PD-L1 inhibitors combined with targeted therapy in HCC.

PD-1/PD-L1 INHIBITORS AND LIMITATIONS

PD-1 is a type I transmembrane glycoprotein receptor and a member of the CD28/cytotoxic T-lymphocyte-associated protein (CTLA)-4 immune checkpoint receptor family. It is mainly expressed in T lymphocytes. Two binding ligands, PD-L1 and PD-L2, are members of the B7 family. They are widely expressed in human immune cells and some tissue cells, as well as in tumor cells[5]. Tumor cells express PD-L1, which binds to PD-1 on the surface of lymphocytes, inhibits the killing effect of lymphocytes and allows tumor cells to escape immune surveillance. PD-1/PD-L1 inhibitors block the binding of PD-1 to PD-L1, thereby terminate the negative regulatory signal in T cells, restore the activity of T cells, reverse the mechanism of tumor immune escape, reestablish the autoimmune response, and finally inhibit and kill tumor cells.

PD-1 inhibitors

Nivolumab: Nivolumab is the world's first recombinant human immunoglobulin (Ig)

G4 monoclonal antibody against PD-1. It can effectively block the PD-1/PD-L1 pathway and restore the antitumor effects of T cells. The CheckMate459 trial[6] is a randomized, global, multicenter phase III clinical trial of the efficacy and safety of nivolumab *vs* sorafenib as the first-line treatment for patients with unresectable HCC (uHCC). The median overall survival (mOS) of the nivolumab group was longer than that of the sorafenib group (16.4 mo *vs* 14.7 mo, $P = 0.0752$), but the difference in mOS did not reach the preset statistically significant threshold. The median progression-free survival (mPFS) was 3.7 mo in the nivolumab group compared to 3.8 mo in the sorafenib group, and the objective response rate (ORR) of the nivolumab group was approximately twice that of the sorafenib group (15% *vs* 7%). The rate of grade 3/4 treatment-related adverse events (TRAEs) was also lower in the nivolumab group than in the sorafenib group (22% *vs* 49%), and the percentage of patients who stopped treatment due to adverse events (AEs) was also lower (4% *vs* 8%). Although the primary endpoint (OS) of the nivolumab group did not reach statistical significance, the OS of the nivolumab group was clinically improved, with a high ORR and good tolerance. Therefore, nivolumab is safe and effective for treating advanced HCC, with manageable AEs.

Pembrolizumab: Pembrolizumab is the second PD-1 inhibitor approved by the US FDA for treating advanced HCC. The KEYNOTE-224 study is a non-randomized, global, multicenter, open-label phase II clinical trial on the efficacy of pembrolizumab in patients with advanced HCC who have previously been treated with sorafenib[7]. The mOS of the pembrolizumab group was 12.9 mo, the ORR was 17%, the disease control rate (DCR) was 64%, and the mPFS was 4.9 mo. The KEYNOTE-240 study[8] is a randomized, double-blind, phase III trial on the efficacy of pembrolizumab as a second-line treatment in patients with advanced HCC. The differences in the mOS (13.9 mo *vs* 10.6 mo, $P = 0.0238$) and mPFS (3.0 mo *vs* 2.8 mo, $P = 0.0022$) in the pembrolizumab group compared to the placebo group did not reach the preset thresholds for statistical significance ($P = 0.0174$ and $P = 0.0020$, respectively). The ORR in the pembrolizumab group was significantly higher than that in the placebo group (18.3% *vs* 4.4%, $P = 0.00007$), and the median duration of overall response (mDOR) was 13.8 mo in the pembrolizumab group compared to 10.6 mo in the placebo group. The safety was similar to that in previous studies of pembrolizumab. Regarding the OS and ORR, the results of the KEYNOTE-240 and KEYNOTE-224 studies were basically the same. The results of these two clinical trials once again confirmed the objective survival benefits of pembrolizumab. A phase III study (KEYNOTE-394) of pembrolizumab as a second-line treatment in Asian patients with HCC is currently under way.

Camrelizumab: Camrelizumab (SHR-1210) is a humanized anti-PD-1 monoclonal antibody. A phase II clinical study was performed to evaluate the efficacy of camrelizumab as a second-line treatment in Chinese patients with advanced HCC[9]. A total of 220 patients were enrolled, and 217 patients received treatment and were included in the analysis. The ORR was 13.8%, the mPFS was 2.1 mo, the DCR was 44.2%, the median time to response (mTTR) was 2.0 mo, the median time to progression (mTTP) was 2.6 mo, the 6-mo OS rate was 74.7%, the 12-mo OS rate was 55.9%, and the mOS was 13.8 mo. Camrelizumab is safe and well tolerated. The results reached the expected goal and confirmed that camrelizumab was effective in patients who had previously experienced failure of systemic therapy or found it intolerable. Camrelizumab has been approved as a second-line treatment for advanced HCC patients in China. It is anticipated that a phase III clinical trial will soon be carried out to improve the treatment of more patients with HCC.

PD-L1 inhibitors

There are few studies of PD-L1 inhibitors for treating HCC.

Durvalumab: Durvalumab is a humanized IgG1 monoclonal antibody against PD-L1. Phase I/II clinical trials of durvalumab for treating solid tumors have been completed. At the 2017 ASCO meeting, Wainberg *et al*[10] reported that 40 patients with advanced HCC who experienced failure of first-line treatment with sorafenib were treated with durvalumab. The mOS was 13.2 mo, the ORR was 10%, the DCR was 33.3%, and the rate of grade 3/4 AEs was 20%. Second-line treatment with durvalumab for advanced HCC is a promising strategy, and it continues to be studied.

Atezolizumab: Atezolizumab is a humanized IgG1 monoclonal antibody that can selectively target PD-L1 and block its interaction with PD-1 and the costimulatory molecule B7.1, thus it activates tumor-specific T cell immunity. The GO30140 study[11] is a global, multicenter, open-label phase Ib clinical trial. The basket design was used

in the study. Group A underwent a single-arm study on the safety and tolerance of atezolizumab plus bevacizumab as a first-line treatment for uHCC patients. The ORR was 36%, the DCR was 71%, the mPFS was 7.3 mo, the 6-mo PFS rate was 54%, the mOS was 17.1 mo, the 6-mo OS rate was 82%, and the 12-mo OS rate was 63% in group A. Group F underwent a controlled study. The patients were treated with atezolizumab or atezolizumab plus bevacizumab. The ORR of the atezolizumab group was 17%, and the mPFS was 3.4 mo in the atezolizumab group compared to 5.6 mo in the atezolizumab plus bevacizumab group [hazard ratio (HR) = 0.55, 95% confidence interval (CI): 0.4-0.74]. The treatment was well tolerated with controllable toxicity. No new safety signals were observed.

Limitations

The effective rate of PD-1/PD-L1 inhibitor monotherapy is low, and the ORR is 15%-20%. Most PD-1/PD-L1 inhibitors have only been assessed in phase I/II clinical trials, and phase III clinical trials have often failed to reach the preset statistical significance thresholds for their main endpoints. PD-1 inhibitors increase the incidence of interstitial pneumonia by blocking the binding of PD-1 to PD-L2[12]. PD-1/PD-L1 inhibitors are expensive. There are few studies on PD-L1 inhibitor monotherapy for HCC.

TARGETED THERAPY AND LIMITATIONS

Since 2007, sorafenib has been approved as a first-line treatment for advanced HCC. In the decade after this, clinical studies failed to provide evidence that any of the new molecular targeted drugs were more effective than or noninferior to sorafenib, but some of these new drugs were studied as second-line treatments after the failure of sorafenib. More specifically, drug development for HCC in the past 10 years has been marked by five failed global phase III trials (of sunitinib[13], brivanib[14], linifanib[15], erlotinib plus sorafenib[16], and sorafenib plus doxorubicin[17]) that did not show noninferiority or superiority to sorafenib in terms of OS as the first-line treatment of HCC. However, this situation changed after several clinical studies were conducted in 2017. The REFLECT study[18] showed that the efficacy of lenvatinib was noninferior to sorafenib as the first-line treatment for advanced HCC, and the RESORCE study[19] confirmed that regorafenib was beneficial as a second-line systemic targeted therapy for patients with HCC who progressed on sorafenib. Research on these agents provides renewed hope for the treatment of advanced HCC patients.

Sorafenib

Sorafenib, an oral tyrosine kinase inhibitor (TKI), is the only molecular targeted agent approved as a first-line treatment for advanced HCC. It can inhibit tumor cell proliferation and angiogenesis[20]. The SHARP study is a randomized, double-blind, placebo-controlled phase III clinical trial conducted in Europe and the United States [21]. The mOS (10.7 mo *vs* 7.9 mo, $P < 0.001$) and mTTP (5.5 mo *vs* 2.8 mo, $P < 0.001$) in the sorafenib group were significantly longer than those in the placebo group. An obvious curative effect was obtained in some patients in the sorafenib group. Subsequently, a randomized, double-blind, placebo-controlled phase III clinical study (the Oriental study) was conducted in the Asia-Pacific region[22]. The mOS (6.5 mo *vs* 4.2 mo, $P = 0.014$) and mTTP (2.8 mo *vs* 1.4 mo, $P = 0.0005$) in the sorafenib group were significantly longer than those in the placebo group. The most common any-grade AEs in the sorafenib group were hand-foot skin reaction (HFSR), diarrhea, hypertension, and anorexia. The results of these two clinical trials not only confirmed the survival benefits of sorafenib for treating advanced HCC patients but also proved its safety and good tolerance and established its status as a first-line treatment for patients with advanced HCC. Although sorafenib monotherapy has modest efficacy in HCC, with low ORR, PFS, and TTP, its manageable toxicity and mechanisms of action support a role for it in combination with other targeted agents. There are also second-line drugs available after the failure of first-line treatment or the emergence of drug resistance.

Lenvatinib

Lenvatinib is a TKI that can inhibit vascular endothelial-derived growth factor receptors (VEGFR) 1-3 and fibroblast growth factor receptors (FGFR) 1-4, thereby inhibiting angiogenesis and cell proliferation[23]. The REFLECT study[18] is a

randomized, global, multicenter, noninferiority phase III study of the efficacy of lenvatinib *vs* sorafenib as the first-line treatment for uHCC patients. The mOS noninferiority margin was set at 1.08. The mOS in the lenvatinib group met the criteria for noninferiority to sorafenib (13.6 mo *vs* 12.3 mo, 95%CI: 0.79-1.06). The mPFS, mTTP, and ORR in the lenvatinib group were significantly greater than those in the sorafenib group (7.4 mo *vs* 3.7 mo; 8.9 mo *vs* 3.7 mo; 24.1% *vs* 9.2%). The most common any-grade AEs in the lenvatinib group were hypertension (42%), diarrhea (39%), decreased appetite (34%), and decreased weight (31%). In short, in terms of OS, lenvatinib was noninferior to sorafenib, and there were statistically and clinically significant improvements in PFS, TTP, and ORR. Additionally, no new safety signals were found. Although lenvatinib did not achieve superiority to sorafenib, lenvatinib was better tolerated, and the PFS, TTP, and ORR were significantly increased. It is expected that in the future, lenvatinib will be more widely adopted for treating advanced HCC patients and will become an important treatment option for this patient group.

Regorafenib

Regorafenib is an oral TKI with a similar structure to sorafenib, and its targets include a variety of kinases in the signaling pathways involved in angiogenesis and tumor growth. The RESORCE study is a randomized, double-blind, placebo-controlled, global, multicenter, phase III clinical trial on the efficacy and safety of regorafenib in patients with HCC who have previously been treated with sorafenib[19]. The mOS in the regorafenib group was significantly longer than that in the placebo group (10.6 mo *vs* 7.8 mo, HR = 0.36), the risk of death was reduced by 37% in the regorafenib group, and the mPFS, TTP, and ORR in the regorafenib group were significantly greater (3.1 mo *vs* 1.5 mo; 3.2 mo *vs* 1.5 mo; 11% *vs* 4%). The most common any-grade AEs in the regorafenib group were hypertension, HFSR, fatigue, and diarrhea. Regorafenib is safe and well tolerated. Exploratory analysis in the RESORCE study showed that sequential therapy with sorafenib and regorafenib resulted in a better survival time (26.0 mo in the sorafenib and regorafenib sequential therapy group *vs* 19.2 mo in the placebo group)[24]. Thus, regorafenib is expected to replace sorafenib and be used in combination with other targeted agents for treating advanced HCC patients who cannot tolerate sorafenib and provide new alternative regimens for assessment in clinical trials.

Cabozantinib

Cabozantinib is a TKI that targets MET, VEGFR1/2/3, ROS1, RET, AXL, NTRK, and KIT[25]. The CELESTIALI study[26] is a global, randomized, double-blind phase III clinical trial to evaluate the efficacy and safety of cabozantinib *vs* placebo for treating advanced HCC patients. The mOS (10.2 mo *vs* 8.0 mo, $P = 0.005$), mPFS (5.2 mo *vs* 1.9 mo, $P < 0.001$), and ORR (4.0% *vs* 0.4%, $P = 0.009$) in the cabozantinib group were significantly better than those in the placebo group. The common grade 3/4 AEs in the cabozantinib group included HFSR (17%), hypertension (16%), transaminase increase (12%), fatigue (10%), and diarrhea (10%). It was well tolerated, and its safety was controllable.

Limitations

New targeted agents continue to emerge. Although many agents have shown excellent therapeutic effects in phase I and II clinical trials, many have not been successful in phase III clinical trials[27]. Resistance against targeted agents develops easily, their duration of effectiveness is short, and it is difficult to control the course of the disease. Predictive biomarkers of targeted agents have not been found[28].

PD-1/PD-L1 INHIBITORS COMBINED WITH TARGETED THERAPY

Targeted therapy takes effect quickly, and the ORR is relatively high, but these treatments produce resistance, and the duration of the effect is short. PD-1/PD-L1 inhibitor monotherapy has a longer duration of efficacy, but the efficacy is lower, and the ORR is only 15%-20%. If the advantages of the two are combined, complementary effects may be produced. In other words, combining PD-1/PD-L1 inhibitors and targeted therapy is a promising combination strategy that can potentially achieve a superposition of 1 + 1 > 2 effects. The combination of PD-1/PD-L1 inhibitors and targeted therapy was selected according to the results of the phase III trials from the website for clinical trials (World Health Organization-International Clinical Trials

Registry Platform websites, and clinicaltrials), and the results showed that its trials made progress in the treatment of advanced HCC (Tables 1 and 2).

Phase I/II trials

Lenvatinib plus pembrolizumab: In an HCC mouse model, the combination of lenvatinib and a PD-1 inhibitor significantly reduced the proportion of monocytes and macrophages, increased the proportions of early activated and effector CD8+ T cells, and enhanced antitumor activity of the PD-1 inhibitor[38]. In theory, the immunomodulatory effect of lenvatinib can supplement the activity of pembrolizumab, thus it can increase the sensitivity of tumors to this combination therapy. A phase Ib study (KEYNOTE-524)[29] was conducted to evaluate the tolerance and safety of lenvatinib plus pembrolizumab in patients with uHCC. The study consisted of two phases: A dose-limited toxicity (DLT) phase and an expansion phase. A total of 100 patients were included. The ORR was 46% based on modified response evaluation criteria in solid tumors (mRECIST) and 36% based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) with independent imaging review (IIR). The complete response (CR) was 11% and 1% based on IIR, the mPFS was 9.3 and 8.6 mo based on IIR, the mDOR was 8.6 and 12.6 mo based on IIR, the mTTR was 1.9 and 2.8 mo based on IIR, the mOS was 22 mo (95%CI: 20.4-NE), the 6-mo OS was 81%, and the 12-mo OS rate was 67.5%. According to the RECIST criteria, progressive disease (PD) is defined as a ≥ 20% increase in the sum of the longest diameter of target lesions, partial response (PR) is defined as a ≥ 30% decrease in the sum of the longest diameter of target lesions, CR is defined as the absence of target lesions, and stable disease (SD) is defined as insufficient increase/decrease to qualify as PD/PR[39]. As seen from waterfall plots of the changes in the diameters of target lesions, most patients achieved PR. Thus, the data and plots confirmed that lenvatinib plus pembrolizumab has antitumor activity in uHCC. The most common TRAEs of lenvatinib plus pembrolizumab were hypertension (36%), diarrhea (35%), fatigue (30%), decreased appetite (28%), and hypothyroidism (25%). The most common grade 3 TRAE was hypertension (17%). The only grade 4 TRAE was leukopenia/neutropenia. In short, lenvatinib plus pembrolizumab showed antitumor activity, the toxicity was controllable, and there were no unexpected safety signals.

Lenvatinib plus nivolumab: Study-117 is an open-label phase Ib study of the tolerance and safety of lenvatinib plus nivolumab in patients with uHCC[30]. A total of 30 patients participated in the trial (part I, n = 6, patients who were not suitable for other treatments due to multiline drug resistance; part II, n = 24, patients who had not previously received treatment for uHCC). The main endpoints were tolerance and safety. According to the mRECIST criteria, the ORR of the total population was 76.7%, the DCR was 96.7%, the CR rate was 10%, the PR rate was 66.7%, the SD rate was 20%, and the clinical benefit rate (CBR) was 83.3%. In part II of the trial, according to the mRECIST criteria, the CR rate was 12.5% and 8.3%, as assessed by the investigator and the independent review committee, respectively. The CBR was 83.3% and 70.8%, the PR rate was 66.7% and 58.3%, the SD rate was 16.7% and 25%, the ORR was 79.2% and 66.7%, and the DCR was 95.8% and 91.7%, respectively. Lenvatinib plus nivolumab was well tolerated in patients with HCC and had antitumor activity. The efficacy of this regimen was considerable, with an ORR of 76.7%. Additionally, AEs were effectively controlled by dose adjustment, interruption, and supportive drug therapy.

Avelumab plus axitinib: Avelumab is a fully human anti-PD-L1 monoclonal antibody, and axitinib is a TKI that selectively inhibits VEGFR1/2/3. The VEGF Liver 100 study is a phase Ib clinical study of the tolerance and safety of avelumab plus axitinib for treating advanced HCC[31]. A total of 22 patients were included. According to the RECIST/mRECIST criteria, tumor shrinkage (shown in waterfall plots) was observed in 15 cases (68.2%) and 16 cases (72.7%), the ORR was 13.6% and 31.8%, and the mPFS was 5.5 and 3.8 mo, respectively. The mOS was 12.7 mo. The most common grade 3 TRAEs were hypertension (50.0%) and HFSR (22.7%), and no grade 4/5 TRAEs occurred. The most common immune-related AEs (irAEs) were hypothyroidism (31.8%) and hyperthyroidism (13.6%), and no grade 3 irAEs occurred. No patient stopped treatment due to TRAEs or irAEs. Overall, avelumab plus axitinib for the first-line treatment of HCC has controllable safety and obvious antitumor activity, and the ORR is higher than that for monotherapy.

Regorafenib plus pembrolizumab: The KN-743 study is a phase Ib study of the safety and tolerance of pembrolizumab plus regorafenib for treating advanced HCC[32]. A total of 36 patients who had not previously received systemic treatment and had Barcelona Clinic Liver Cancer (BCLC) stage B/C and Child-Pugh grade A were

Table 1 Combination therapy for hepatocellular carcinoma

Combination therapy	Trial name	Phase	Number of patients	Control	Outcome (months or rate)	Ref.
Lenvatinib + pembrolizumab	KEYNOTE-524	Ib	100	None	ORR: 46% by mRECIST and 36% by RECIST v1.1; mPFS: 9.3 mo by mRECIST and 8.6 mo by RECIST v1.1; mOS: 22.0 mo	Finn *et al*[29]
Lenvatinib + nivolumab	Study-117	Ib	30	None	ORR: 76.7%, DCR: 96.7%, CBR: 83.3%	Kudo *et al*[30]
Avelumab + axitinib	VEGF liver-100	Ib	22	None	mOS: 12.7 mo, 1-yr OS rate: 54.5%; ORR: 13.6% by RECIST v1.1 and 31.8% by mRECIST	Kudo *et al*[31]
Pembrolizumab + regorafenib	KN-743	Ib	36	None	ORR: 28%, DCR: 91%	Galle *et al*[32]
Camrelizumab + apatinib	RESCUE	II	190	None	ORR for first- and second-line treatment: 34.3% and 22.5%, mPFS: 5.7 and 5.5 mo; 12-mo OS rate: 74.7% and 68.2%	Xu *et al*[33]
Atezolizumab + bevacizumab	IMbrave150	III	501	Sorafenib	mOS: 19.2 mo *vs* 13.4 mo; mPFS: 6.9 mo *vs* 4.3 mo	Finn *et al*[34]
Lenvatinib + pembrolizumab	LEAP-002	III	750	Lenvatinib + placebo	Ongoing	Llovet *et al*[35]
camrelizumab + apatinib	NCT03764293	III	510	Sorafenib	Ongoing	National Cancer Institute[36]
Cabozantinib + atezolizumab	COSMIC-312	III	740	Sorafenib or cabozantinib	Ongoing	Kelley *et al*[37]

CBR: Clinical benefit rate; DCR: Disease control rate; HCC: Hepatocellular carcinoma; HR: Hazard ratio; MOS: Median overall survival; MPFS: Median progression-free survival; MRECIST: Modified response evaluation criteria in solid tumors; RECIST v1.1: Response evaluation criteria in solid tumors version 1.1; NE: Not estimable; ORR: Objective response rate; OS: Overall survival; VEGF: Vascular endothelial-derived growth factor.

Table 2 Grade 3/4 adverse events in combination therapy groups

Combination therapy group	Phase	Grade 3/4 adverse events (%)
Lenvatinib + pembrolizumab group (n = 100)	Ib	Hypertension (17), AST increased (11), diarrhea (5), asthenia (5), fatigue (4)
Lenvatinib + nivolumab group (n = 30)	Ib	Palmar-plantar erythrodysesthesia (56.7), dysphonia (53.3)
Avelumab + axitinib group (n = 22)	Ib	Hypertension (50.0), HFSR (22.7)
Pembrolizumab + regorafenib group (n = 36)	Ib	AST increase (19), ALT increase (14), hypertension (14), bilirubin increase (14), lipase increase (11)
Camrelizumab + apatinib group (n = 190)	II	Hypertension (34.2), gamma-glutamyltransferase increase (11.6), neutropenia (11.1)
Atezolizumab + bevacizumab group (n = 329)	III	Hypertension (15.2), AST increase (7.0), ALT increase (3.6), platelet count decrease (3.3), proteinuria (3.0)
Lenvatinib + pembrolizumab group	III	Ongoing
Camrelizumab + apatinib group	III	Ongoing
Cabozantinib + atezolizumab group	III	Ongoing

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HFSR: Hand–foot skin reaction.

included. The study included two stages: A DLT stage and an expansion stage. Overall, the median duration of treatment with regorafenib was 2.5 mo (0.2-15.9 mo) and that of pembrolizumab was 3.5 mo (0.03-19.2 mo). Of the 32 patients who could be included in the evaluation of the curative effect, 9 (28%) reached PR, 20 (63%) reached SD, and 2 (6%) reached PD. The most common grade 3 TRAEs were aspartate aminotransferase (AST) increase (19%), alanine aminotransferase (ALT) increase (14%),

hypertension (14%), bilirubin increase (14%), and lipase increase (11%). The safety of pembrolizumab plus regorafenib is controllable, and there is antitumor activity.

Camrelizumab plus apatinib: In a phase I clinical trial of camrelizumab plus apatinib for treating HCC, gastric cancer, and esophageal cancer[40], 43 patients were included. Among the 18 hepatitis B virus (HBV)-related HCC patients, the ORR was 50%, DCR was 93.8%, mPFS was 5.8, and mOS was not achieved in the 16 patients who could be included in the evaluation of the efficacy. The RESCUE study[33] was conducted to evaluate the efficacy and safety of camrelizumab plus apatinib for treating advanced HCC patients. The study is a non-randomized, open-label, multicenter, phase II clinical trial involving 70 patients with advanced HCC who had not previously received treatment and 120 patients who were refractory/intolerant to first-line targeted therapies. The ORR of patients treated with camrelizumab plus apatinib as first- and second-line treatments was 34.3% and 22.5%, the mPFS was 5.7 and 5.5 mo, the 9-mo OS rate was 86.7% and 79.1%, the 12-mo OS rate was 74.7% and 68.2%, and the 18-mo OS rate was 58.1% and 56.5%, respectively. The most common TRAEs were hypertension (72.6%), AST increase (63.2%), proteinuria (61.6%), and hyperbilirubinemia (61.6%). There were reports of grade ≥ 3 TRAEs in 77.4% of cases, of which hypertension was the most common (34.2%). There were also reports of irAEs in 27.9% of cases, of which hypothyroidism (8.4%), rash (3.7%), and hyperglycemia (3.2%) were the most common. The incidence of reactive cutaneous capillary endothelial proliferation, a unique AE caused by camrelizumab, was significantly decreased in the camrelizumab plus apatinib group. Therefore, camrelizumab plus apatinib shows promising efficacy and manageable safety in patients with advanced HCC.

Phase III trials

Atezolizumab plus bevacizumab: Bevacizumab is a type of anti-VEGF monoclonal antibody that inhibits angiogenesis and tumor growth. It is the first agent to be used as an antitumor agent based on its inhibition of angiogenesis. In the treatment of tumors with bevacizumab plus atezolizumab (which targets PD-L1), bevacizumab can further enhance the effectiveness of atezolizumab by reversing VEGF-mediated immunosuppression and promoting T cell infiltration into tumors by tumor vascular normalization[41]. The phase Ib GO30140 study [11] showed that atezolizumab plus bevacizumab has good tolerance, safety, and antitumor activity in patients with advanced HCC. Based on these results, a global, multicenter, open-label phase III clinical study (IMbrave150) was conducted to evaluate the efficacy and safety of atezolizumab plus bevacizumab (A + T) compared to standard therapy (sorafenib) as the first-line treatment in patients with uHCC[42]. A total of 501 patients were randomly assigned to the A + T group (n = 336) or the sorafenib group (n = 165) at a ratio of 2:1. The primary endpoints of the trial were OS and PFS, and the secondary endpoints were ORR and DOR. The mOS (NE *vs* 13.2 mo), 6-mo OS rate (84.8% *vs* 72.2%), and 12-mo OS rate (67.2% *vs* 54.6%) in the A + T group were greater than those in the sorafenib group. The mPFS (6.8 mo *vs* 4.3 mo) and the 6-mo PFS rate (54.5% *vs* 37.2%) in the A + T group were greater than those in the sorafenib group. In terms of the secondary endpoints, the ORR (27.3% *vs* 11.9%) and DCR (73.6% *vs* 55.3%) in the A + T group were higher than those in the sorafenib group. The median time to deterioration of quality of life in the A + T group was longer than that in the sorafenib group (11.2 mo *vs* 3.6 mo) and improved the quality of life of the patients. The study also released data on the Chinese subgroup. The Chinese patients in the A + T subgroup had higher rates of HBV infection, macrovascular invasion/extrahepatic metastasis, alpha fetoprotein ≥ 400 ng/mL, and other adverse prognostic factors, and the mOS of the Chinese patients in the A + T subgroup was NE *vs* 11.4 mo (HR = 0.44, 95%CI: 0.25-0.76), which reduced the risk of death by 56%. The PFS of the Chinese patients in the A + T subgroup was 5.7 mo compared to 3.2 mo in the sorafenib subgroup (HR = 0.60, 95%CI: 0.40-0.90). The 6-mo OS rate reached 87% in the Chinese A + T subgroup, which was better than that in the whole A + T group (84.8%). The most common TRAEs in the A + T group were hypertension (29.8%), fatigue (20.4%), proteinuria (20.1%), and AST increase (19.5%). The safety of A + T was consistent with the known safety profile, with no new safety signals. In short, A + T therapy exhibited statistically and clinically significant improvements in OS and PFS, and the 12-mo OS rate of the patients increased to 67.2%. After an additional 12-mo follow-up[34], the mOS was 19.2 mo in the A + T group compared to 13.4 mo in the sorafenib group (HR = 0.66, 95%CI: 0.52-0.85), and the mPFS was 6.9 mo in the A + T group compared to 4.3 mo in the sorafenib group (HR = 0.65, 95%CI: 0.53-0.81). The mOS of the Chinese patients was 24.0 mo in the A + T subgroup compared to 11.4 mo in the sorafenib group (HR =

0.53, 95%CI: 0.35-0.80). The A + T subgroup continued to show consistent and clinically significant treatment benefits. A + T therapy represents the main breakthrough in HCC treatment over the last decade or more. These results further support the use of A + T as a first-line treatment in patients with uHCC.

Lenvatinib plus pembrolizumab: The LEAP-002 study[35] is an ongoing multicenter, double-blind, randomized, controlled, phase III study of lenvatinib plus pembrolizumab *vs* lenvatinib plus placebo as the first-line treatment for uHCC. The study included 750 patients with BCLC stage B/C HCC for whom radical local therapy was not suitable. They were randomly divided into the two groups at a ratio of 1:1. The primary endpoints are OS and PFS. The patients have been enrolled in the groups and are currently being followed.

Camrelizumab plus apatinib: A global, open-label, multicenter, phase III clinical study of camrelizumab plus apatinib *vs* sorafenib as the first-line treatment for advanced HCC is currently underway[36], the results of which are anticipated. A total of 550 patients are scheduled to be enrolled (350 cases in China and 200 cases in the United States and Europe). The primary endpoints are OS and PFS.

Cabozantinib plus atezolizumab: The COSMIC-312 study[37] is an ongoing global, randomized, open-label phase III trial to evaluate the efficacy and safety of the first-line therapy with cabozantinib plus atezolizumab *vs* sorafenib or cabozantinib in patients with advanced HCC. Approximately 740 eligible patients with advanced HCC have been randomized at a 2:1:1 ratio to receive cabozantinib plus atezolizumab, sorafenib, or cabozantinib.

ADVERSE EVENTS

Immune checkpoint inhibitors combined with targeted therapy can improve the curative effect of treatment. However, AEs are also increased, which necessitates additional caution in clinical settings. If doctors find a need for a new type of immunotherapy for a patient with HCC, they should conduct a detailed evaluation of the tumor type, tumor localization, number of tumors, and gene mutations and treat the patient under the guidance of a clinical oncologist to reduce the risk of serious AEs.

Immune checkpoint inhibitor therapy can cause irAEs, which are usually temporary but can sometimes be severe or fatal[43]. The most common irAEs in patients treated with immune checkpoint inhibitors are skin toxicity (28%-50% reported itching, rash, and/or eczema), diarrhea (8%-19%, generally mild to moderate), colitis (1.3%, increased to 11.8% under combination therapy), hepatotoxicity (< 5%), immune-associated nonspecific interstitial pneumonia (approximately 10%), and endocrine diseases [commonly manifest as hypophysitis or thyroid dysfunction with autoimmune-mediated endocrine toxicity of the thyroid in grade 1-2 hypothyroidism (4%-8%), hyperthyroidism (2%-3%), and rare acute thyroiditis (1%)]. Other rare toxicities include nephrotoxicity (immune-mediated glomerulonephritis and renal insufficiency, approximately 1%), pancreatic toxicity (approximately 1%-2%), ophthalmic toxicity, arthritis, and nervous system abnormalities.

AEs caused by targeted therapy can be divided into fatal and nonfatal AEs[44]. Nonfatal AEs include skin reactions (HFSR, rash, and stomatitis), digestive tract reactions (diarrhea, nausea, vomiting, abdominal pain, and abdominal distension), cardiovascular reactions (hypertension and cardiotoxicity), liver function damages (liver cirrhosis and chronic hepatitis), and other reactions (fatigue, hemocytopenia, weight loss, headache, muscle soreness, hoarseness, and other flu-like symptoms). Fatal AEs include congestive heart failure, cerebral infarction, hemorrhage, liver failure, intestinal perforation, myocardial infarction, respiratory failure, pulmonary infarction, sepsis, and sudden death. The incidence of fatal AEs is very low.

Clinicians should be highly vigilant and pay attention not only to the antitumor effect but also to the AEs. They should fully understand the common AE types, grades, diagnosis, and treatment methods, ensure early AE diagnosis and early treatment, and control the AEs at a low level to reduce risks and improve the prognosis.

DISCUSSION

The incidence of HCC is high, with a high degree of heterogeneity. The proportion of HCC patients with BCLC stage B/C is also high, and the treatment is complicated. We

still need to thoroughly understand the molecular mechanisms of immunotherapy, rationally design clinical studies, and actively explore combinations of various immune-regulatory agents or immunotherapy with other treatment modalities to significantly improve the survival time and quality of life of patients with advanced HCC. In the coming years, research hotspots will include identifying sensitive biomarkers of efficacy and drug resistance and screening for patients with these biomarkers to achieve individualized treatment, more precise use of targeted therapy, and timely modifications of treatment plans.

Immunotherapy combined with targeted therapy is promising, but the best combination therapy agents need to be further explored. At present, several phase III studies are underway. Combination therapy assessment requires a larger sample size. In addition, optimal selection of combination therapy agents relies on the results of future phase III studies.

In this era of emphasis on precision medicine, it is imperative to identify appropriate predictive markers of efficacy. Identifying clinical indicators and serum or tissue biomarkers is essential, as they will allow specific effective drugs to be selected for individualized treatment of each HCC patient. At present, there are still no clear indexes for selecting an enriched target population or for predicting the prognosis or the curative effect[45].

Understanding mechanisms of resistance to anti-PD-1/PD-L1 agents is indispensable to improve outcomes by using combination therapies[46].

In HCC patients with HBV infection, lenvatinib seems to be more effective than sorafenib, and sorafenib seems to be more effective in HCC patients with HCV infection than in patients with other risk factors. There are currently no prospective studies on the effects of molecular targeted therapy based on the etiology of liver cancers.

CONCLUSION

Overall, PD-1/PD-L1 inhibitors combined with targeted therapy represent potentially beneficial regimens. With continued research, more effective immunotherapy combined with targeted therapy is expected in the future.

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MINIREVIEWS

Transanal minimally invasive surgery using laparoscopic instruments of the rectum: A review

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Abstract

Transanal minimally invasive surgery (TAMIS) was first described in 2010 as an alternative to transanal endoscopic microsurgery (TEM). The TAMIS technique can be access to the proximal and mid-rectum for resection of benign and early-stage malignant rectal lesions and also used for noncurative intent surgery of more advanced lesions in patients who are not candidates for radical surgery. TAMIS has a shorter learning curve, reduced device setup time, flexibility in instrument use, and versatility in application than TEM. Also, TAMIS shows similar results in a view of the operation time, conversion rate, reoperation rate, and complication to TEM. For these reasons, TAMIS is an easily accessible, technically feasible, and cost-effective alternative to TEM. Overall, TAMIS has enabled the performance of high-quality local excision of rectal lesions by many colorectal surgeons. As TAMIS becomes more broadly utilized such as pelvic abscess drainage, rectal stenosis, and treatment of anastomotic dehiscence, the acquisition of appropriate training must be ensured, and the continued assessment and assurance of outcome must be maintained.

Key Words: Transanal minimally invasive; Rectal cancer; Laparoscopic transanal excision; Endoscopic resection; Minimally invasive surgery; Transanal endoscopic microsurgery

Core Tip: Transanal minimally invasive surgery (TAMIS) was introduced in 2010 as a crossover between single-incision laparoscopic surgery and transanal endoscopic microsurgery (TEM). The TAMIS technique can be resected to the proximal and mid-rectal lesion for benign, early-stage cancer, and more advanced lesions in selective patients. TAMIS is an easily accessible, technically feasible, and cost-effective alternative to TEM. TAMIS has proven its usefulness in a wide range of applications

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outside of local excision, including pelvic abscess drainage, rectal stenosis, and treatment of anastomotic dehiscence. TAMIS like TEM and transanal endoscopic operation with platform difference can achieve the high-quality excision superior to traditional TAE or endoscopic resection, despite the limitations of evidence for large volume or randomized controlled studies.

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INTRODUCTION

Traditionally, proctectomy with total mesorectal excision (TME) has been a gold standard for curative treatment of rectal tumors[1,2]. However, its postoperative morbidity and mortality risks are high, with a negative impact on the patient's quality of life (QoL)[3-6]. These significant complications have interested the use of sphincter preserving local excision in certain patients who have benign or early-stage rectal cancer with a low risk of lymphovascular metastasis[3,4]. Conventional transanal excision (TAE) uses open surgery instruments under direct vision. Because of limited visualization, TAE is performed when the tumor was located within 6 to 8 cm of the anal verge and was less than 4 cm in diameter. Additionally, it also shows poor oncologic outcomes and higher specimen fragmentation[7,8].

To overcome these limitations, Dr. Gerhard Buess introduced transanal endoscopic microsurgery (TEM) in 1983[9]. TEM is technically more advanced than TAE, with better visualization, more proximal approach, and less fragmentation. Due to these advantages, TME results in improved oncologic outcomes compared to conventional TAE in early rectal cancer[10,11]. Despite its feasibility and efficacy, TEM is not widely implemented Despite its feasibility and efficacy, TEM is not widely implemented for various reasons, such as the expensive instruments for specialized shape, its high learning curve, and risk of defective anorectal function[12,13].

Transanal minimally invasive surgery (TAMIS) is the new and innovative technique to perform excision of rectal lesions as a feasible alternative to TME, which is a novel hybrid between TEM and single port laparoscopy[13]. TAMIS was designed to be used before any single-access multichannel port, ordinary laparoscopic instruments including cameras and standard CO_2 insufflator systems. Since it was first described in 2010, TAMIS provides benefits of low cost with familiar instruments, minimal setup time, and total exposure of the rectal lumen without repositioning during the operation, while TEM requires higher or lower repositioning[13].

PREOPERATIVE STAGING

If there is a rectal lesion, a patient must undergo colonoscopy to exclude any synchronous lesions, and subsequently a rectal lesion biopsy. Physical examination including digital rectal exam and rigid proctoscopy should be performed by the surgeon to assess the size of tumor, mobility, location, circumferential involvement, and distance from the anal verge. If the biopsy returns a malignant lesion, further work up is necessary for accurate staging using endorectal ultrasound (EUS) or magnetic resonance imaging (MRI) of the rectum. Also, computed tomography (CT) scan of the chest, abdomen, and pelvis should be performed to exclude metastatic lesions.

PATIENT SELECTION

TAMIS has indications similar to compare with conventional TAE and TEM, for benign and early-stage malignant lesions[14,15]. For early-stage malignant masses, which are found to be confined to the submucosal layer on preoperative rectal MRI or

EUS, TAMIS is generally an appropriate technique. If the patients with early-stage cancer on preoperative staging return poor histologic features (lymphatic/vascular/perineural invasion, poor differentiation, tumor budding) or deeper invasion (submucosal levels: Sm^2 or sm^3) as defined by the Kikuchi classification which may mean potential metastasis to lymph nodes, they should be managed as having T2 (tumor staging: 2) lesions[15,16].

For patients with indetermined lesions (T1 *vs* T2) without evidence of lymph node metastasis, TAMIS can provide as definitive tumor staging, approving and managing further treatment of the finalized pathology. Such patients should be advised pre-operatively, that if the tumor becomes as a T1 lesion with good pathologic features, curative surgery would be performed without any further intervention. If, however, it becomes as a T1 tumor with poor pathologic features or a T2 tumor, they may still require further radical surgery or intervention.

TAMIS is not generally an appropriate technique in patients with advanced lesions (T3). However, in select patients who are medically unfit to have a more radical surgery, TAMIS can be considered. Lee *et al*[17] reported that 10 patients with pT3 cancer did not undergo radical surgery or chemoradiotherapy after TAMIS due to extensive comorbid diseases. The indications for TAMIS can be extended to include local excision of clinical T0 (cT0) lesions after neoadjuvant chemoradiotherapy, about locally advanced rectal cancer for confirming pathologic complete response (pCR: ypT0)[18-20]. This method can be considered a valid surgical option as the risk of occult node positivity for ypT0 Lesions is predictably low, at 3%–6%[21-23].

Other indications for TAMIS were including anastomotic dehiscence, rectal stenosis, the patients required re-excision for R1 resection in previous excision, and inappropriate candidates for endoscopic lesion removal, because of the tumor size, localization, and morphology *etc*. Based on the National Comprehensive Cancer Network (NCCN) guidelines, localized TAE was performed in selected rectal lesions such as movable and nonfixed rectal tumors, small sized tumors less than 3 cm, tumors invading less than one-third of the circumference of the rectal wall.

SURGICAL PREPARATION

All patients should be prepared by following standard protocols for colorectal surgery, however, there are differences in the details of pre-surgical preparation according to the surgeon's preference. A commonly used perioperative antibiotic for prophylaxis is intravenous cephalosporin. Surgeons in some studies used cephalosporin and oral or intravenous metronidazole[17,24]. Deep vein thrombosis (DVT) is a major complication after colorectal cancer surgery, and hence, prophylaxis is important; the most commonly used anticoagulant was intravenous low-molecular weight heparin. However, in Asian races, especially in Koreans, intravenous DVT prophylaxis was not recommended initially due to the low incidence rate of DVT; mechanical prophylaxis (graduated compression stocking or intermittent pneumatic compression) was generally performed[25]. Beta blockers were used to decrease bowel motility. However, as most of the patients were not priorly used to TAMIS, some surgeons used Buscopan (hyoscine butylbromide) which has an effect similar to beta blockers for reduce bowel movement[26]. Bowel preparation is essential, but it is up to the surgeon's preference to decide the type. The most commonly performed preparation was complete mechanical bowel preparation; however, distal bowel preparation by flexible sigmoidoscopy (oral laxative and two enemas) was also performed[27].

Lithotomy position was used generally in TAMIS, regardless of the location of the mass. This facilitated faster setting time in the operating room and was preferred by most anesthesiologists because of the better airway control and less risk of perioperative complications associated with it. Prone jack-knife or lateral decubitus position have also been described subject to the location of the lesion. The prone jack-knife position can be considered for anteriorly located lesions, although having to reposition the patient in this position is difficult for approach during peritoneal entry.

Endotracheal general anesthesia was performed in most TAMIS procedures. This is done to decrease bowel movement and so that the patients do not experience bowel discomfort due to gas insufflation during the procedure. In only one study, the surgeons performed spinal anesthesia for over 20 cases, and stated that it was adequate for the TAMIS procedure[28].

EQUIPMENT

The GelPOINT Path (Applied Medical, Rancho Santa Margarita, CA) and SILS Port (Covidien, Mansfield, MA) are medical devices used for transanal access in TAMIS and have been approved by the Food and Drug Administration. These devices are easy to place transanally and provide gas insufflation for pneumorectum through a designated channel. However, most surgeons were observed to be using the SILS port for TAMIS[12]. The SILS port has an advantage as its shape adapts easily to the anatomical shape of the anal canal. It is also produced by a sponge-like substance that is flexible, soft and of a smaller diameter, so as to avoid anal sphincter injuries[26,29]. Pneumorectum was achieved using a CO_2 insufflator within a typical laparoscopic tower case. Initial gas pressure was set between 10 and 20 mmHg and could be increased if there was difficulty visualizing and maintaining abdominal distention.

A 30- or 45-degree angled 5 mm laparoscope, ideally with inline or right-angled optical cables, was found to provide better maneuverability and visualization during dissection than a 0-degree scope. Bariatric length laparoscopes and flexible tipped scopes could also be used to prevent instrument size conflicts[27,30]. Maryland graspers, or a similar instrument, may be used for retraction, and a hook-type monopolar electrocautery was adequate for dissection in general. This apparatus can be connected to a standard suction irrigator to facilitate the suctioning of fluid or smoke during the procedure. Advanced bipolar energy devices such as a harmonic scalpel can also be used. These are excess for submucosal dissection but may be suitable for a full- thickness resection. Recently, robotic technique has been spreading globally and is generally adopted in various operations; it is also being attempted for TAMIS. Robotic instruments, including scopes, have flexible and articular movement, which overcome the limitation of ordinary straight laparoscopic instruments. However, the cost of the former is higher than the latter[31,32].

The defect could be closed with simple laparoscopic suturing using standard needle holders, or advanced laparoscopic closure devices such as a laparoscopic linear stapler. These devices are more expensive but shorten the operating time, as a defect closure is one of the most time-consuming parts of the entire procedure. Laparoscopic suture clips can be used to decrease the closure time as well. However, the indication of each of these devices is limited, and the final decision of which laparoscopic closure device must be used is based on the surgeon's preference.

TAMIS TECHNIQUE

Resection of lesions should be performed while maintaining high-quality through an adequate resection margin and no fragmentation. Benign lesions can be resected in the submucosal plane with negative resection margins of at least 5 mm. In case of malignant lesions, a 1-cm margin should be marked around the entire mass prior to a full-thickness resection. It is of utmost importance that the device remains perpendicular to the tumor, so as to not compromise the deep margins.

Rectal wall defect closure is one of the most time-consuming parts of the entire procedure. Submucosal resection (such as, for a benign lesion) can be open, while a full-thickness resection defect is generally closed. Resection of a posterior rectal defect can be left open in select cases[33]; however, this matter is still controversial. The closure is generally performed with absorbable interrupted sutures. Closure can also be performed in an interrupted suture with knot-tying facilitated by disposable-suture devices such as the Cor- Knot® System (LSI Solutions) or by laparoscopic knot pushers. Alternatively, in recent times, continuous V-Loc™ suture (Covidien) has also been used to maintain tension, negating the need for knot-tying. The defect is closed transversely to prevent narrowing of the lumen of the rectum. Laparoscopic linear stapler can also be used for large rectal wall defects; however, it is not possible to close the defect transversely with this device, and hence, it can cause rectal stenosis or stricture.

In the middle or upper third of the rectum, lesions that are located anteriorly carry with them a higher risk of peritoneal entry, because of the lower peritoneal reflection on the anterior and lateral surfaces of the rectum. If peritoneal entry occurs, the patient should be placed on the steep Trendelenburg position to displace the abdominal contents from the pelvic cavity. Although most peritoneal entries can be closed through the TAMIS port, sometimes it can be difficult to maintain pneumorectum and sufficient visualization of the peritoneal defect. In this case, converting to a laparoscopic-assisted approach should not be delayed to help the defect[16]. Some authors

recommended that the patients be placed in the prone position if peritoneal entry is likely, so that the abdominal pressure limits the amount of gas insufflation that can get into the peritoneal cavity[34].

In very distal lesions located at or just above the dentate line, a hybrid approach with traditional TAE and TAMIS instrument can make resection easy[35]. The distal margin should be incised using the conventional TAE platform by the standard transanal retractor, and then, the TAMIS port inserted to be used for the rest of the proximal dissection. This approach better visualization of the proximal extent of the tumor and less fragmentation of the specimen. The closure of the distal defect is easier, as a single stitch can be placed on the proximal edge in the midline of the excision site and used to re-approximate the distal edge *via* a standard transanal approach[12,16].

OPERATIVE OUTCOMES

Although there is no large-scale randomized controlled study on TAMIS yet, 1241 TAMIS procedures performed in 41 retrospective studies and case series for more than 5 cases have been published between 2009 and 2020. Some studies were excluded because the cases were duplicated or cited in a learning curve study.

Studies to date have shown that TAMIS is safe and feasible not only for oncologic outcomes but also for postoperative results, demonstrating hospital stay, positive resection margins, low specimen fragmentation, high concordance rate between preoperative and postoperative diagnosis and low recurrence (Table 1).

Endoscopic mucosal resection (EMR) using snaring for rectal mass (1.5-2 cm) is most cost-effective, safe, and feasible. However, the rate of en bloc and R0 resection of rectal masses (> 2 cm) that require piecemeal resection is lower than that of lesions (< 2 cm), and the recurrence rate increases by more than 20%[36-38]. Endoscopic submucosal resection (ESD) was introduced to overcome the limitations of EMR and has been widely applied with the development of injectable lifting solutions, adaptive electrosurgical generators, and endoscopic knives and scissors. Oka *et al*[39] showed that ESD lowers the local recurrence rate (ESD *vs* EMR = 1.4% *vs* 6.8%), allows larger tumor resection (ESD *vs* EMR = 39.6 mm *vs* 26.7 mm) and has higher en bloc resection rate (ESD *vs* EMR = 95% *vs* 53.2%) than EMR[39]. EMR, ESD has higher en bloc resection and curative resection rate and lower recurrence rate than EMR in some meta-analysis and systematic reviews[36-38]. However, ESD is performed selectively according to the following indications by European Society of Gastrointestinal Endoscopic clinical guideline; colorectal lesions with high tendency for superficial submucosal invasion, and lesions cannot be radically removed by snare-based techniques such as standard polypectomy or EMR[40].

To date, there is no randomized controlled trial comparing TAMIS and ESD, but Arezzo *et al*[41] reviewed TEM which is similar to TAMIS and ESD; for large noninvasive rectal lesions, R0 and en bloc resection rates, and recurrence rate were significantly better in TEM; 74.6%, 87.8%, and 5.2% in ESD, 88.5%, 98.7%, and 2.6% in TEM, respectively ($P < 0.001$). They concluded that TEM was advantageous in terms of higher R0 resection and en bloc resection rates by full thickness resection, and reduced need for further interventions such as transanal resection and abdominal resection [41]. In patients who need radical surgery for residual or recurrent neoplasia after ESD, TAMIS could become an alternative to radical surgery. The reason why TAMIS can be used to accurately evaluate the depth of submucosal invasion because full-thickness resection including muscular layer is possible, and it can be performed in patients with submucosal fibrosis from previous endoscopic procedures that interferes with EMR or ESD. Clancy *et al*[11] showed that TEM is superior oncologically with higher negative resection rate, lower specimen fragmentation rate, and recurrence than traditional TAE[11].

There were five retrospective studies comparing TEM or transanal endoscopic operation (TEO) (n = 452) and TAMIS (n = 317), including TEO with a rigid proctoscopy platform similar to TEM. There was no significant difference in resection margin involvement, complication or recurrence rate in these studies. In a case matched cohort study by Lee *et al*[42], which has the largest sample size, TAMIS was shown to have advantages of less operative time, less blood loss, shorter length of hospital stay, and higher defect closure rate compared to TEM, and there was no difference in poor quality excision, intraperitoneal entry, and postoperative complications. TAMIS is, therefore, an oncologically safe and feasible technique with no difference in cumulative 5-year disease free survival[42].

Table 1 Operative outcomes and pathologic results of transanal minimally invasive surgery case reports and retrospective studies

Ref.	Pts, *n* (%)	LOS (day)	Size (cm)	location from the AV (cm)	Pathology											R0 (%)	SF, *n* (%)	CR (%)
					AD	NET	AC	pCR	T0	Tis	T1	T2	T3	GIST	Other			
Atallah *et al*[13], 2010	6	5/6	3	9	3	1	2	0	0	1	1	0	0	0		83.3	0	100
Van den Boezem *et al*[55], 2011	12	1	3.5	7	9	0	3	0	0	0	1	2	0	0		100	0	75.0
Hompes *et al*[56], 2012	14	0.7 (0-5)	3.4	5	6	1	6	0	0	0	3	1	2	0	Residual rectal fold (1)	85.7	-	85.7
Lim *et al*[26], 2012	16	3 (2-6)	0.5 (0-1.5)	7.5 (4-10)	0	4	11	5	0	1	3	1	1	0	Mucocele (1)	100	-	100
Barendse *et al*[57], 2012	15	2.5	3.6	6	7	1	4	0	0	0	1	3	0	0	Fibrosis (1)	92.3	-	-
Alessandro *et al*[58], 2012	8	1	-	6.5	5	0	3	0	0	0	1	2	0	0		100	0	-
Ragupathi *et al*[59], 2012	20	1.1	3.0	10.6	14	6	1	0	0	0	0	1	0	0		95.0	-	95
Canda *et al*[60], 2012	6	-	4.75	7.2	5	0	1	0	0	1	0	0	0	0		100	0	83.3
Albert *et al*[30], 2013	50	0.6 (0-6)	2.75	8.2	23	2	23	0	0	1	16	3	3	0	HP (2)	94.0	2	98
Sevá-Pereira *et al*[61], 2014	5	1	4 (2-6)	4 (1-6)	2	0	4	0	0	2	0	1	0	0		100	0	60
McLemore *et al*[27], 2014	32	2.5 (1-10)	3 (0.5-7.5)	4.1 (1-11)	10	2	11	0	0	1	6	4	0	0	NRT (9)	100	-	90.6
Schiphorst *et al*[53], 2014	37	1 (1-23)	4.2	7	23	0	12	0	0	6	4	1	1	0	NRT (1)	78.4	0	100
Lee and Lee[28], 2014	25	4 (3-8)	2.3 (0.6-6)	9 (6-17)	6	9	9	0	0	0	0	0	0	1	NRT (6)	100	0	80
Hahnloser *et al*[33], 2015	75	3.4 (1-21)	4	6.4	35	1	38	3	4	11	13	9	1	0	Hamartoma (1); NRT (4)	96.0	6	-
Karakayali *et al*[51], 2015	10	0	2.6 (0.4-5)	5.6 (3-10)	1	0	9	0	0	5	4	0	0	0		100	0	50
Gill *et al*[62], 2015	32	1.1 (0-4)	2.1 (0.3-5)	7.5 (2-13)	11	4	15	0	0	0	0	0	0	0	Hamartoma (1); HP (1); NRT (10)	100	0	78.1
Noura *et al*[49], 2016	6	7 (6-8)	2.4 (1.5-3.0)	4.3 (3-6)	0	0	6	0	0	0	5	1	0	0		100	-	-
Quaresima *et al*[63], 2016	31	3 (2-7)	2.4 (1-5)	9.5 (6-15)	10	2	17	0	0	0	17	0	0	2		96.8	-	-
Keller *et al*[35], 2016	75	1 (0-6)	3.2	10 (6-16)	59	0	17	0	6	0	6	4	1	0		93.3	1	85.3
Sumrien *et al*[43], 2016	28	1.5 (0-4)	4.4 (1.2-11.5)	-	17	0	11	0	0	0	0	0	0	0		75.0	5	-
Verseveld *et al*[52], 2016	24	1 (1-3)	2.4	8 (2-17)	20	0	4	0	0	0	4	0	0	0		-	-	-
Melin *et al*[64], 2016	29	-	3.9	6.79	23	0	6	0	0	0	3	0	0	0		89.7	-	-
Mege *et al*[65], 2017	33	4 (1-60)	4 (1-10)	9 (0-12)	24	0	9	0	1	0	0	0	0	0	NRT (1)	78.8	-	-

Lee *et al*[24], 2018	200	1	2.9	7.2 (2-17)	85	10	100	3	11	25	41	10	10	0	NRT (11)	93.0	9	94.5
García-Flórez *et al*[66], 2017	32	-	3.4	5.6 (4-10)	15	1	12	0	0	0	4	4	4	1	Pelvic abscess (1)	96.9	2	84.4
Caycedo-Marulanda *et al*[44], 2017	50	1.1	2.5 (1-4.9)	7 (2-15)	23	1	16	0	0	0	0	0	0	0	Lipoma (1)	84.0	4	72.0
Clermonts *et al*[67], 2017	42	1 (1-24)	4.3	7.5 (0-19)	26	0	16	0	0	5	10	1	0	0		90.5	0	-
Lee *et al*[42], 2017	181	0	2.8	6.1	75	8	96	0	0	0	0	0	0	0	2	92.8	9	73.5
Lee *et al*[68], 2017	35	4 (3-7)	-	5 (4-9)	0	0	35	18	0	2	4	9	2	0		97.1	-	-
Chen *et al*[69], 2018	25	2.7	1.1	8.4	3	16	6	0	0	0	5	0	1	0		80.0	-	-
Clermonts *et al*[48], 2018	37	1 (1-5)	4.8	6.5 (0-19)	23	0	14	0	0	5	8	1	0	0		89.2	0	-
Dufresne *et al*[70], 2018	5	-	-	11 (8-14)	2	1	2	0	0	0	2	0	0	0		80.0	-	-
Llano *et al*[71], 2019	27	1.1	5.3 (2-9)	7 (5-9)	14	5	6	0	0	6	0	0	0	0	Cicatrical fibrosis (1); Leiomyoma (1)	1	2	-
Westrich *et al*[72], 2019	38	3 (1-7)	4 (1.5-9.0)	8 (5-12)	19	2	11	0	0	1	8	1	1	0	Granulation (8)	4	4	89.5
Van den Eynde *et al*[73], 2019	68	2 (1-3)	4.5	6 (5-10)	44	0	24	0	6	0	12	6	0	0		8	2	-
Lee *et al*[17], 2019	21	0.4	4.1	7.8	15	1	4	0	1	0	1	2	0	1		2	-	-
Abutaka *et al*[74], 2020	17	1.5 (1-6)	2.62 (1.2-7)	7.5 (3-18)	6	3	11	0	6	0	1	4	0	0	HP (1); IP(1)	100	1	64.7
Kang *et al*[45], 2020	30	4.3	1.6 (0.3-7.1)	7	5	18	4	0	0	0	0	0	0	0	Rectal stenosis (1), Rectal sinus (1), Anastomosis site dehiscence (1)	1	-	-
Goldenshluger *et al*[50], 2020	23	2.65	4.07	7.4	10	1	6	0	0	1	5	0	0	0	Granulation (6)	-	-	82.6

LOS: Length of stay; AV: Anal verge; AD: Adenoma; NET: Neuroendocrine tumor; AC: Adenocarcinoma; pCR: Pathologic complete response; GIST: Gastrointestinal stromal tumor; R0: R0 resection; SF: Specimen fragmentation; CR: Concordance rate of pathologic diagnosis between preoperative and postoperative results; HP: Hyperplastic polyp; NRT: No residual tumor; IP: Inflammatory polyp.

Thirty-seven of 41 studies with TAMIS showed resection margin status, which were positive in 101 of 1173 patients (8.6%). Although some studies included advanced rectal cancer and palliative resection for symptom relief, R0 resection rate was 91.4%. Of the 78 patients with positive resection margin as a result of pathology in 22 studies, 29 of 359 (8.1%) patients had rectal cancer and 49 of 505 (9.7%) had a benign tumor, and there was no significant difference in positive resection margin rate.

Positive resection margins in benign tumors frequently occurred in larger carpet adenomas. Sumrien *et al*[43] showed that the average tumor size with positive resection margin was 57 mm (40–93 mm), and Caycedo-Marulanda *et al*[44] explained

that most of the large adenomas were fragmented specimens due to piecemeal resection, making it difficult to evaluate resection margins, and that positive resection margins occurred frequently[43,44]. Kang *et al*[45] also reported that the positive margin in adenomas was larger than 7 cm. In the case of margin positivity in benign tumors, closed follow-up or treatment with re-TAMIS or colonoscopic resection was performed[45]. Of 29 patients with positive resection margin in malignant tumors, 26 patients were treated with radical resection (n = 15), radiotherapy (n = 4), closed surveillance (n = 4), re TAMIS (n = 1), palliative chemotherapy (n = 1), and chemoradiotherapy (n = 1), and three patients refused treatment.

The rate of specimen fragmentation was found to be 42/797 (5.3%) by analyzing 18 studies. Lee *et al*[42] reported similar results in a matched cohort study comparing TAMIS and TEM with specimen fragmentation of 4% and 3%, respectively[42]. In another retrospective study of 200 TAMIS procedures, tumor fragmentation occurred in 5%, and there was no difference between benign and malignant lesions[24]. Conversely, Hahnloser *et al*[33] showed that 6 (8%) patients with specimen fragmentation only had a benign lesion[33].

Most of the studies (21/26, 80.8%) showed length of hospital stay to be within 3 d, and discharge was possible after surgery on the same day. The possibility of ambulatory surgery can be explained through studies showing the results of short hospital stay within 1 d.

Pathologic findings of 1235 patients were benign adenoma (n = 683, 55.3%), adenocarcinoma (n = 595, 48.2%), neuroendocrine tumor (n = 100, 8.1%), Gastrointestinal stromal tumor (n = 5, 0.4%) and others such as cicatricial fibrosis, leiomyoma, granulation, hyperplastic polyp, and inflammatory polyp. TAMIS was also used to treat rectal stenosis, rectal sinus, and for anastomosis, in which granuloma was found in the biopsy results.

The concordance rate between preoperative and postoperative diagnosis was 81.6% (n = 528/647). In patients with diagnosis discordance, 71.4% (n = 85/119) were underestimated at initial workup and upstage such as from adenoma to malignancy or worsening T stage was observed. Caycedo-Marulanda *et al*[44] showed that 12% of cases were overestimated and 16% cases were underestimated on initial workup; the overall rate of diagnostic discordance was 28%[44]. The rate of discordance may be high because the indication of TAMIS includes masses which are too large to be removed endoscopically, and due to accuracy rate of initial workup, and requiring re-resection due to positive margins after EMR. Forty-nine upstage patients were treated with radical LAR (n = 14), observation (n = 12), re-TAMIS (n = 2) radiotherapy (n = 2) TAE (n = 1), and abdominoperineal resection (n = 1), while four patients refused treatment.

Recurrence was described in 16 papers, and the rate was 54/746 (7.2%) (Table 2). After diagnosis of recurrence, 3 patients refused salvage by radical resection. Nine patients with recurrence were previously recommended to undergo radical surgery for rectal cancer with high-risk features after TAMIS, but the patients refused. The mean time to recurrence was 14.3 mo (2.1–40 mo). Treatments of recurrence included re-TAMIS, endoscopic snaring, colonoscopic resection, or closed surveillance in benign tumors and re-TAMIS, radical salvage resection, adjuvant radiotherapy, or chemotherapy in rectal cancer.

COMPLICATIONS

By analyzing 31 recent papers on TAMIS, we found that the rate of complication is 18.4% (n = 222/1205). The types of complications including postoperative complications, reoperation, re-admission, conversion, and penetration into peritoneal cavity are summarized in Table 3. The postoperative complication that mainly occur after TAMIS include bleeding, postoperative urinary retention, fever, and penetration into the peritoneal cavity. Most complications are resolved with conservative treatments such as antibiotics and blood transfusions, but surgical treatment is required in 9.9% of the cases.

Caycedo-Marulanda *et al*[44] showed that peritoneal injuries can be closed with transanal sutures on the TAMIS platform, but anterior injuries are not easy to suture, and therefore laparoscopic sutures may often be required[44]. Lee *et al*[24] reported that the lesions in patients with peritoneal entry mostly occurred more than 10 cm from the anal verge, especially in the anterior or lateral side of the rectum[24]. Mean tumor distance from anal verge in retrospective studies about TAMIS was found to be 7.18 cm (0–20 cm). Tumors far from the anal verge have a higher probability of

Table 2 Recurrence characteristics

Ref.	Pts, *n* (%)	No. of recurrence	Pathology	RM status	Risk factor	Time to recurrence (months)	Type	Treatment
Hompes *et al* [56], 2012	14	1	TVA	+	Absence	6	L	Refuse treatment
Ragupathi *et al* [59], 2012	20	1	VA	-	Absence	7	L	Re-TAMIS
Albert *et al*[30], 2013	50	1	VA	+	Absence	18	L	Re-TAMIS
		1	T1 sm3 adenocarcinoma	-	LVI, DI	6	L	Re-TAMIS
Schiphorst *et al* [53], 2014	37	1	Tis	-	Absence	9	L	Re-TAMIS
		1	Adenoma	+	Absence	8	L	Re-TAMIS
Gill *et al*[62], 2015	32	2	FAP; sigmoid colon cancer	ND	Absence	NA	Non-local recurrent disease	NA
Quaresima *et al* [63], 2016	31	1	Adenoma	+	Absence	18	L	Colonoscopic resection
Keller *et al*[35], 2016	75	1	T1 adenocarcinoma	-	DI	9	L	APR
		3	Adenoma	-	NA	NA	L	Re-TAMIS
		1	Adenoma	-	NA	NA	L	Closed surveillance
Sumrien *et al* [43], 2016	28	1	Adenoma	-	NA	NA	L	Endoscopic snaring
		1	Rectal cancer	NA	NA	NA	L	NA
		1	Rectal cancer	NA	NA	11	L	Palliative radiotherapy
		1	Unresectable rectal cancer	+	Palliative debulking	NA	L	Required further endoscopic resection
Melin *et al*[64], 2016	29	1	Adenoma	+	Absence	NA	L	Re-TAMIS
		1	T1 adenocarcinoma	-	DI	10	L	APR, neoadjuvant CRT
Mege *et al*[65], 2017	33	1	Rectal cancer	NA	NA	NA	NA	NA
Lee *et al*[24], 2018	200	1	TVA	+	Absence	17.6	L	Re-TAMIS (index operation)
		2	Adenoma	+	Absence	NA	L	Re-TAMIS
		1	Tis carcinoma in situ	-	Absence	15		Re-TAMIS
		1	Tis carcinoma in situ	-	Absence	11		Re-TAMIS
		1	T1 adenocarcinoma	-	Absence	17.5	L, D (lung)	Re-TAMIS, chemoradiation
		1	T1 adenocarcinoma	-	PD	6.8	D (lung)	Chemotherapy
		1	T2 adenocarcinoma	-	DI	10.8		Definitive chemoradiation
		1	T2 adenocarcinoma	-	DI	28.9		Robotic LAR
		1	T3 adenocarcinoma	-	DI	2.1	D (lung)	Refuse treatment
		1	T2 adenocarcinoma	-	DI	12	L, D	Refuse treatment
García-Flórez *et al*[66], 2017	32	1	T3 adenocarcinoma	-	DI	12	L	Radical surgery
		1	T2 adenocarcinoma	-	DI	8	L	Radical surgery
		1	Adenoma	-	NA	NA	L	NA

Caycedo-Marulanda *et al* [44], 2017	50	1	Adenoma	NA	NA	13	L	Re-TAMIS
		1	NA	NA	NA	35	L (presacral mass), D (multiple liver)	Palliative chemotherapy
		1	T2 adenocarcinoma	+	DI	16	L	Re-TAMIS, palliative chemotherapy
		1	T2 adenocarcinoma	NA	DI	NA	L	APR
Clermonts *et al* [67], 2017	42	1	T1 adenocarcinoma	-	NA	9	L	Re-TAMIS
Lee *et al*[68], 2017	35	1	T1 adenocarcinoma	NA	NA	3	L (TAMIS site)	Hartmann`s operation
		1	T2 adenocarcinoma	NA	DI	40	L (perirectal LN)	Mass excision, chemotherapy
		1	T2 adenocarcinoma	NA	DI	16	L (perirectal LN), D (liver)	Chemotherapy
		1	T2 adenocarcinoma	NA	DI	37	D (lung)	Chemotherapy
		1	T0 adenocarcinoma	NA	NA	4	D (lung)	Wedge resection, chemotherapy
Westrich *et al* [72], 2019	38	4	Adenoma			26	L	re-TAMIS
		1	T1 adenocarcinoma	Closed RM (1 mm)	NA	9	L	APR
		1	T1 adenocarcinoma	-	PNI	24	L, D	Adjuvant radiotherapy, chemotherapy
		1	T3 adenocarcinoma	-	DI	10	L	Adjuvant radiotherapy
		2	NA	NA	NA	NA	D	

RM: Resection margin; TVA: Tubulovillous adenoma; VA: Villous adenoma; FAP: Familial adenomatous polyposis; LVI: Lymphovascular invasion; TAMIS: Transanal minimally invasive surgery; PD: Poorly differentiated adenocarcinoma; DI: Deep invasion; APR: Abdominoperineal resection; CRT: Chemoradiotherapy; PNI: Perineural invasion; L: Local recurrence; D: Distant metastasis; LN: Lymph node; NA: Not available.

peritoneal injury, and it is important to determine whether the tumor is located anteriorly, laterally or posteriorly by colonoscopy.

The conversion rate of TAMIS was 5.1% (n = 41/810), mainly due to intrarectal retractor expansion failures, a large prostate gland, failed anal dilatation, close distance to the tumor, and single port and peritoneal violation. At the time of conversion, TAMIS was replaced with other surgical methods such as TAE, TEO, TEM, low anterior resection, endoscopic debulking, laparoscopic suturing, a hybrid method combining TAMIS and laparoscopic repair, or a stoma.

Peritoneal entry occurred in 6.0% of patients, and most of them were treated with transanal repair or laparoscopic repair, but open laparotomy was sometimes performed when there was heavy intraperitoneal contamination or laparoscopic repair was difficult, as reported by Hahnloser *et al*[33]. Reoperation was performed due to bleeding, rectal perforation, residual cancer, pelvic abscess, and nonhealing wound. Khan *et al*[46] reported closure of the rectal defect, which accounts for a major part of the operating time. It has also been reported that defect closure reduces the risk of re-bleeding, but has no effect on postoperative infection and hospital stay[46]. However, in the case of peritoneal entry, complications and the possibility of reoperation may increase, and hence, it is better to perform defect closure.

FUNCTIONAL OUTCOMES AND QUALITY OF LIFE

To avoid immediate postoperative complications, functional problems, and impaired QoL due to radical surgical resection, TAE including TEM, TEO, and TAMIS was introduced in highly selective patients including low risk T1 cancer, endoscopically unresectable benign neoplasms, or palliative resection.

Table 3 Postoperative Complications and it's treatment

Ref.	Pts, *n* (%)	Complications, *n* (%)	Type of complications, *n* (%)	Reoperation	Re-admission	Conversion	Treatment of PPC
Van den Boezem *et al* [55], 2011	12	1	Bleeding (1)	0	0	TAE (2)	0
Hompes *et al* [32], 2014	14	2	Fever (1); Bleeding (1)	Positive for deep margin (1)	0	CAD fail (1); TEM assist (1)	0
Barendse *et al* [57], 2012	15	2	Pneumoscrotum (1); Hemorrhage (1)	0	Bleeding (1)	TEM (2)	0
Ragupathi *et al* [59], 2012	20	1	Abscess (1)	Inadequate surgical margin within 1mm (2)	0	0	0
Albert *et al*[30], 2013	50	4	Bleeding (1); Scrotal emphysema (1); PPC (1); COPD exacerbation (1)	0	Bleeding (1)	0	TAMIS repair (1)
Sevá-Pereira *et al*[61], 2014	5	1	Partial dehiscence of the suture line (1)		0	L-LAR (1)	
McLemore *et al* [27], 2014	32	8	FI (3); UTI (1); CD diarrhea (1); Afib (1); Rectal stenosis (1); Bleeding (1)	0	Bleeding (1)	TAE (1)	0
Schiphorst *et al* [53], 2014	37	6	Rectal perforation (2); Heamorrhage (2); Abscess (1); Rectal stricture (1)	Pelvic abscess (1)	Bleeding (3); Pelvic abscess (1)	L-AR (1)	L-AR (1). Pelvic abscess drainage (1)
Lee and Lee [28], 2014	25	1	POUR (1)	0	0	0	0
Hahnloser *et al* [33], 2015	75	21	Local infection (6); Postoperative bleeding (5); Intraoperative bleeding (3); Penetrate peritoneal cavity (3); Pneumoscrotum (3); UTI (2); POUR (2)	Rectal perforation (1)	NA	TAMIS + LR (2), Open laparotomy (1)	TAMIS + LR (2), Open laparotomy (1)
Gill *et al*[62], 2015	32	16	Bleeding (4); Diarrhea (4); POUR (3); Perianal pain (2); Ulceration (4); Hypovolemia (1); Rectal abscess (1); Aspiration pneumonia (1); FI (1)	Rectal perforation (1)	Aspiration penumoia (1); Rectal abcess (1)	TEM (1)	0
Quaresima *et al* [63], 2016	31	8	Penetrate peritoneal cavity (5); UTI (1); Subcutaneous emphysema (1); Hemorrhoidal thrombosis (1)	0	0	TAE (4)	TAMIS repair (4); TAE (1)
Keller *et al*[35], 2016	75	3	Bleeding (1); Rectal stricture (1); Rectovaginal fistula (1)	0	Rectal bleeding (1)	TAMIS + LR (2), DS (1), Diagnostic laparoscopy (1)	TAMIS + LR (1); TAMIS + DS (1)
Sumrien *et al* [43], 2016	28	10	POUR (6); Bleeding (1); PPC (1); Stricture (1); Fever (1)	Bleeding (1)	Rectal bleeding (1)	L-AR (2), O-AR (1), Endoscopic debulking (1)	TAMIS repair (1)
Verseveld *et al* [52], 2016	24	2	Bleeding (2)	Re-bleeding (1)	1	0	NA
Melin *et al*[64], 2016	29	3	Bleeding (1); POUR (1); PPC (1)	Bleeding (1), Resudual rectal polyp (1)	0	0	TAMIS repair (1)
Mege *et al*[65], 2017	33	4	NA	NA	NA	NA	2
Lee *et al*[24], 2018	200	31	Intraoperative complications (8); Bleeding (9); POUR (4); Scrotal or subcutaneous emphysema (3) Mild fecal incontinence (2); Self-limiting fever (2); Perianal pain (2); Perirectal inflammation (1); DVT (1); Heparin-induced thrombocytopenia (1); Rectovaginal fistula (1); UTI (1); Non-healing rectal wound (1)	DS for nonhealing wound (1)	Nonhealing rectal wound (1); Perirectal inflammation (1), Rectovaginal fistula (1)	TAMIS + LR (4)	TAMIS repair (4); TAMIS + LR (4)
García-Flórez *et al*[66], 2017	32	13	Fever (3); Hematuria (3); Rectal bleeding (3); PPC (2); Purulent	1	1	0	Transanal repair (2)

			peritonitis (1); Stenosis (1)				
Caycedo-Marulanda *et al* [44], 2017	50	13	Bleeding (4); UTI (1); Suture line leak (1); POUR (1); PPC (5); Anal structure (1)	Penetrate peritoneal cavity (1)	Bleeding (4)	Hybrid (3)	Transanal repair (5)
Clermonts *et al* [67], 2017	42	6	Hemorrhage (4); Abscess (1); Rectal stricture (1)	Pelvic abscess (1)	4	0	0
Lee *et al*[42], 2017	181	16	Bleeding (4); Local infection (6); POUR (2); Complication requiring operation (2)	2	NA	LR (2); DS (1)	TAMIS repair (4), LR (2)
Lee *et al*[68], 2017	35	1	Suture line dehiscence (1)	0	0	0	0
Clermonts *et al* [67], 2017	37	4	Bleeding (3); Abscess (1)	Pelvic abscess (1)	4	0	0
Llano *et al*[71], 2019	27	6	PPC (2); Rectal bleeding (1); POUR (1); Advanced cancer (1); Stenosis (1)	0	0	LR (1)	TAMIS repair (1); LR (1)
Westrich *et al* [72], 2019	38	8	Fever (4); Bleeding (2); PPC (1); Major complication (1)	Rectal perforation (1)	Rectal perforation (2), bleeding (2)	0	TAMIS repair (1)
Van den Eynde *et al*[73], 2019	68	19	Bleeding (1); Complications ≥ grade 3 (1)	Bleeding (5)	3	NA	NA
Lee *et al*[17], 2019	21	2	POUR (1); PPC (1)	0	0	LR (1)	LR (1)
Abutaka *et al* [74], 2020	17	3	Bleeding (1); PPC (2)	0	0	LR (1)	TAMIS repair (1); LR (1)
Kang *et al*[45], 2020	30	4	Diarrhea (2); FI (1); Fluid collection (1)	0	0	TAE (2)	0
Goldenshluger *et al*[50], 2020	23	3	Bleeding (1); Fever (1)	0	0	0	0

TAMIS: Transanal minimally invasive surgery; Afib: Atrial fibrillation; FI:Fecal incontinence; UTI: Urinary tract infection; DVT: Deep vein thrombosis; CD: Clostrium difficle; COPD: Chronic obstructive pulmonary disease; POUR: Postoperative urinary retention; PPC: Penetrate peritoneal cavity; -: Not available; LR: Laparoscopic repair; DS: Diverting stoma; TAE: Conventional transanal excision; L-AR: Laparoscopic anterior resection; O-AR: Open anterior resection.

Marinello *et al*[47] systematically reviewed that the functional outcomes after TEM and TAMIS are assumed to have no effect on continence and QoL. Since this review was based on a heterogenous group without standardized functional tests and the same questionnaire, the possibility of functional deterioration after surgery may have been underestimated[47].

Clermonts *et al*[48] conducted a case-matched study comparing the QoL of 37 patients who underwent TAMIS for rectal neoplasms with a healthy population through the Short-Form 36 Health Survey (SF-36) questionnaire and Fecal Incontinence Severity Index (FISI) questionnaire. This study showed that patients had an impaired QoL in the domains of physical functioning, general health perception and social functioning, and higher QoL in the mental health and bodily pain domain in comparison with the healthy reference group. At the three-year follow-up, 26 of 37 patients had fecal incontinence. Based on FISI score, 9 patients had improved, 19 patients had deteriorated, and 9 patients had remained same. There was no correlation between fecal incontinence severity and QoL[48].

On the contrary, Noura *et al*[49] evaluated fecal incontinence using the Wexner score at 3-, 6-, 9-, and 12 mo following TAMIS. Fecal incontinence improved over time, and continence was recovered after 9 mo[49]. Goldenshluger *et al*[50] demonstrated that TAMIS achieved good long-term outcome in the evaluation of bowel function using the low anterior resection syndrome (LARS) score[50]. Approximately 73.9% of the patients had no definitive LARS after TAMIS. The use of the validated Cleveland Clinic Incontinence Score questionnaire (CCIS) to assess the fecal incontinence severity following TAMIS was studied by Karakayali *et al*[51] They enrolled ten patients; the CCIS score increased three weeks after TAMIS, flatus incontinence, and defecation urge were seen in one patient, and symptoms resolved after six weeks. According to anorectal manometric parameters, the minimum rectal sensory volume significantly decreased 3 wk postoperatively, but the rectoanal inhibitory reflex and sphincter reflex

contraction was well maintained[51]. Verseveld *et al*[52] evaluated the functional outcome and QoL using the FISI, Fecal Incontinence Quality of Life (FIQL) and generic (EuroQol EQ-5D) questionnaires at the preoperative stage and six months after TAMIS; the mean FISI score decreased at postoperatively. Fifteen of 24 patients were completely continent, and five patients with deterioration in the FISI score had a mass closer to the dentate line, and a larger tumor. Coping behavior in the FIQL subscale and general QoL score improved six months after TAMIS[52].

Schiphorst *et al*[53] also demonstrated that the FISI score decreased and continence improved after TAMIS, especially in patients with impairment of continence preoperatively. Postoperative soiling developed in three of 18 patients with normal continence, and two of them recovered after 6 mo. Out of 17 patients who had an increase in FISI score before surgery, 15 patients (88%) improved postoperatively. However, there were no independent factors associated with improvement or deterioration of FISI score after TAMIS in the univariate linear regression analysis[53].

In the study results of TEM, it was reported that the FISI score improved after surgery, similar to TAMIS. Fenech *et al*[54] described the reasons for which patients with large villous adenomas had higher FISI scores: Large villous adenomas can cause symptoms by producing mucus, and decrease anorectal function by inducing persistent internal anal sphincter reflex through the mass of the tumor itself. These patients have symptoms and tend to have a higher FISI score and continence in them may improve significantly after surgery[54]. In Schiphorst's study, the average tumor area was 18.0 cm^2; contrarily, in Lee's study, including all patients with normal FISI, the average tumor area was 5.4 cm^2, and the average tumor area may have affected preoperative continence[53]. Lee and Lee[28] reported that FISI score and EUS 3 mo after TAMIS did not show anal sphincter injury or fecal incontinence-related signs. They explained that TAMIS might decrease chances of sphincter injury in comparison with TEM because of the smaller diameter of the platform and flexible port material [28]. Although these studies have shown various results, TAMIS does not reveal serious impairment of continence and QoL through the FISI score, manometric score, EUS, and various questionnaires related QoL.

FOLLOW-UP

The most important factor for follow-up is the decision of the treatment direction after surgery based on the results of biopsy. Because full thickness excision is performed in most cases of TAMIS, the depth of invasion can be accurately determined. Surgery is recommended if a T1 Lesion has high-risk features including positive margins, lymphovascular invasion, poorly differentiated tumors, or sm^3 invasion. Radical salvage resection or chemoradiotherapy is recommended in patients with pT2 or pT1 with high-risk features. The schedule of postoperative follow-up was found to be different in each study. However, it is recommended to determine the method of surveillance after TAMIS by referring to the NCCN guidelines. Currently, more frequent colonoscopies are recommended in patients with colorectal cancer before age 50. Proctoscopy with EUS or MRI for detecting anastomotic or local recurrence is only recommended for patients undergoing transanal local excision.

In the reviewed studies, surveillance for TAE only included proctoscopy with EUS or MRI with contrast evaluation every three to six months for the first two years postoperatively, and then every six months for a total of five years. Standardized postoperative follow-up for rectal cancer consisting of a physical examination, including digital rectal examination, complete blood count, liver function test, serum CEA analysis, and chest radiography, was performed every three to six months for the first two postoperative years, and then every six months for a total of five years. Positron emission tomography and CT (PET-CT) was not recommended. Benign lesions underwent repeat endoscopic evaluation at six to twelve months and then additional follow-up as indicated.

Mean follow up period after TAMIS was 19.5 mo (2.1-60 mo) in 24 studies. In these studies, the minimum time to recurrence was 2.1 mo; therefore, proctoscopy or sigmoidoscopy at three months after surgery is recommended.

CONCLUSION

Despite limitations of lack of large scale randomized controlled trial or meta-analysis, TAMIS can achieve excision superior in quality to traditional TAE or endoscopic

resection, based on the available literature retrospective studies. As measures of oncologic outcomes including recurrence, rate of positive resection margin and specimen fragmentation, TAMIS shows results similar to TEM in terms of operation time, conversion rate, reoperation rate, and complications. TAMIS uses existing laparoscopic instruments which are familiar to surgeons and does not require special instruments such as proctoscopy used in TEM. TAMIS is mostly performed for the resection of low risk early-stage rectal cancer, malignant polyps, lesions with inadequate or unknown margin, post-endoscopic excision or polypectomy and recurrent polyps following previous excision by any kind of surgery. Currently, TAMIS can be implemented for additional indications such as pelvic abscess drainage, rectal stenosis, and treatment of anastomotic dehiscence. Transanal TME is based on the concept of a "down-to-up" or "bottoms up" procedure through the TEM, TEO, and TAMIS with laparoscopic assistant. TAMIS is developing toward synergic effect in combination with other surgical procedure.

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MINIREVIEWS

Current surgical management of duodenal gastrointestinal stromal tumors

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Abstract

Duodenal gastrointestinal stromal tumors (D-GISTs) are uncommon mesenchymal tumors and are managed differently to common duodenal epithelial tumors. They may pose surgical challenges due to their unique but complex pancreaticoduodenal location of the gastrointestinal tract near the ampulla of Vater, pancreas, mesenteric blood vessels, biliary and pancreatic ducts. The surgical management of D-GISTs can be performed safely with good oncological outcomes provided an adequate resection margin can be achieved. The current surgical options of resectable primary D-GISTs varies with increasing complexity depending on the location, size and involvement of surrounding structures such as wedge resection with primary closure, segmental resection with small bowel anastomosis or radical pancreaticoduodenectomy. Laparoscopic approaches have been shown to be feasible and safe with good oncological outcomes in experienced hands. The minimally invasive techniques including robotic-assisted approach will likely increase in the future. D-GISTs have a prognosis comparable to gastric and other small bowel GISTs. However, the heterogeneity of different studies and the limited use of systemic tyrosine kinase inhibitor in the neoadjuvant and adjuvant settings may influence the overall survival of resected D-GISTs. The use of limited resection when condition allows is recommended due to lower surgical morbidity, less postoperative complications and better oncologic outcomes.

Key Words: Duodenum; Gastrointestinal stromal tumors; Limited resection; Pancreaticoduodenectomy; Survival

Core Tip: Duodenal gastrointestinal stromal tumors are an uncommon subset of small

quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

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intestinal tumors and may pose surgical challenges in curative-intent resection. I herein discuss the outcomes of current surgical resection techniques of duodenal gastrointestinal stromal tumors. A range of surgical armamentarium is therefore necessary to deal with this uniquely located duodenal gastrointestinal stromal tumor of varied sizes and degree of invasion into the surrounding structures.

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INTRODUCTION

The World Health Organization histological classification of the small intestine tumors are categorized into epithelial, non-epithelial, malignant lymphomas, secondary tumors and polyps[1]. Under non-epithelial small intestine tumors, sarcomas account for about 14%, and a vast majority of duodenal mesenchymal tumors are gastrointestinal stromal tumors (GISTs)[2,3]. These mesenchymal tumors are primarily located in the submucosa within the muscularis propria or subserosa. GISTs are thought to originate from the pacemaker cells of the intestinal tract called interstitial cells of Cajal. The discovery of gene mutations in *KIT*, *PDGFRA* and *BRAF* led to the understanding of pro-growth signaling that drives GISTs[4-6]. About 12%–15% of adult GISTs lack *KIT*, *PDGFRA* or *BRAF* mutations, and about 7.5% are succinate dehydrogenase-deficient GISTs[7,8].

GISTs are the commonest mesenchymal tumors of the gastrointestinal tract with the reported incidence at 10-15 per million per year[3,9-11]. The median age of diagnosis is in the mid-60s with 60% of cases age > 60 years[12]. GISTs have equal gender distribution in most studies. The anatomical location of GISTs is frequently in the stomach (60%-70%) and small bowel (25%-35% of which 4.5% is in duodenum) and are less commonly found in the colon and rectum (5%), esophagus (< 2%) and other/various locations (5.5%)[11,13-16].

The standard curative treatment for resectable primary GIST is complete surgical excision of the lesion with an adequate margin and no dissection of clinically negative lymph nodes[17]. An adequate margin can be defined as tumor-free margin or R0 resection. The invasion spread of these mesenchymal tumors behave differently to epithelial tumors, particularly the risk of lymphatic spread is rare. Hence lymphadenectomy is usually not warranted unless there is gross evidence of lymphadenopathy. Local recurrence of the tumor can occur in any residual positive microscopic R1 resection, and in almost 100% cases of tumor rupture and spillage[18]. Adjuvant therapy with tyrosine kinase inhibitors such as imatinib mesylate (IM) for 3 years is the standard treatment of patients with significant risk of recurrence according to the National Institutes of Health's consensus criteria (Fletcher's criteria based on size and mitotic count) and the Armed Forces Institute of Pathology criteria (Miettinen's criteria based on size, mitotic count and tumor site) of risk prediction. For advanced or metastatic GISTs, the standard treatment is IM, whilst the decision for surgical resection should be individualized or considered for patients with limited disease progression while on IM[19-21].

CLINICAL MANIFESTATIONS AND SURGICAL CHALLENGES

Most patients diagnosed with duodenal GISTs (D-GISTs) present with gastrointestinal bleeding in the form of anemia or melena (42.7%) and abdominal pain (18.7%), whilst a minority present with abdominal mass (3.7%), abdominal discomfort (3.7%) and anorexia (2%). Incidental finding of D-GISTs reported on imaging studies in asymptomatic patients ranges from 5%-40%[11,12,22-24].

Due to their unique biological and molecular profile of GISTs, the possibilities of performing oncological adequate but limited resection in a variety of ways either by open, laparoscopic or endoscopic-assisted surgery were recognized[25]. Surgical resection of these D-GISTs may be difficult and challenging due to the complex

anatomical proximity of surrounding organ structures such as the pancreas, hepato-biliary tree and mesenteric blood vessels. This surgical challenge is coupled by the low incidence of D-GISTs, the lack of surgical volume and the operative experience in most centers.

PREOPERATIVE DIAGNOSIS AND STAGING SCANS

Accurate preoperative diagnosis and staging of D-GIST is therefore critical to guide the most appropriate treatment option and so to establish the prognosis. The tumor size and mitotic count of GISTs are good predictors of prognosis, whilst the surgical outcomes are related to the adequacy of surgical resection of D-GISTs.

Esophagogastroduodenoscopy is routinely used to image-capture the features of submucosal tumors and to annotate any mucosal ulceration, intramural mass or bleeding (Figure 1). Standard endoscopic forceps biopsy has not provided reliable histological diagnosis due to submucosal location of GISTs and may even add additional risk of bleeding and perforation.

Endoscopic ultrasound scan (EUS) can add further endoscopic imaging evaluation of the hypoechoic mass, size, location, shape, layers of origin and vascularity of the D-GISTs. EUS-guided fine needle aspiration (FNA) or biopsy is useful for histological diagnosis prior to surgery planning, for neoadjuvant therapy or palliative-intent therapy for GISTs in general. However, the diagnostic cytology yield and sensitivity of EUS-guided FNA in a study of 37 patients to confirm D-GISTs was noted to be poor compared to gastric GISTs (0% *vs* 84.4%). This limitation was influenced by size, location, shape, and layer of origin[26].

Interestingly, a recent study of 142 patients diagnosed with D-GISTs showed that EUS has higher sensitivity and positive predictive value than computed tomography (CT) and magnetic resonance imaging (MRI) scans (P = 0.047 and P = 0.005, respectively). EUS-FNA also provided higher histological diagnosis of D-GISTs than conventional endoscopic biopsy (73% *vs* 33.3%, P = 0.006)[27]. These findings may be explained by the overall improvement of diagnostic equipment and operator experience over the years.

Staging CT and MRI scans are standard imaging modalities commonly used to evaluate the location and size of primary GISTs and to determine any invasion to local structures or distant metastatic disease (Figure 2). Multidetector CT has excellent discriminators of periampullary tumors in arterial phase for distinguishing duodenal adenocarcinoma and pancreatic ductal adenocarcinoma from D-GISTs[28]. Unlike EUS-FNA, CT- or US-guided transabdominal biopsy for resectable GISTs is not recommended due to the risk of pseudo-capsule rupture and tumor spillage in the peritoneal space[25].

Positron emission tomography scans may add further value by differentiating active tumor from inactive scar tissue and the likelihood of malignant tumor from benign tissue. It is a useful imaging modality to assess recurrent or metastatic GISTs before consideration for further surgical resection or second-line tyrosine kinase inhibitors therapy.

Another vital role of imaging studies either by EUS, CT or MRI scan is for interval surveillance of D-GIST < 2 cm in size. Patients with small tumor < 2 cm with benign EUS features are offered regular EUS surveillance or surgery if they wish. Any subsequent increase in size of D-GISTs would warrant consideration for surgical resection.

A study on EUS surveillance involving 93 patients with submucosal tumor for a mean period of 17.3 mo (range 6-42 mo) showed 3 patients (13.0%) had interval increase in tumor size, and surgery was performed[29]. It remains debatable whether EUS surveillance for small tumors originating from the muscularis propria in the upper gastrointestinal tract is useful. Nevertheless, EUS has better sensitivity than CT or MRI scan. It must be recognized that some patients with D-GIST < 2 cm do not wish to undergo invasive surveillance EUS but opted for non-invasive surveillance CT or MRI scan instead. Although the optimal follow up schedules are not known, the suggested frequency and imaging modality used for patients who underwent surgical resection of D-GISTs can follow the previously published algorithm for the management of GISTs[30].

Location and size of D-GISTs

According to the European Society for Medical Oncology and European Reference Network for Rare Adult Solid Cancers clinical practice guidelines for diagnosis,

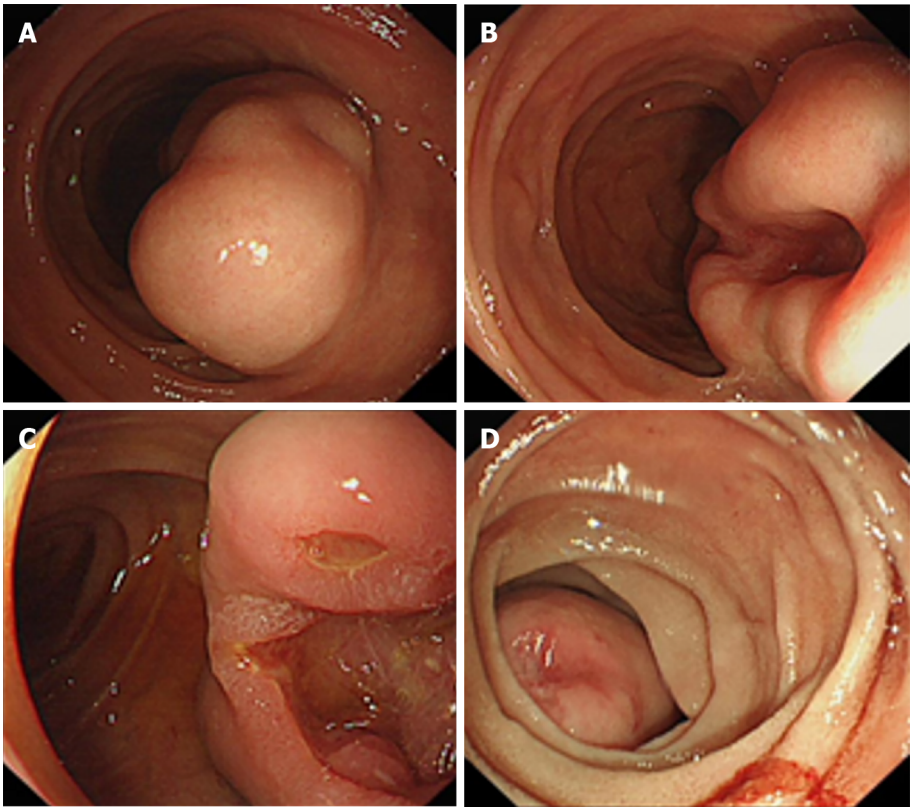


Figure 1 Esophagogastroduodenoscopy view of duodenal gastrointestinal stromal tumor. A: D1 gastrointestinal stromal tumor (GIST) at the anti-mesenteric border; B: D2 GIST at the anti-mesenteric border with central mucosal ulceration; C: D3 GIST at the anti-mesenteric border with a few mucosal ulcerations; D: D4 GIST occupying most of the lumen of the duodenum with a recent bleed.

treatment and follow up on GISTs, duodenal nodules < 2 cm should have EUS assessment and then follow-up, whilst tumor > 2 cm should have biopsy or surgical excision[31]. For a resectable primary tumor, it is important to determine the location and the size of D-GISTs to guide the ideal surgical approach at the pancreaticoduodenal complex. The cohort studies of resected D-GISTs in terms of location and size are summarized in Table 1.

The order of frequency of D-GISTs in most case series is highest at the second (D2) (33.00%-65.40%) followed by third (D3) (16.22%-31.40%), first (D1) (7.00%-22.97%) and fourth (D4) (3.00%-20.00%) part of duodenum[32-37]. The median size of resected D-GISTs ranges from 3.3 to 6.7 cm in some studies. The smallest size recorded was 1 mm, whilst the largest was 32 cm in diameter[12,38-40].

SURGICAL MANAGEMENT AND APPROACH CONSIDERATION

The indication for surgical resection of D-GIST is not only in asymptomatic patients with tumor size > 2 cm but also in those with symptoms at presentation such as gastrointestinal bleeding and abdominal pain regardless of the tumor size. The mainstay of resectable primary D-GIST is complete surgical resection with an adequate margin *en bloc* without breaching the pseudo-capsule. After considering the location, size and involvement of surrounding duodenal structures of D-GISTs, there are a few things to take note before embarking on surgical resection.

First, we need to consider the local expertise in utilizing the available instruments such as endoscopy, laparoscopy and robotic-assisted equipment. Second, we need to consider the route of access such as endo-luminal, open laparotomy, minimally invasive (laparoscopic or robotic-assisted) and hybrid endo-laparoscopic surgery. Third, we need to consider the future intact remnant and the size of the created duodenal defect. Fourth, we need to consider the type of reconstruction techniques to restore the gastrointestinal continuity and function restoration.

The use of laparoscopic or endo-laparoscopic surgery in managing GISTs have been increasingly adopted with the advancement of endoscopy, minimally invasive instruments and the development of safe technical skills in the last few decades[41,

Table 1 Summary of cohort studies on duodenal gastrointestinal stromal tumors

Ref.	Duodenal location D1-D4 (%)	Median size (cm) in all patients	Surgical approach	Operative complications or morbidity & mortality	Pathological risk classification using NIH or AFIP criteria	Survival in all patients
Liu *et al*[12] (*n* = 300)	D1 (15.8); D2 (51.5); D3 (24.4); D4 (8.3)	4 (0.1-28.0)	LR *n* = 199 (66.3%); PD *n* = 78 (26.0%); Not available *n* = 13 (4.3%); No surgery *n* = 10 (3.3%)	Not available	Very low *n* = 23 (12.8%); Low *n* = 87 (48.6%); Intermediate *n* = 2 (1.1%); High *n* = 67 (37.4%)	1-, 3-, 5-, 10-yr DFS: 94.4%, 75.2%, 64.4%, 46.5%; 1-, 3-, 5-, 10-yr DSS: 99.5%, 93.4%, 80.9%, 54.5%
Liang *et al*[23] (*n* = 28)	D1 (14.3); D2 (60.7); D3 (17.9); D4 (7.1)	5.8 (1.6-20.0) (95%CI: 5.3-8.6)	WR *n* = 5 (17.9%); SR *n* = 13 (46.3%); PD *n* = 10 (35.7%)	Morbidity 35.7%; Mortality 3.6%	Low *n* = 11 (39.3%); High *n* = 17 (60.7%)	2- and 5-yr RFS: 83.3% and 50.0%; Median OS: 64.5 mo
Colombo *et al*[32] (*n* = 84)	D1 (11); D2 (39); D3 (30); D4 (20)	5 (1-19)	LR *n* = 56 (66.6%); PD *n* = 28 (33.3%)	LR 9%; PD 36%	Low *n* = 35 (45%); Intermediate *n* = 4 (5%); High *n* = 39 (50%)	3, 5 yr OS: 98%, 89%; 3-, 5-yr DFS: 67%, 64%
Daffaud *et al*[33] (*n* = 117)	D1 (7); D2 (33); D3 (24); D4 (13)	5.0 (0.4-31.0)	Operated *n* = 109; LR *n* = 82 (74%); PD *n* = 23 (21%)	LR 18%; PD 26%	Very low *n* = 43 (39.0%); Low *n* = 52 (54.7%); High *n* = 19 (16.0%)	2-, 5-yr EFS: 82.0%, 54.5%; 3-, 5-yr OS: 94.9%, 86.5%
Shen *et al*[34] (*n* = 74)	D1 (22.97); D2 (47.30); D3 (16.22); D4 (13.51)	5.08 ± 2.90	WR *n* = 18 (24.3%); SR *n* = 39 (52.7%); PD *n* = 17 (23.0%)	WR 5.6%; SR 2.6%; PD 23.5%	Low *n* = 32 (43.24%); Intermediate *n* = 8 (10.81%); High *n* = 34 (45.96%)	1-, 3-, 5-yr RFS: 93.9%, 73.7%, 69.0%; 1-, 3-, 5-yr OS: 100%, 92.5%, 86.0%
Lee et al[35] (*n* = 60)	D1 (12); D2 (63); D3 (22); D4 (3)	5.2 (3.5-8.8)	LR *n* = 37 (62%); PD *n* = 23 (38%)	LR 24%; PD 70%	Very low/Low *n* = 24 (40%); Intermediate *n* = 12 (20%); High *n* = 24 (40%)	5-yr RpFS, RFS, OS: LR 56%, 53%, 72%, PD 81%, 64%, 76%
Zhang *et al*[36] (*n* = 52)	D1 (9.6); D2 (65.4); D3/4 (25.0)	5.0 (0.5-13.5)	LR *n* = 45 (26.9%); PD *n* = 37 (71.2%)	LR 10.8%; PD 21.4%	Low *n* = 16 (45.7%); Intermediate *n* = 7 (20.0%); High *n* = 12 (34.3%)	1-, 3-, 5-yr RFS: 93.5%, 77.8%, 72.9%; 1-, 3-, 5-yr OS: 100%, 94.6%, 89.1%
Lee *et al*[37] (*n* = 118)	D 1 (8.5); D2 (51.7); D3 (31.4); D4 (8.5)	3.9 (3.0-5.4)	LR *n* = 73 (61.8%); PD *n* = 45 (38.1%)	LR 20.4%; PD 37.8%	Very low *n* = 13 (11.0%); Low *n* = 63 (53.4%); Intermediate *n* = 19 (16.1%); High *n* = 23 (43.2%)	5-, 10-yr OS: 94.9%, 89.9%
Tien *et al*[38] (*n* = 25)	D1 (12); D2 (52); D3 (25); D4 (16)	6.7 ± 5.2	LR *n* = 16 (64%); PD *n* = 9 (26%)	LR 12.5%; PD 44.0%	Very low *n* = 3 (12%); Low *n* = 8 (32%); Intermediate *n* = 5 (20%); High *n* = 8 (32%)	7 disease recurrence with median follow up 18-mo (9-92)
Kamath *et al*[39] (*n* = 41)	D1 (7.3); D2 (63.4); D3 (19.5); D4 (9.7)	3.3-6.2 (0.5-17.0)	LR *n* = 19 (43.0%); SR *n* = 11 (26.8%); PD *n* = 11 (26.8%)	Morbidity 29.2%; Mortality 0%	Low *n* = 27 (65.8%); Intermediate *n* = 5 (12.1%); High *n* = 9 (21.9%)	3-, 5-yr OS: 85%, 74%; 3-, 5-yr DFS: both 80%
Johnston *et al*[40] (*n* = 96)	D1 (8.4); D2 (49.0); D3/4 (42.7)	4.0 (0.1-32.0)	LR *n* = 58 (60%); PD *n* = 38 (40%)	LR 29.3%; PD 57.9%	Very low *n* = 8 (8.3%); Low *n* = 46 (47.9%); Intermediate *n* = 25 (26.0%); High *n* = 16 (16.7%); Unknown *n* = 1 (1.0%)	1-, 2-, 5-yr RFS: 94.2%, 82.3%, 67.3%; 1-, 2-, 5-yr OS: 98.3%, 87.4%, 82.0%
Zhou *et al*[54] (*n* = 48)	D1 (22.9); D1/2 (16.7); D2 (35.4); D2/3 (8.3); D3 (12.5); D4 (4.2)	4.7 (2.0-15.0)	LR *n* = 34 (70.8%); PD *n* = 14 (29.2%)	LR 11.8%; PD 35.7%; Mortality in LR 5.9% (*n* = 2)	Low *n* = 28 (58.3%); Intermediate *n* = 11 (22.9%); High *n* = 9 (18.8%)	1-, 3-yr DFS: 100%, 88%
Yang *et al*[56] (*n* = 22)	D1 (13.6); D2 (63.6); D3/4 (22.7)	3.75 (1.40-14.00)	LR *n* = 10 (45.0%); SR *n* = 3 (13.6%); PD *n* = 6 (27.0%); PPPD *n* = 3 (13.6%)	LR 15.4%; PD 88.9%	Very low *n* = 3 (13.6%); Low *n* = 7 (31.8%); Intermediate *n* = 7 (31.8%); High *n* = 5 (22.7%)	1-, 2-, 5-yr RFS: 95%, 89.5%, 86.7%
Shi *et al*[64] (*n* = 61)	D1 (14.8); D2 (54.1); D3 (21.3); D4 (9.8)	4.0 (1.0-16.0)	LR *n* = 45 (73.8%); PD *n* = 16 (26.2%)	LR 33.3%; PD 56.3%	Very low *n* = 8 (13.1%); Low *n* = 29 (47.5%); Intermediate *n* = 14 (23.0%); High *n* = 10 (16.4%)	3-, 5-yr RFS: 93.3%, 81.3%
Chen *et al*[66] (*n* = 64)	D1 (21.9); D2 (46.9); D3 (17.2); D4 (14.1)	4.25 (1.00-15.00)	LR *n* = 41 (64%); PD *n* = 23 (36%)	LR 31.7%; PD 69.6%	Very low *n* = 4 (6.3%); Low *n* = 27 (42.2%); Intermediate *n* = 8 (12.5%); High *n* = 25 (39.1%)	3-, 5-yr RFS: 62.9%, 44.3%; 3-, 5-yr OS: 85.7%, 59.5%

Sugase *et al*[69] (*n* = 25)	D1 (12); D2 (56); D3/4 (32)	3.8 (1.5-16.0)	LR *n* = 16 (64%); PD *n* = 9 (36%)	LR 31%; PD 33%	Very low *n* = 4 (16%); Low *n* = 12 (48%); Intermediate *n* = 0 (0%); High *n* = 9 (36%)	2-yr RFS, 2-yr OS, 5-yr OS: LR 85%, 100%, 89%; PD 34%, 80%, 45%

AFIP: Armed Forces Institute of Pathology; CI: Confidence interval; DFS: Disease-free survival; DSS: Disease-specific survival; EFS: Event-free survival; LR: Limited resection; NIH: National Institutes of Health; OS: Overall survival; PD: Pancreaticoduodenectomy; PPPD: Pylorus preserving pancreaticoduodenectomy; RFS: Recurrence-free survival; RpFS: Relapsed-free survival; SR: Segmental resection; WR: Wedge resection.

42]. However, open surgery remains an important surgical access for safety and oncologic reason especially in major complex resection and reconstruction[38,43,44].

Endoscopy has been widely used for diagnostic purposes for decades since the 1950s. It is now increasingly used for endoluminal therapeutic purposes such as endoscopic mucosal resection, endoscopic submucosal dissection, submucosal tunneling and endoscopic resection or per-oral endoscopic tumor resection and endoscopic full thickness resection in benign, pre-malignant or early malignant disease [45-48]. Although endoscopic mucosal resection and endoscopic submucosal dissection in the duodenum is possible, it is exceedingly difficult to safely performed, and hence D-GISTs are best managed by surgical resection[49]. The risks of incomplete resection and pseudo-capsule rupture precludes the use of pure endoscopic resection alone, and future research is needed in this area.

To overcome the limitations of pure endoscopic resection alone, the introduction of hybrid endo-laparoscopic surgery has been attractive. There are a few endo-laparoscopic techniques such as the laparoscopic-assisted endoscopic resection, laparoscopic endoscopic cooperative surgery, inverted laparoscopic endoscopic cooperative surgery, laparoscopic-assisted endoscopy full-thickness resection and endoscope-assisted laparoscopic wedge resection. These hybrid techniques have been described in the resection of gastric tumors and duodenal neuroendocrine tumors, adenoma and adenocarcinoma[42,50-53].

There are several operative techniques described in resecting D-GISTs in the literature with a spectrum of invasiveness and complexities shown in Figure 3. The operative description of limited resection (LR) of D-GISTs include local excision or wedge resection (WR) and segmental resection, whilst for more extended resection means requires pancreaticoduodenectomy (PD), also known as Whipple's procedure or pylorus preserving pancreaticoduodenectomy[23,33,38,54,55].

WR is a local excision with primary closure without duodenal transection or anastomoses. Segmental resection involves duodenal transection with reconstruction. Reconstruction may be in the form of Billroth I gastroduodenostomy, Billroth II or Roux-en-Y gastrojejunostomy, end-to-end duodenoduodenostomy and end-to–end or end-to-side duodenojejunostomy (DJ) anastomosis[23,44]. PD is a complex procedure as it involves resection of duodenum, head of pancreas, common bile duct, gallbladder and sometimes pylorus and creation of three anastomoses namely gastrojejunostomy, choledochojejunostomy and pancreaticojejunostomy. Another equally effective procedure is pylorus preserving pancreaticoduodenectomy when the pyloric remnant is left intact[56].

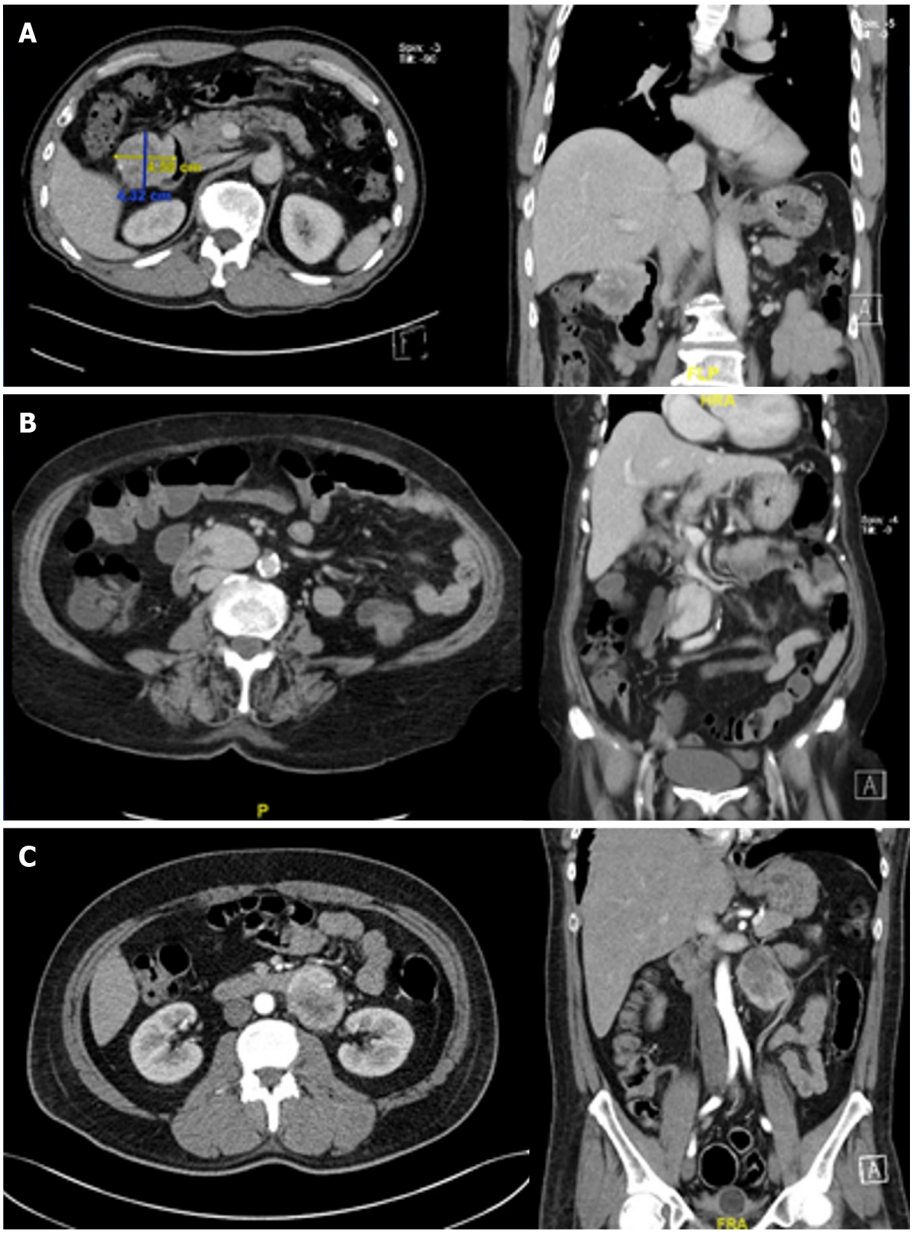


Figure 2 Computed tomography scan images of duodenal gastrointestinal stromal tumor in axial and coronal view. A: A 4.58 cm × 4.32 cm heterogeneous enhancing mass located at the anti-mesenteric border of the second part of the duodenum; B: A 3.4 cm × 2.9 cm homogeneous enhancing lobulated soft tissue involving the third part of the duodenum showing both intra- and extraluminal component; C: An enhancing mixed density partly necrotic mass measuring 4.7 cm × 6.6 cm arising from the fourth part of the duodenum with a large exophytic component posteriorly.

DISCUSSION

Is the current surgical approach in D-GISTs a matter of anatomical location and size?

For smaller-sized and mainly exophytic D-GIST, a longitudinal WR resulting in only limited defects of the duodenal wall can be primarily close in transverse direction. This surgical approach can be applied to any segment of the anti-mesenteric border of the duodenum including the D2 where ampulla of Vater can be retained. Traditionally, this technique was performed *via* open operation. Currently, there is evidence to suggest laparoscopic LR of D-GISTs is feasible and safe for both short- and long-term outcomes. In a case series of 6 consecutive patients with duodenal GISTs who underwent laparoscopic LR of D-GIST[42], there was minimal median blood loss of 10 mL, with median operative time of 2 h, no conversions to open surgery and no intraoperative or postoperative complications. All patients underwent curative resection with negative surgical margins, none had recurrence of their duodenal GISTs, and all patients were alive at the end of the follow-up period of 54 mo. In

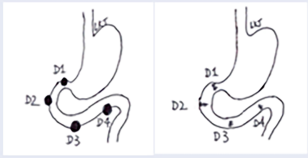
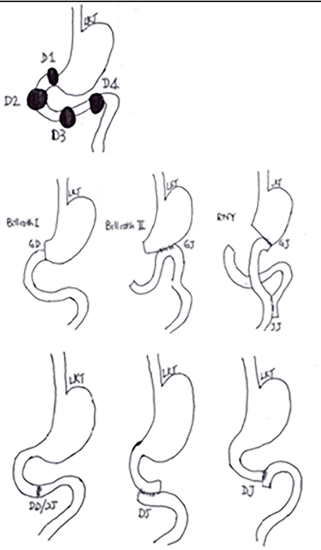
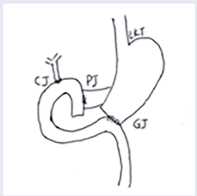
Operative techniques	Operative description	Anatomical diagrams
Wedge resection	Local resection with primary closure, without duodenal transection or anastomosis	
Segmental resection	Duodenal transection with a) Billroth I gastroduodenostomy b) Billroth II gastrojejunostomy c) Roux-en-Y gastrojejunostomy or i) duodenoduodenostomy or ii) duodenojejunostomy	
Pancreaticoduodenectomy also known as Whipple's procedure	Resection of duodenum, head of pancreas, distal common bile duct, gallbladder, pylorus and creation of four anastomoses namely gastrojejunostomy, choledochojejunostomy and pancreaticojejunostomy	

Figure 3 Description of operative techniques and anatomical diagrams for duodenal gastrointestinal stromal tumors.

addition, in another study of 53 patients with D2/D3-GISTs, the laparoscopic LR group had less perioperative complications (16.7% *vs* 24.4%, $P = 0.574$) with shorter operative duration (155.0 min *vs* 218.8 min, $P = 0.013$) and postoperative length of stay (12.0 d *vs* 19.4 d, $P = 0.036$) than those in the open LR group[37].

An alternative LR for a larger-sized D-GIST located at the second or third part of the duodenum without the involvement of the ampulla of Vater is a partial duodenectomy and a side-to-side Roux-en-Y DJ at the site of the duodenal wall defect[43]. Similarly, for a larger-sized D-GIST located at the fourth part of the duodenum, a segmental duodenectomy and reconstruction with side-to-side Roux-en-Y DJ can be performed [22].

The indication for PD is reserved for D-GIST that invades the ampulla of Vater, pancreas or pancreatic duodenal wall. According to the retrospective analysis of combined series of 300 patients with D-GISTs, about two-thirds (66.3%) received LR. In the other one-third (33.7%) who received PD, the D-GISTs were found to be larger in size or arose from D2 (both $P < 0.05$)[12]. However, it is important to take note that PD has higher perioperative complications and longer postoperative length of stay compared to other LR options[40].

A recent study of 22 patients with D-GISTs located opposite the ampulla of Vater, both laparoscopic PD and laparoscopic pancreas-sparing duodenectomy have been shown to confer comparable safety and oncological benefits[57]. It is important to take note that the laparoscopic pancreas-sparing duodenectomy group had shorter operative duration (364.2 ± 58.7 *vs* 230.0 ± 12.3 min, $P < 0.001$), less blood loss (176.9 ± 85.7 *vs* 61.1 ± 18.2 mL, $P < 0.001$) and much shorter recovery time (10.9 ± 3.8 *vs* 20.6 ± 11.1 d, $P = 0.021$), resulting in lower total cost (76972.4 ± 11614.8 yuan *vs* 125628.7 ±

46356.8 yuan, P = 0.006). However, the authors concluded laparoscopic pancreas-sparing duodenectomy should only be performed in selected patients by experienced surgeons.

Recent case reports of robotic-assisted resection of large D-GISTs have demonstrated the feasibility with either primary closure or Roux-en-Y DJ re-construction[58-60]. However, it is still debatable if such robotic-assisted procedures will translate into value-added care in the general population, and further research is required to address this issue.

Three systematic reviews and meta-analyses comparing patients who underwent LR *vs* PD for D-GISTs showed that LR was associated with lower surgical morbidity, less postoperative complications and better oncologic outcomes as shown in Table 2[61-63]. PD on the other hand was associated with longer operative duration, more intraoperative blood loss needing blood transfusion requirement, more surgical complications and longer length of hospital stay[62,63].

It is reasonable to state that the factors contributing to the decision in the surgical approaches and the choice of LR *vs* PD are anatomical location, the size and the local invasion of D-GIST into the surrounding structures. Although minimally invasive techniques have shown to confer some benefits in surgical morbidity and postoperative length of stay, it is the complexity of surgical resection that determines the overall surgical morbidity and outcomes (Table 1).

When counselling the patients with D-GISTs for surgical resection, it is important to provide the information on the overall morbidity rate, which ranges from 8.2%-33.3% in LR group and 21.4%-88.9% in PD group, whilst the mortality rate is about 3.6%-6.0%[23,36,54,56,64].

Is the survival of patients with resected D-GISTs worse than other located-GISTs?

It is debatable whether the location and size of the D-GISTs play a role in overall survival in comparison to gastric and other small bowel GISTs. A study comparing 202 patients with D-GISTs and 253 patients with gastric GISTs (G-GISTs) showed significantly different results with respect to tumor size, mitotic count and National Institutes of Health risk category (all P < 0.05). The 5-year disease-free survival (DFS) (64.4% *vs* 94.9%, P < 0.001) and disease-specific survival (80.9% *vs* 92.6%, P = 0.049) of D-GISTs were worse than that of G-GISTs (both P < 0.05)[12].

In contrast to another study analyzing the data extracted from the Surveillance, Epidemiology and End Results database from 1998 to 2011. The overall survival (OS) and cancer-specific survival (CSS) of patients with small bowel GIST were not statistically different from those with G-GIST when adjustment was made for confounding variables on a population-based level. Hence, the notion of small bowel GIST patients having a worse prognosis than that of G-GIST patients should be revisited, and the adjuvant treatment be reviewed[65].

Based on the anatomical location, the 5-year OS of all sizes of GISTs in stomach, duodenum, ileum/jejunum, colon, rectum and peritoneum were 86.3%, 88.2%, 85.0%, 68.4%, 89.0% and 68.8%, respectively. One must interpret the data carefully as the data comprised of 6% (n = 313) D-GIST, 25% (n = 1288) jejunal/ileal GISTs and 59% (n = 3011) G-GISTs, which could potentially lead to some bias. However, in multivariate analyses, the OS and CSS of patients with D-GISTs [OS, hazard ratio (HR) 0.95, 95% confidence interval (CI): 0.76-1.19; CSS, HR 0.99, 95%CI: 0.76-1.29] and the jejunal/ileal GISTs (OS, HR 0.97, 95%CI: 0.85-1.10; CSS, HR 0.95, 95%CI: 0.81-1.10) were similar to those of patients with G-GIST. The 5-year OS of non-metastatic D-GISTs of all sizes was 88.2%. More importantly, when the D-GISTs were categorized into ≤ 2 cm, > 2 to ≤ 5 cm, > 5 to ≤ 10 cm, > 10 cm, the 5-year OS was 100%, 97.4%, 83.5% and 78.5%, respectively[65].

Is the survival of patients with resected D-GISTs depending on the surgical approach?

Earlier studies have shown that tumor biology and tumor factors predict the prognosis and survival rather than the surgical approach[12,40]. Other studies have suggested the recurrence of D-GISTs was correlated to tumor biology rather than the type of operation performed such as organ invasion of D2, higher degree of tumor mitosis and higher malignant risk classification[32,54,61,62,66].

From these studies, it is not surprising to note that patients with D-GISTs in the PD group had a higher incidence of mitotic count > 5/50 high power fields, a higher incidence of high-risk classification, a higher incidence of tumors located at D2, a larger tumor size > 5 cm and an increased recurrence rate than those in the LR group.

Table 2 Summary of systematic review and meta-analysis and propensity score matching studies comparing limited resection *vs* pancreaticoduodenectomy for duodenal gastrointestinal stromal tumors

Ref.	Outcome parameters	LR group	PD group
Systematic review and meta-analysis			
Chok *et al*[61] (*n* = 162)	Surgical morbidity; Oncologic outcomes	Better (20.7%); Better DFS (HR 2.07, 95%CI: 1.07–4.01), lower rate of distant metastasis (8.9% *vs* 25.8%, OR 0.28, 95%CI: 0.13–0.59)	Worse (48.3%) (RR 2.34, 95%CI: 1.61–3.42). Worse: Related to large tumor (≥ 5 cm) (76.0% *vs* 36.6%, OR 5.49, 95%CI: 1.8–16.76), high mitotic count ≥ 5/50 HPF (33.7% *vs* 18.5%, OR 2.23, 95%CI: 1.22–4.08), high-risk classification (60.3% *vs* 32.0%, OR 3.23, 95%CI: 1.65–6.34) and which were located at D2 (80.5% *vs* 28.6%, OR 10.33, 95%CI: 5.22–20.47)
Shen *et al*[62] (*n* = 623)	Complications; Long term prognosis	Less; Better	More (OR 2.90; 95%CI: 1.90-4.42; $P < 0.001$); Worse (HR 1.93; 95%CI: 1.39-2.69; $P < 0.001$); Related to invasion of the D2, higher degree tumor mitosis (> 5/50 HPF) and high-risk classification ($P < 0.001$)
Zhou *et al*[63] (*n* = 1103)	Surgical outcomes	Better	Worse: Related to higher incidence of mitotic index > 5/50 HPF, high-risk classification, D2 tumor, tumor size, operative duration, intraoperative blood loss, blood transfusion requirement, morbidity, length of hospital stay and recurrence rate ($P < 0.001$)
Propensity score matching study			
Wei *et al*[67] (*n* = 325)	Impact of surgical modalities on long term survival outcomes	Similar	Similar: OS (HR 1.160; 95%CI: 0.662-2.033); DSS (HR 1.208; 95%CI: 0.686-2.128)
Uppal *et al*[68] (*n* = 1084 of which 874 had resection)	Lymph node and stage; Survival; Adjuvant systemic therapy rate	Fewer and negative for disease; Better. 21.5%	Higher T3/4 stage, extra nodal involvement and performed more at academic center. Poorer, higher mortality, uninsured status. 31.3%

CI: Confidence interval; DFS: Disease-free survival; DSS: Disease-specific survival; HPF: High power field; HR: Hazard ratio; LR: Limited resection; OR: Odds ratio; OS: Overall survival; PD: Pancreaticoduodenectomy; RR: Relative risk.

A study of 114 cases of D-GISTs by the French Sarcoma group showed 5-year OS and event-free survival rates of 86.5% and 54.5%, respectively. More importantly, the event-free survival was similar in the LR and PD groups of patients ($P > 0.05$)[33]. In a Korean study of 118 patients with localized duodenal GISTs who underwent curative resection, the 5-year OS and DFS were 94.9% and 79.2%, respectively. The 5-year OS and DFS rates were not statistically significant between the LR and PD groups (OS: 91.9% *vs* 96.2%, $P > 0.05$, DFS: 84.0% *vs* 72.6%, $P > 0.05$)[37].

A more recent study using the Surveillance, Epidemiology and End Results database identified 325 patients who underwent surgery for D-GISTs between 1986 and 2016 showed 5-year OS and disease-specific survival in PD was significantly better than those in the LR group (71% *vs* 54.1%, $P = 0.014$; 66.6% *vs* 49.1%, $P = 0.025$). Propensity score matching performed after adjusting covariates and the type of surgery did not show any significant impact of the OS and disease-specific survival. These results may argue that surgical modalities do not have significant impact on long-term survival outcomes in patients with D-GISTs and should be dependent on tumor location and size[67].

However, in contrast to a study using the National Cancer Database examining the surgical resection of 874 cases of D-GISTs, it showed that local resection was associated with improved OS compared to radical resection after controlling for tumor factors and systemic treatment[68]. According to the National Cancer Database, most of the resected D-GIST patients did not receive adjuvant systemic therapy with only 31.3% in the PD group *vs* 21.5% in the LR group. This data may explain the reason neoadjuvant and adjuvant systemic therapy was not associated with improved OS.

As recommended by the National Comprehensive Cancer Network and European Society for Medical Oncology-European Reference Network for Rare Adult Solid Cancers guidelines of resected D-GIST, the intermediate risk group should receive adjuvant IM for at least 1 year, and the high-risk group should receive treatment for at least 3 years. However, not every population has access to IM readily and hence the risk of bias in the interpretation of survival after surgical resection of D-GISTs. For an example, only 3.0% to 5.2% of D-GISTs received neoadjuvant therapy and 13% to 17% received adjuvant therapy even when in the high-risk National Institutes of Health category, which accounted for 37.5% in the LR group *vs* 76.1% in the PD group[12].

The limitation in this review article on the overall survival outcomes of resected D-GIST is due to the heterogeneity of neoadjuvant and adjuvant IM therapy, which could influence the interpretation of these prognostication results. In summary, the 5-year

OS of non-metastatic D-GISTs of all sizes ranges from 59.5% to 94.9%[37,66]. When taking the surgical approach into account, the 5-year OS is 72%-89% in the LR group *vs* 45-76% in the PD group[32,35,69].

CONCLUSION

The surgical management of D-GISTs can be performed safely with good oncological outcomes provided an adequate resection margin can be achieved. The surgical option of resectable primary D-GISTs varies with increasing complexity depending on the location, size and involvement of surrounding structures.

The surgical approach for D-GISTs located at D1 and D2 proximal to the ampulla is distal gastroduodenectomy with Billroth II or Roux-en-Y gastrojejunostomy anastomosis. WR resulting in only a limited defect of the duodenal wall can be closed primarily for smaller D-GISTs located at anti-mesenteric border of the duodenum where the ampulla can be retained. Segmental resection with DJ anastomosis is indicated for larger D-GISTs located at D3 and D4 distal to the ampulla. Any large D-GISTs located at D1 and D2 involving the ampulla, a PD is the treatment of choice. Laparoscopic approaches for LR and PD have been shown to be feasible and safe with good oncological outcomes in experienced hands. The minimally invasive techniques including robotic-assisted approach will likely increase in the future.

D-GISTs have a prognosis comparable to gastric and other small bowel GISTs. The use of LR when conditions allow is recommended due to lower surgical morbidity, less postoperative complications and better oncologic outcomes.

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MINIREVIEWS

Gastric endoscopic submucosal dissection in Western countries: Indications, applications, efficacy and training perspective

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Abstract

Endoscopic submucosal dissection was introduced in Japan for the mini-invasive treatment of early gastric cancer, as part of national screening program considering high prevalence of disease in these latitudes. This technique allows *en-bloc* curative oncological excision and to obtain in a single step R0-resection, characterization, histological staging and potential cure of the tumor with a very high cost-benefit balance. Over the years, Western endoscopists have adopted endoscopic submucosal dissection, achieving good rates of efficacy, long-term improved outcomes and safety, with low risk of local recurrence comparable to those obtained in Asian institutes. However, according to some authors, the excellent outcomes from East country could not be representative of the Western experience. Despite epidemiological differences of early gastric cancer, scant volume data and limitations in training opportunities between Western and Eastern countries, European Society of Gastrointestinal Endoscopy have adopted Japanese guidelines and developed a European core curriculum for endoscopic submucosal dissection training. Endoscopists should be able to estimate the probability of performing a curative resection by considering the benefit/risk relationship case-by-case in order to implement a correct decision-making process.

Key Words: Endoscopic submucosal dissection; Western experience; Early gastric cancer; Curative oncological excision; Long-term outcome; Training perspective

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Core Tip: In Western countries, endoscopic submucosal dissection (ESD) is an accepted first-line therapy of superficial gastric neoplasia, including dysplastic and recurrent lesions. This technique allows a high rate of curative resection and a good safety profile compared with other therapeutic approaches, including surgery, which can be reserved as a rescue therapy. Despite there certainly being some obstacles to its diffusion in the West, European Society of Gastrointestinal Endoscopy has developed a European core curriculum for ESD practice across Europe, with the aim of high quality ESD training. Probably nowadays, Western endoscopists are slowly reaching the same level of expertise and proficiency of the colleagues from the East.

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INTRODUCTION

Resection of early-stage gastric neoplasia, including dysplatic lesions and tumors limited to the mucosa or submucosa, is the core business of endoscopists in Eastern world, unlike their Western colleagues who are more involved in the removal of colon lesions. Although from 1970 to 2015 Europe observed a reduction in incidence and mortality rates from gastric cancer, its prevalence has increased and represents a problem in our continent. Adapting to the Eastern countries, the turning point in early gastric cancer (EGC) study occurred in 1998 with the "Vienna Classification" of gastrointestinal (GI) epithelial tumors for predicting lymph node metastases. Obviously, endoscopic resection should be reserved for patients with negligible nodal risk metastases; nowadays, there are two recognized techniques for minimally invasive treatment of early GI neoplastic lesions: endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). Introduction of the EMR technique showed good results compared to traditional surgery with lower risk of adverse events. However, EMR has the disadvantage of not facilitating *en-bloc* removal of gastric lesions greater than 15-20 mm and non-lifting or flat lesions, increasing the risk of residual/recurrence adenomatous tissue. Furthermore, piecemeal EMR carries the risk of missing areas with deeper invasion, and of an inadequate histology assessment [1].

ESD was first described in 1999 by Gotoda as "... a new EMR"[2] for rectal flat lesions, now rapidly spreading around the globe, to overcome the limits of EMR, reducing the rates of *en-bloc* unresectable lesions and leading to radically oncological removal[3]. This process is able to trigger a *"virtuous circle"*, as in a single-step, it is possible to obtain R0-resection, characterization, diagnosis and histological staging of the lesion with a very high cost-benefit balance, which has almost no comparison in any other medical procedure (Figure 1). In an editorial published in 2014, Professor Lightdale of Columbia University says that: "In the history of gastrointestinal endoscopy, every once in a while a new therapeutic method comes to the fore that seems difficult and risky, yet so elegant and dramatic in its benefits and possibilities that it fires the desire of interventional endoscopists worldwide to perform it. One such technique is ESD"[4]. Nevertheless, EMR and ESD should be considered complementary.

Therefore, if it is endoscopically feasible, *en-bloc* excision incorporating marking of the lesion within the resection specimen is the only acceptable therapeutic outcome to achieve the possibility of endoscopic cure. In most cases, gastric EMR lacks this level of precision and ESD is undoubtedly more exact and effective.

In the following sections, we will focus on the Western gastric ESD with respect to the technique, indications, efficacy, long-term outcomes and training considerations.

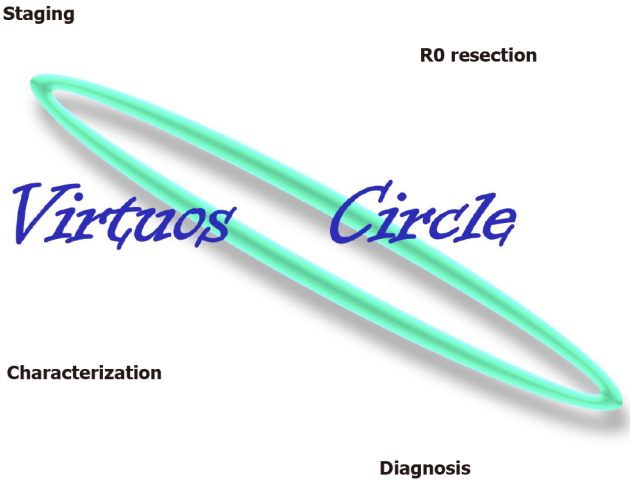

Figure 1 The "virtuous circle": In a single step, it is possible to obtain R0-resection, characterization, diagnosis and histological staging of the lesion.

TECHNICAL CONSIDERATION

Diagnostic planning procedure

Diagnostic strategic planning is performed as a separate session before the treatment procedure and without any hurry. Endoscopic differentiation of a dysplastic focal lesion from EGC, or prediction of submucosal invasion, is more difficult and less accurate than in the colon, especially in Western countries. Furthermore, with conventional imaging, lesion margins are less distinct and this carries a risk of incomplete resection. The inspection of the lesion using (vital or virtual) chromoendoscopy plus magnification is crucial for evaluating the margins of the lesions[5], macroscopic features, submucosal scarring and target biopsies in order to establish the feasibility of endoscopic resection and an appropriate "working therapeutic project". A very useful tool for evaluating the lesions, spread in Eastern countries is represented by The Magnifying Endoscopy Simple Diagnostic Algorithm for gastric cancer (MESDA-G), based upon evaluation of the microvascular and micro-surfaces irregularities of the lesion[6].

This process involves a broad photographic documentation. Findings associated with irregular surface, marked marginal elevation, and clubbing, or fusion of converging folds are suggestive of submucosal disease and therefore ESD probably is not feasible. Although in the West the endoscopists should be familiar with the macroscopic and pit pattern classification of superficial neoplastic lesions (*i.e.* Paris classification), biopsies in the stomach are always mandatory. Endoscopic ultrasonography (EUS), abdominal computer tomography or other procedures are not routinely recommended. EUS can be reserved for few selected cases. It is recommended a discussion on the therapeutic proposal with the patient, based on the endoscopic findings, as it provides a more solid base for the informed consent process and discussion of risks, benefits and alternatives to ESD.

ESD strategy

ESD can be carried out with a wide range of knives, which have been developed over time. Three types of knives are currently available, namely the needle, insulated and scissors types. The scissors are neither currently available in the United States nor in routine use in Western countries. Among the needle type knives, we must remember the most used and approved in the Western countries like the Dual knife (KD-650L and KD-650U; Olympus America, Center Valley, PA, United States), Hybrid knife (ERBE USA, Marietta, GA, United States), and IT 2 and IT nano (Olympus America) -- these last two are insulated tip knives --, and the Hook knife and triangular tip knife (Olympus America)[7]. In addition, multitasking devices are commercially available, such as the single-use electrosurgical knife with the water-jet function; it enables the user to effectively perform multiple procedure steps, to reduce procedural time and costs and mark the target lesion, submucosal injection, mucosal incision and submucosal dissection (Figure 2).

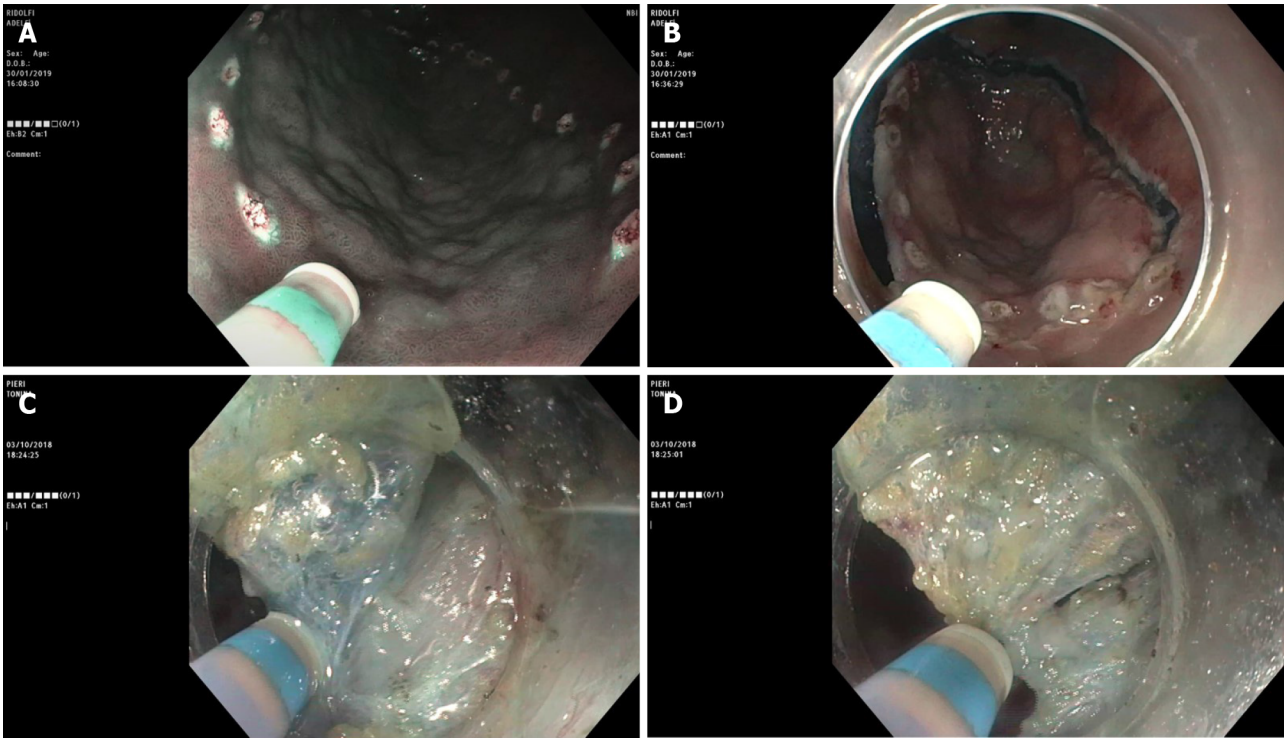

Figure 2 Multitasking device for multiple procedure steps. A: Marking; B: Mucosal incision; C: Submucosal infiltration; D: Submucosal dissection.

Although during ESD general rules need to be followed, technical steps may vary among endoscopists and differ significantly according to devices confidence, type (*i.e.* degree of fibrosis, histology), morphology (*i.e.* depressed/ulcerated), and size and location (*i.e.* proximal third of the stomach) of the lesion. After marking the lesion to isolate the area, lifting agents (different solutions have been used, *i.e.* saline, sodium hyaluronate, 10% glycerin) are injected in order to create a submucosal fluid cushion. In most of the cases, partial incision should be preferred, in order to avoid fluid escape from the submucosal layer and, therefore, to obtain long-lasting lift, resulting in fewer reinjection, and much safer dissection. The submucosal dissection is the most difficult phase and must take place through small accurate, coordinated movements, mostly in a retrograde direction with twist on the longitudinal axis scope, remaining with the endoscopic tip constantly close to the lesion. The need for a certain force of counter-traction to assist ESD has been attempted in different ways by many authors; this factor can improve the dissection in difficult locations and in several lesions with a prevalent fibrosis component and can also result in time-saving during the procedure; although, this latter aspect did not result in a statistically significant outcome[8]. One of the most used and simple is the traction technique, so-called “clip-with-line”. It consists of attaching the distal part or oral side of the lesion to a clip with line and applying a reasonable countertraction in order to do a dissection in a forward plane instead of a reverse position, that in some sites, like pylorus for example or cardia, become difficult to obtain[9]; this technique is useful both for gastric ESD and esophageal as well as colonic ESD. Different types of the intraluminal traction method are reported; the tools most generally used to obtain the countertraction, in order to pull up the lesion and open the resection margins, are the two clips attached to a rubber ring or line, a so-called “medical ring”[10], the stainless spring-assisted ESD [11]. Other more complex methods are percutaneous traction, such as the forceps traction method (*e.g.*, forceps traction method, magnet anchor method, and second-endoscope method) and the double-channel endoscope method.

The use of the cap on the endoscopic tip is very important. In fact, the distal attachment represents the operating "second arm", and helps to anchor the lesion, maintaining scope stability and opening the submucosal gap (otherwise, it is as if a surgeon operated with one hand!). The ESD knife should exit slightly from the distal cap and the submucosal plane should be dissected parallel to the muscular layer.

Prophylactic coagulation of the base vessels

Submucosal vessels should be preferably visualized before the area is cut through.

Once a vessel has been identified, a prophylactic hemostatic maneuver should be carried out with the ESD knife or with hemostatic forceps (Figure 3). The number and thickness of blood vessels vary in different gastric segments. Indeed, in the gastric antrum and in the lesser curvature such density is low; thus, the dissection is usually clear and quite easy. On the contrary, in the greater curvature, the anterior/posterior wall of the stomach, the number of submucosal vessels is high and, therefore, the dissection must be carried out very carefully. After resection, visible blood vessels on the artificial ulcer must be coagulated by using coagrasper to prevent delayed bleeding.

Specimen handling

Keeping the whole resected specimen for an accurate pathological evaluation represents an ESD crucial key point to identify high-risk features requiring surgery. Indeed, tumor infiltration depth is statistically correlated to the lymph node metastases whose incidence is negligible if the lesion is confined to the shallow submucosal layer (sm1, ≤ 500 μm). ESD showed significantly higher rates of *en-bloc* R0 curative and histologically complete resection, as well as lower recurrence frequency, in comparison to a piece-meal technique[12]. The lesion is pinned down on a polystyrene or cork block and then placed in formalin (Figure 4).

INDICATIONS

Despite the lowest prevalence of gastric cancer, the scant volume data and the limited experience in both Western and Eastern countries, endoscopists have adopted Japanese guidelines[13]. ESD has to be considered in case of a dysplastic lesion measuring > 20 mm in diameter or with high suspicion of superficial submucosal invasion that, otherwise, cannot be radically removed by snare-based techniques. The European Society of Gastrointestinal Endoscopy (ESGE) guidelines strongly recommend endoscopic resection for the treatment of gastric superficial neoplastic lesions that possess a very low risk of lymph node metastasis or when the risk of metastasis is lower compared to the risk of mortality possibly related to surgery[14] (Table 1). Regardless of the technique adopted, the goal is to have a curative resection according to the criteria of the Japanese Gastric Cancer Association (JGCA); the intramucosal neoplasia must be well-differentiated, lateral (> 2 mm) and vertical (> 500 μm) margins free from neoplasia (R0) and with absence of lymphovascular invasion[15].

EFFICACY AND LONG-TERM OUTCOME

Several comparative Asian studies indicate that clinical outcomes of ESD in EGC are comparable when absolute and expanded criteria are considered[16]. A recent meta-analysis[17] of a large data set from surgically resected specimens suggests that the various components of the expanded criteria do not carry equal prognostic significance. In the largest series to date on ESD for EGC in the Western world, Probst *et al*[18] compared their results favorably with the previous Japanese ESD series in terms of efficacy and safety. The authors reported high rates of curative treatment using the expanded criteria and recommend ESD as treatment of choice not only for guideline criteria EGCs but also for intramucosal non-ulcerated EGCs, regardless of their diameter. Real-life experience shows that ESD is feasible, effective and safe in Western settings and affords the best chance for ECG treatment[19]. ESD instead of surgery is now recommended by both the JGCA and ESGE for expanded criteria lesions[20].

Italian single-center studies substantiated that ESD outcomes were comparable to those achieved in Asian institutions. In a prospective study, Repici *et al*[21] showed *en-bloc* removal of early gastric lesions was successful in 100% of cases, whereas R0 was achieved in 92.8% of patients. Clinical results from another study[22] based on a retrospective collected database of gastric ESD procedures between 2005 and 2014 confirmed high rates of complete, curative and *en-bloc* resection among the study periods. From a recently published multi-center Italian series[23] on ESD procedures for gastric neoplastic lesion, *en-bloc* and R0 resection rates were very high, with low incidence of adverse events, even though the curative rate for EGC needs to be improved to achieve Eastern results. Similarly, Pagano *et al*[24] showed the same

Table 1 Absolute and expanded criteria for endoscopic submucosal dissection according the European Society of Gastrointestinal Endoscopy guideline

	Absolute criteria		Expanded criteria			
			A	B	C	D
Histology	Dysplasia	Differentiated	Differentiated	Differentiated	Undifferentiated	Differentiated
Tumor size in mm	Any	≤ 20	> 20	≤ 30	≤ 20	≤ 30
Ulceration	Negative	Negative	Negative	Positive	Negative	Negative
Depth invasion	None	T1a	T1a	T1a	T1a	sm1, ≤ 500 μm

sm1: Shallow submucosal layer.

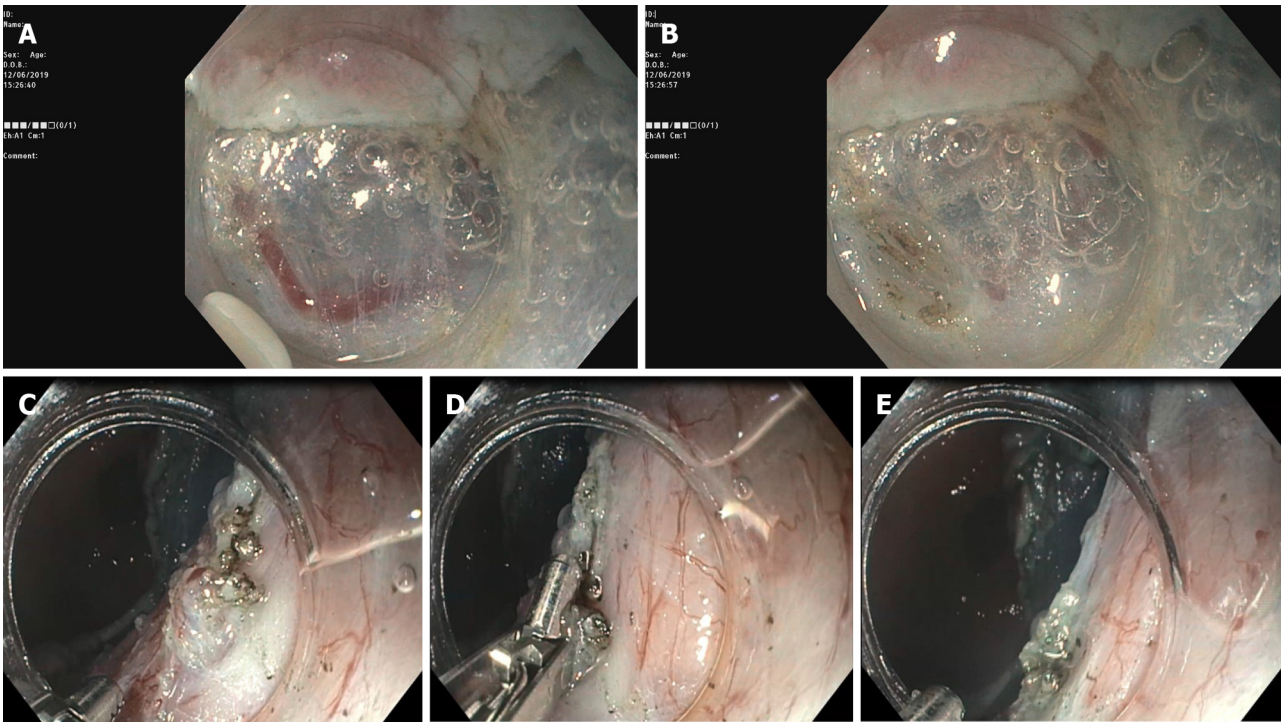

Figure 3 Hemostatic maneuver. A: Submucosal visible vessel; B-E: Coagulation of the vessels with the endoscopic submucosal dissection knife or with forceps.

favorable therapeutic results.

Unfortunately, only two Western clinical trials have assessed the long-term results of EGC. In a Portuguese series[25], ESD was performed in 194 lesions between 2005 and 2014. *En-bloc* and complete resection rates were 95.3% and 93.8%, respectively, and the patients' overall survival rates (median follow-up of 40 mo) were 95% and 90% at 1 and 3 years, respectively. A German study[18] showed a high *en-bloc*/R0 resection, and low adverse event and low local recurrence rates. No gastric cancer-related death was observed and long-term survival was comparable among patients who meet the absolute and expanded criteria. A systematic review and meta-analysis[26] that included 238 publications and 84318 patients (although there was an unequal distribution of studies between both groups) showed that ESD performed in Eastern countries is associated with better outcomes compared to Western countries with regard to R0, *en-bloc* and curative resection rates.

Many comparative studies between ESD and EMR have been published in the literature in order to balance ECG overall benefit costs. In Western meta-analysis[27] including 10 retrospective studies (8 full text and 2 abstracts), overall data on 4328 lesions, 1916 in the ESD and 2412 in the EMR group, were pooled and analyzed. ESD showed a superior efficacy with respect to EMR in terms of *en-bloc* and histological complete resection rates, as well as a lower recurrence frequency. However, a higher adverse event rate was observed in the ESD group but this could be also justified by anatomical features (*i.e.* the gastric wall thickness means that submucosal infiltration is

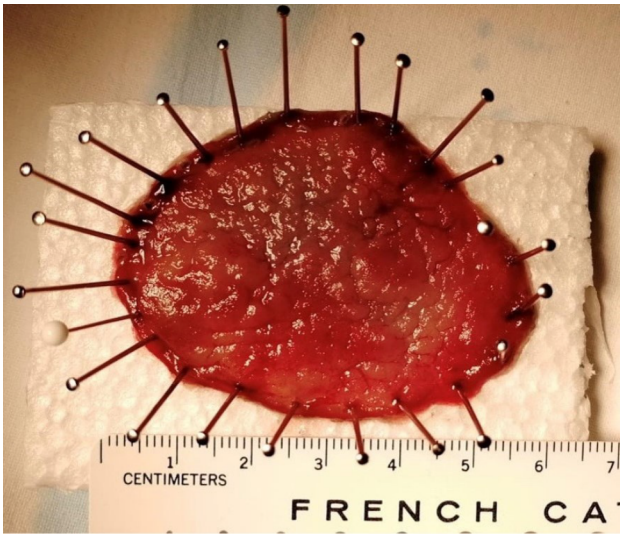

Figure 4 Whole resected specimen pinned down on a polystyrene block.

partially performed with poor lifting, unlike other GI tract regions where the mucosa is less tenaciously attached to the underlying structures).

There are few comparative data between ESD and surgery. Overall, retrospective data did not show statistically significant differences in oncological outcomes with respect to *en-bloc* resection, recurrence and overall survival[28,29]. However, the results showed that surgery required a longer operative time, longer and more expensive patients' hospital stay, and higher adverse event rate, altering native organ and digestive function.

Taken together, these data indicate that ESD should be the first-line therapy for all potentially endoscopically resectable superficial gastric neoplasia. Surgery can be reserved and used as a rescue therapy.

TRAINING PERSPECTIVES

The limited number of ESDs for EGC in the West is due above all to the lower incidence of this pathology. On the other hand, the high incidence of gastric neoplasia in the East led to the implementation of screening programs and surveillance, consequently developing and improving the ESD technique. Although there is a significant awareness of the technique, its diffusion in Europe remains limited by a whole series of factors, including cultural, logistical, aptitude, technological and, last but not least, remunerative. Eastern endoscopists have greater manual skills and dexterity (it is possible that use of handling chopstick in Asian culinary traditions can facilitate!), have vast technological capabilities that offer greater flexibility as well as meticulous training to achieve expertise. Some of the operators have a surgical background and training that makes them more comfortable in taking risk and less afraid of adverse events, overall resulting in better cost-performance. Training programs differ substantially between the East and West. In Japan, ESD training is well documented and established. Trainees first obtain a formal didactic teaching in ESD, followed by a careful observation by senior and renowned endoscopists. Then, they assist in ESD procedures, and they finally perform ESD under expert supervision on less challenging lesions, usually in the gastric antrum. This process can take years to achieve. ESD training for Western endoscopists may follow the pathway of observership in a high-volume Eastern center, practice on animal models, followed by preceptorship with an expert mentor, beginning with resection of smaller gastric antral lesions. A step-up training protocol recently developed in a German study[30] has shown that ESD training can lead to a high level of competency with a low adverse event rate within a short period of time, at least for easier locations in the rectum and lower stomach. In a recent Italian national survey, it has been observed that endoscopists performing ESD have achieved a good competence level, even if there is a high degree of variability in training protocols, initial supervision of procedures and practice settings[31]. Despite the differences and various proposed training algorithms to Western endoscopists[12], ESD has become increasingly popular, to the point that

ESGE has developed a European core curriculum for ESD practice across Europe with the aim of high-quality ESD training[32].

Besides the lower incidence of EGC in Western countries and a widespread use of proton pump inhibitors that could mask gastric cancers still in the early stages, the reasons for the low ability to diagnose in our latitudes compared to the Asian ones are essentially attributable to methodological problems. Unfortunately, gastroscopy is performed in a few minutes and therefore more prone to lesion and characterization oversight. It is advisable for all the GI endoscopist fellows to (1) perform an advanced endoscopy diagnostic practice before starting ESD training, (2) gain proficiency to perform basic techniques in EMR (loop polypectomy, standard EMR, *etc.*), and (3) train in managing adverse events, such as bleeding, perforations *etc.* Moreover, trainees have to learn and become proficient at the surveillance strategy after endoscopic treatment.

CONCLUSION

ESD is widely accepted as a treatment of gastric superficial epithelial tumors and recurrent neoplasia with scars after previous resection, without risk of lymph node metastases, allowing a high rate of curative resection with a good safety profile compared with other therapeutic approaches, including surgery. Promising Western data were reported from centers with a higher case volume. Instead, poor results of ESD have to be considered at the beginning of the learning curve and from lower volume case centers. Over the years, the ESD technique has increasingly expanded in Western countries, achieving a good efficacy and safety standards according to European guidelines, and opening new frontiers of mini-invasive oncological resection [33]. There are certainly some obstacles to its diffusion, including the low incidence of suitable gastric lesions (reference centers will deal with no more than 20 cases/year!) [34], essential requirements for beginner ESD endoscopists, the poor familiarity of endoscopists to detect and characterize early gastric lesions, and the overall lack of qualified trainers[35]. Furthermore, it would also be important to have national registers in order to optimize resources. Although in gastric ESD studies there were no meaningful differences between Western and Eastern endoscopists by evaluating the main endpoints such as curative resection and adverse events, outcomes from centers in Asia could not be representative of the Western experience[12,34]. The optimal treatment strategy must be modulated on a case-by-case basis according to the characteristics of lesions, to the patient's condition and to the level of local experience and expertise available.

From an ethical point of view, patients should be referred to specialized institutes where advanced diagnostic and therapeutic endoscopy is standardized, there are multidisciplinary teams for appropriate management, and certified training programs are implemented for a limited number of junior endoscopists. Therefore, when it is asked whether Western endoscopists are reaching the same level of expertise and proficiency of the colleagues from the East, "the answer is probably yes, but slowly, and only in high-volume centers"[20].

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ORIGINAL ARTICLE

Case Control Study

Laparoscopy for Crohn's disease: A comprehensive exploration of minimally invasive surgical techniques

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Abstract

BACKGROUND

Along with the unceasing progress of medicine, Crohn's disease (CD), especially complex CD, is no longer a taboo for minimally invasive surgery. However, considering its special disease characteristics, more clinical trials are needed to confirm the safety and feasibility of laparoscopic surgery for CD.

AIM

To investigate the safety and feasibility of laparoscopic enterectomy for CD, assess the advantages of laparoscopy over laparotomy in patients with CD, and discuss comprehensive minimally invasive surgical techniques in complex CD.

METHODS

This study prospectively collected clinical data from patients with CD who underwent enterectomy from January 2017 to January 2020. It was registered in the Chinese clinical trial database with the registration number ChiCTR-INR-16009321. Patients were divided into a laparoscopy group and a traditional laparotomy group according to the surgical method. The baseline characteristics, operation time, intraoperative blood loss, temporary stoma, levels of abdominal adhesion, pathological characteristics, days to flatus and soft diet, postoperative complications, hospitalization time, readmission rate within 30 d, and hospitalization cost were compared between the two groups.

RESULTS

A total of 120 eligible patients were enrolled into the pre-standardized groups,

publication of this article.

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including 100 in the laparoscopy group and 20 in the laparotomy group. Compared with the laparotomy group, the postoperative hospitalization time in the laparoscopy group was shorter (9.1 ± 3.9 d *vs* 11.0 ± 1.6 d, $P < 0.05$), the days to flatus were fewer (2.8 ± 0.8 d *vs* 3.5 ± 0.7 d, $P < 0.05$), the days to soft diet were fewer (4.2 ± 2.4 d *vs* 6.2 ± 2.0 d, $P < 0.05$) and the intraoperative blood loss was less (103.3 ± 80.42 mL *vs* 169.5 ± 100.42 mL, $P < 0.05$). There were no statistically significant differences between the two groups in preoperative clinical data, operation time (149.0 ± 43.8 min *vs* 159.2 ± 40.0 min), stoma rate, levels of abdominal adhesion, total cost of hospitalization, incidence of postoperative complications [8.0% (8/100) *vs* 15.0% (3/20)], or readmission rate within 30 days [1.0% (1/100) *vs* 0.00 (0/20)].

CONCLUSION

Compared with laparotomy, laparoscopic enterectomy promotes the recovery of gastrointestinal function, shortens the postoperative hospitalization time, and does not increase the incidence of postoperative complications. Laparoscopic enterectomy combined with varieties of minimally invasive surgical techniques is a safe and acceptable therapeutic method for CD patients with enteric fistulas.

Key Words: Crohn's disease; Minimally invasive surgery; Rapid recovery; Inflammatory bowel disease; Ultrasound

Core Tip: The purpose of this research was to investigate the safety, feasibility, and short-term efficacy of laparoscopic enterectomy for Crohn's disease (CD). For this purpose, we analyzed the clinical data of CD patients treated at our center over the past 4 years. Compared with the laparotomy group, the postoperative hospitalization time in the laparoscopy group was shorter, the days to flatus and soft diet were fewer, and the intraoperative blood loss was less. Also, the application of pre-operative ultrasound and intraoperative balloon dilatation for CD was explored specifically in the research.

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that affects the entire gastrointestinal tract, especially the terminal ileum and cecum[1]. Despite considerable progress in drug therapy, 70%-90% of patients need to undergo at least one surgical treatment in their lifetime due to the progression of CD[2]. Moreover, the postoperative recurrence rate and reoperation rate are increasing year by year, which seriously endangers the physical and mental health of patients and brings a heavy burden to society[3]. The 2016 edition of the European Guidelines for CD indicates that laparoscopic surgery should be given priority for patients with ileocecal disease in experienced surgical centers[4]. Compared with laparotomy, laparoscopic surgery for CD has the advantages of less injury, less pain, faster return of enteric function, and shorter postoperative hospitalization stay[5]. In addition, patients with CD are often at risk of recurrence and multiple operations. Laparoscopic surgery can reduce abdominal adhesions and improve conditions for reoperation[6]. However, complex CD was considered a contraindication to laparoscopic surgery due to the extensive inflammation, abdominal abscess, enteric fistulas, and even enteric fistulas between adjacent organs (such as the bladder and vagina) that made the operation difficult[7]. Over the years, with the rapid advances in medical technology and the improvement in surgical skills, there is no longer an untouchable taboo associated with complex CD [8,9].

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In patients with CD disease who have undergone multiple operations, extensive intraperitoneal adhesions often occur and the "dark chamber" is formed simultaneously. In such cases, it is often difficult to successfully insert the first laparoscopic trocar without damaging the abdominal organs and blood vessels. Previous studies have shown that ultrasound (US) can be used to assess preoperatively the degree of intraperitoneal adhesion, which is beneficial to laparoscopic surgery[10]. The activity of the abdominal wall and internal organs can be identified by US to determine the degree of adhesion, so as to locate the puncture point, thus alleviating the difficulty of laparoscopic surgery for CD. At the same time, CD patients often have multiple intestinal strictures. In order to retain more of the intestine during the operation, an ileus tube can be inserted through the nasal or small intestinal stoma, and the strictured intestine can be expanded using a balloon, thus promoting the remission of CD.

The purpose of this research was to investigate the safety, feasibility, and short-term efficacy of laparoscopic enterectomy for CD. For this purpose, we analyzed the clinical data of CD patients treated at our center over the past 4 years. By comparing the short-term efficacy of laparoscopic enterectomy with traditional laparotomy, the clinical advantages of laparoscopic enterectomy for CD were evaluated. Finally, we summarize the experience with laparoscopic enterectomy for CD in our center.

MATERIALS AND METHODS

Patients

This is a prospective cohort study, with continuous enrollment of CD patients who underwent surgery at our center from January 2017 to January 2020. The inclusion criteria for patients were: (1) CD combined with ileus, stenosis, fistula, abscess, and ineffective conservative treatment causing hemorrhage of the digestive tract requiring excision of the ileum and colon anastomosis; (2) Age 18-75 years; (3) Females without pregnancy plans and strict birth control; and (4) Agreement to participate in the study and signing the consent form. The exclusion criteria were: (1) Rapidly deteriorating or end-stage disease, which may increase the risk of death during the study procedure; (2) Enrollment in another clinical trial; or (3) Infliximab use before surgery. All operations were performed by two experienced laparoscopic colorectal surgeons, and standardized treatment regimens were used during the perioperative period. The study was registered in the Chinese clinical trial database with the registration number ChicTR-InR-16009321 and approved by the Ethics Committee of the Shanghai Tenth People's Hospital affiliated to Tongji University School of Medicine. Data collection included general information [gender, age, body mass index (BMI), smoking history, American Society of Anesthesiologists (ASA) class, CD duration, and family history], clinical characteristics, laboratory indexes (WBC, CRP, ESR, ALB, HB, PLT, PT, and APTT), imaging evaluation, operation and pathologic data, and postoperative treatment.

Preoperative preparation

Preoperative preparation included physical examination, computed tomography, magnetic resonance imaging, ultrasonography, and colonoscopy. Indications for surgery included drug treatment failure, enterostenosis, intestinal obstruction, intraperitoneal abscess, internal and external fistula, perforation, bleeding, and canceration. For patients with preoperative malnutrition or severe intestinal inflammation, more than 2 wk of enteral or parenteral nutritional support was administered. In patients with long-term hormone use, the dosage was gradually reduced until the hormone was discontinued. For intraperitoneal abscess, percutaneous drainage or double cannula flushing was performed to relieve local infection and inflammatory edema before surgery. All patients received 200 mL of 10% glucose orally at 10 h and 2 h before surgery, unless contraindicated.

Surgical procedure

The laparotomy was performed routinely. For laparoscopic surgery, preoperative abdominal US was performed to evaluate the degree of abdominal adhesion, as well as the range of diseased bowel to determine the position of the trocar. The diseased bowel and its mesenteric vasculature were isolated in the abdominal cavity, and then the bowel was exteriorized through the auxiliary incision for resection and anastomosis (Figure 1). Conversion to laparotomy was defined when the length of the incision was greater than 7 cm or larger than the size required for the resection of the

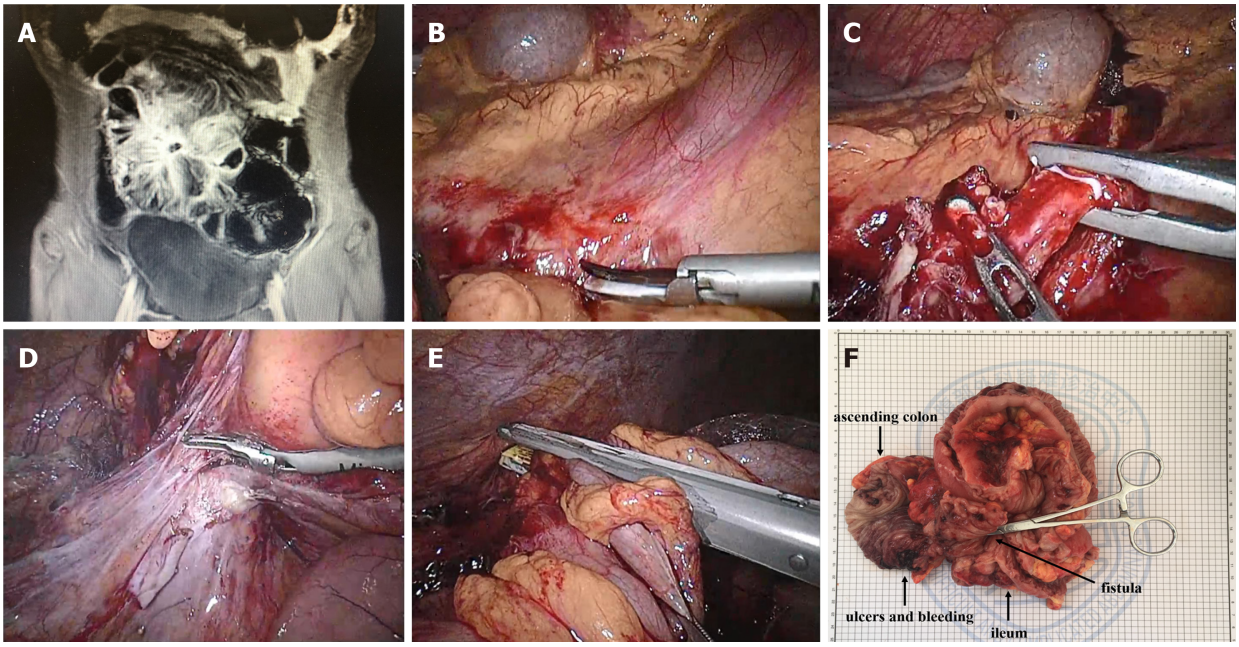

Figure 1 Laparoscopic ileocecal resection. A: Magnetic resonance enterography showed that the ileum was adhered into a mass with the possible formation of partial enteral fistula; B: Separation of the superior mesenteric vein; C: Isolation of the ileal blood vessels; D: Separation of the ileocecum; E: Disconnection of the small intestine; F: Specimen of the diseased bowel.

intestines outside the abdominal cavity.

Statistical analysis

SPSS 24 statistical software was used to analyze the data. Quantitative data are expressed as the mean ± SD (range). Student's *t*, Kruskal-Wallis, and χ^2 tests were used to analyze the data. $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 120 patients diagnosed with CD were included in the study: 100 who underwent laparoscopic surgery and 20 who underwent open surgery. There were no statistically significant differences between the two groups in gender, age, BMI, smoking history, ASA class, CD duration, past medical history, or hematologic examination (Table 1). However, for indications of surgery, we tended to choose open surgery for patients with intestinal perforation because such patients tend to have unstable vital signs.

Characteristics of intraoperative and postoperative observation indexes

The laparoscopy group was superior to the laparotomy group in terms of intraoperative blood loss (103.3 ± 80.42 mL in the laparoscopy group *vs* 169.5 ± 100.42 mL in the laparotomy group), days to flatus (2.8 ± 0.8 d *vs* 3.5 ± 0.7 d), days to soft diet (4.2 ± 2.4 d *vs* 6.2 ± 2.0 d), and length of postoperative hospitalization stay (9.1 ± 3.9 d *vs* 11.0 ± 1.6 d) ($P < 0.05$) (Tables 2 and 3). There were no statistically significant differences in the operation time, stoma rate, levels of abdominal adhesion, hospital cost, or total postoperative complications between the two groups. Except for one patient in the laparoscopy group who received surgical treatment again due to anastomotic fistula, all of the other complications were cured by conservative treatment. Only one patient in the laparoscopy group was readmitted 30 d after discharge, and this was because of non-specific abdominal pain.

DISCUSSION

At present, most researchers believe that laparoscopic surgery affords a rapid recovery

Table 1 Baseline characteristics

Variable	Laparoscopy (*n* = 100)	Laparotomy (*n* = 20)	*P* value
Age, yr, mean (range)	40.0 (19-71)	41.0 (19-72)	NS
Gender, male	71	14	NS
BMI, kg/m^2, mean ± SD	19.08 ± 2.60	20.88 ± 3.70	NS
Smoking history, *n* (%)	25 (25.0)	6 (30.0)	NS
ASA class, *n* (%)			NS
I	18 (18.0)	3 (15.0)	
II	70 (70.0)	12 (60.0)	
III	12 (12.0)	5 (25.0)	
Crohn's duration, mo, mean ± SD (range)	76.2 ± 56.0 (1-240)	59.1 ± 52.8 (1-144)	NS
Past medical history, *n* (%)			
Enterectomy	32 (32.0)	3 (15.0)	NS
Anal fistula	19 (19.0)	3 (15.0)	NS
Appendicectomy	13 (13.0)	1 (5.0)	NS
Others	18 (18.0)	2 (10.0)	NS
Indications for resection, *n* (%)			
Enterostenosis	50 (50.0)	5 (25.0)	NS
Intestinal obstruction	42 (42.0)	4 (20.0)	NS
Intraperitoneal abscess	13 (13.0)	2 (10.0)	NS
Fistula	36 (36.0)	7 (35.0)	NS
Intestinal perforation	4 (4.0)	5 (25.0)	$P < 0.05$
Hematologic examination			
WBC (/L)	6.4 ± 2.69	9.59 ± 6.50	NS
CRP (mg/L)	36.3 ± 44.23	56.49 ± 72.47	NS
ESR (mm)	33.0 ± 20.22	29.0 ± 20.43	NS
ALB (g/L)	38.1 ± 6.56	38.99 ± 6.82	NS
Hb (g/L)	116.0 ± 21.32	125.6 ± 26.89	NS
PLT (/L)	298.0 ± 115.10	272.1 ± 226.50	NS
PT (s)	12.5 ± 1.28	13.90 ± 6.37	NS
APTT (s)	31.4 ± 5.73	35.1 ± 20.03	NS

BMI: Body mass index; ASA: American Society of Anesthesiologists; WBC: White blood cell count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; ALB: Albumin; Hb: Hemoglobin; PLT: Platelets; PT: Prothrombin time; APTT: Activated partial thromboplastin time; NS: Not significant.

and diminishes immune and inflammatory responses, thus reducing the risk of postoperative recurrence, and possibly reducing postoperative abdominal adhesion [11,12]. The prospective cohort study in our center showed that laparoscopic surgery is safe and feasible for both simple and complex CD. Compared with open surgery, laparoscopic enterectomy can promote the recovery of gastrointestinal function, shorten the postoperative hospitalization stay, and does not increase the incidence of postoperative complications. In conclusion, laparoscopy is a safe and effective method for the treatment of CD complicated with enteric fistulas.

Due to the special disease characteristics of CD, some patients had to undergo surgical treatment to alleviate their condition due to drug treatment failure, intestinal stricture, intestinal obstruction, internal and external fistula, perforation, bleeding and/or cancerization[13]. For CD patients with multiple surgical histories, the abdominal cavity has lost its normal anatomical structure, so that the usual surgical

Table 2 Operative and pathologic data

Variable	Laparoscopy (*n* = 100)	Laparotomy (*n* = 20)	*P* value
Operative time, min	149.0 ± 43.8 (70-300)	159.2 ± 40.0 (90-260)	NS
Estimated blood loss, mL	103.3 ± 80.42 (20-400)	169.5 ± 100.42 (50-400)	$P < 0.05$
Extent of surgery, *n* (%)			
Ileal resection	13 (13.0)	5 (25.0)	NS
Ileo-colic resection	70 (70.0)	11 (55.0)	NS
Colonic resection	15 (15.0)	3 (15.0)	NS
En bloc resection with pelvic organ	2 (2.0)	1 (5.0)	NS
Intestinal resection with temporary stoma	49	5	NS
Levels of abdominal adhesion			NS
Level 0	19	2	
Level 1	17	3	
Level 2	43	8	
Level 3	15	5	
Level 4	6	2	
Clinicopathologic features			
Stricture	50	5	NS
Proximal dilatation	43	4	NS
Fistula	36	7	NS
Intestinal perforation	4	5	$P < 0.05$

NS: Not significant.

techniques of interstitial separation are often difficult to follow. In addition, the associated complications such as abdominal abscess, internal and external intestinal fistula, and inflammatory mass may increase the difficulty of surgery. The intestinal mesentery of CD patients is thickened with contracture and prone to bleeding, which aggravates the difficulty of separating the blood vessels. A limited visual field and poor exposure are often caused by thickened inflammatory mesenteric blood vessels and a dilated bowel. These difficulties are not only a great challenge for open surgery, but also for laparoscopic surgery[14,15].

Currently, many clinical studies have shown that laparoscopic ileocecal resection can be used for treating CD[16,17], and it has several advantages. First, patients with CD frequently are in poor general health, and often receive hormone and immunosuppressive therapy, resulting in low immune function and poor ability to fight infection. The minimally invasive method of laparoscopy can reduce the stress response brought on by the surgery as much as possible, which is conducive to a rapid recovery[18]. Second, less invasive laparoscopic surgery can reduce the incidence of abdominal adhesions, which is more conducive to secondary abdominal surgery should it be required by CD patients. Third, laparoscopic surgery is associated with less postoperative pain, faster recovery of intestinal peristalsis, earlier oral intake, and shorter postoperative hospitalization stay. Fourth, most CD patients are young and laparoscopic surgery meets the aesthetic requirements of the incision[19].

At present, in our center, the use of laparoscopy can greatly accelerate the recovery of patients after surgery, and achieve comprehensive and systematic treatment of the complications of CD in the gastrointestinal tract. In addition, the minimally invasive incision minimizes the rates of infection and pain at the surgical incision, so as to speed up rehabilitation training. Since CD affects the whole digestive system, strictures in the intestine can be treated minimally through stricturoplasty and intraoperative balloon dilatation. Although enterotomy can completely remove the strictured intestine, for patients with CD who have had multiple operations, there is a risk of developing short bowel syndrome with repeated resections. For stricturoplasty, conventional techniques such as HM strictureplasty and Finney strictureplasty are the

Table 3 Short-term (30-d) outcomes

Variable	Laparoscopy (*n* = 100)	Laparotomy (*n* = 20)	*P* value
Days to			
Flatus, d, mean ± SD (range)	2.8 ± 0.8 (1-4)	3.5 ± 0.7 (2-5)	$P < 0.05$
Soft diet, d, mean ± SD (range)	4.2 ± 2.4 (2-8)	6.2 ± 2.0 (3-12)	$P < 0.05$
Total postoperative complication, *n* (%)	8 (8.0)	3 (15.0)	NS
Anastomotic hemorrhage	1	0	
Anastomotic leakage	1	0	
Ileus	0	0	
Intraabdominal abscess	0	0	
Pelvic effusion	2	0	
Wound infection	2	2	
Urinary tract infection	0	1	
Reoperation	1	0	
Readmission after discharge	1	0	NS
Length of stay, d, mean ± SD (range)	9.1 ± 3.9 (4-36)	11.0 ± 1.6 (9-15)	$P < 0.05$
Cost (RMB)	72534.6	75032.6	NS

NS: Not significant.

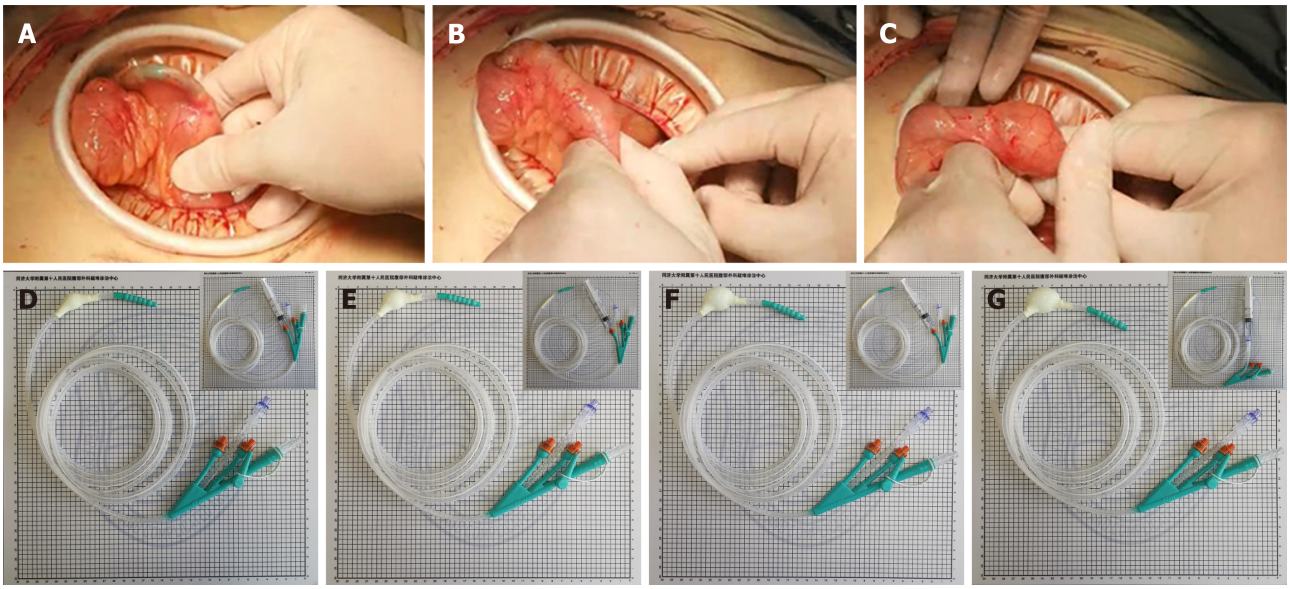

Figure 2 Intraoperative balloon dilatation and different balloon sizes of the ileus tube. A: Balloon prior to segment of enterostenosis; B: Balloon passes through segment of enterostenosis; C: Balloon posterior to segment of enterostenosis; D: A balloon with a diameter of 1.5 cm can be formed by injecting 3 mL of sterilized water; E: A balloon with a diameter of 2 cm can be formed by injecting 5 mL of sterilized water; F: A balloon with a diameter of 2.5 cm can be formed by injecting 8 mL of sterilized water; G: A balloon with a diameter of 3 cm can be formed by injecting 10 mL of sterilized water.

commonly used methods. Although complications such as anastomotic leakage, fistula, and abscess formation may occur, some reports have shown no statistical difference in CD recurrence rates between strictureplasty and enterostomy[20]. For intraoperative balloon dilatation, an obstruction catheter is inserted through the intestinal stoma or the nose, and the size of the balloon is determined according to the degree of intestinal stenosis (Figure 2). Importantly, compared with traditional endoscopic balloon dilatation[21], this method is safe for continuous dilatation of the bowel with multiple narrow segments under direct vision. At the same time, an ileus tube has a good protective effect in patients with extensive abdominal adhesions[22]. If

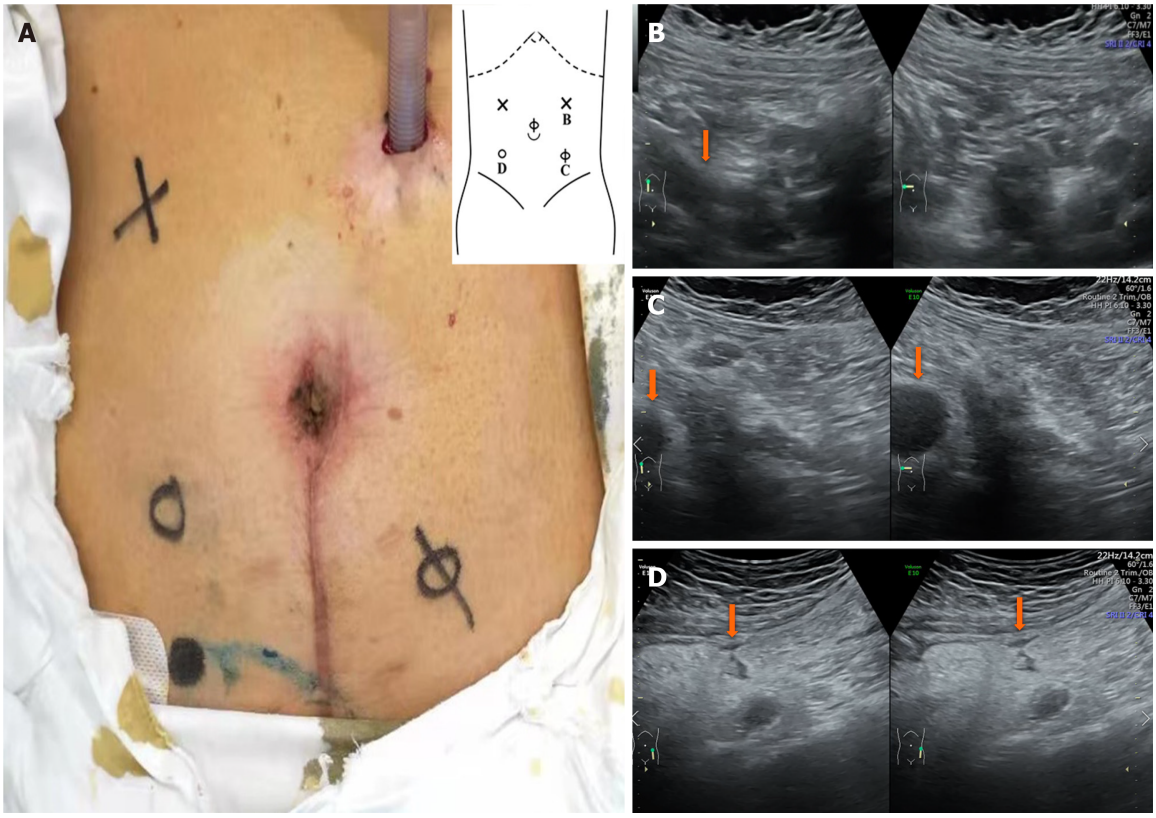

Figure 3 With the changes during respiration, B-ultrasonography was used to examine different areas to determine the activity between the abdominal wall and viscera. A: The degree of intraperitoneal adhesion is indicated by the annotations "×", "Φ", and "loop". "×" means that the activity is greater than 30 mm, the activity is better in the abdominal cavity, and no adhesion is considered. "Φ" means that the activity is greater than 5 mm, but less than 30 mm, and moderate intraperitoneal activity and moderate adhesion are considered. "loop" means that the activity is less than 5 mm, and severe adhesion is considered; B: In (A), the area denoted "×" in the left upper abdomen is seen under ultrasound. The blood vessels disappear from the screen, as shown in the arrow. Considering that there is no adhesion, it is the first place to puncture; C: In (A), the area denoted "Φ" in the right lower abdomen is seen under ultrasound. The range of intraperitoneal vessels with respiration is shown by the arrow; D: In (A), the area denoted "loop" in the right lower abdomen is seen under ultrasound. The range of intraperitoneal vessels with respiration is shown by the arrow.

an ileus tube is required, we will intubate through the enterostomy to the flexor ligament, which not only provides conditions for enteral nutrition, but also avoids pneumonia caused by nasal insertion. According to our statistics, about 70% (37/50) of people with CD have pulmonary ventilation dysfunction.

According to our experience, US is widely employed as an objective, accurate, non-invasive, and convenient examination method for evaluating CD[23]. To determine the first trocar position in patients with complex CD (Figure 3), preoperative abdominal US is useful for evaluating the degree and location of abdominal adhesions, as well as the range of diseased bowel[24]. In general, we will choose the area where the activity between the abdominal wall and viscera is greater than 30 mm to insert the first trocar.

When establishing pneumoperitoneum, it is necessary to observe the pressure value carefully and determine whether the abdominal bulge is symmetrical. If there are any abnormalities, the lens may not penetrate into the abdominal cavity, but accidentally enter the adhesion site. For patients who have had multiple surgeries, it is not recommended to perform the procedure on a routine basis, as it usually results in intraoperative collateral damage.

According to clinical practice, our center classifies abdominal adhesions into five levels (Figure 4): Level 0, no adhesion; level 1, slight adhesion (strip adhesion), which can be separated bluntly; level 2, moderate adhesion (membrane adhesion or tight adhesion), which can be directly sharply separated, without bleeding, or tight adhesion that can be seen between the bowel and abdomen, or between bowel and bowel, but there is a certain gap so that it can be cut with scissors but readily oozes blood; level 3, severe adhesion (fusion adhesion or complex adhesion), in which the naked eye is unable to distinguish the boundary between the intestines and the abdominal wall, and some intestines even fuse with the abdominal wall, so that adhesion separation can easily cause bleeding and intestinal damage; level 4, extremely heavy adhesion (wide compound adhesion), in which it is necessary to

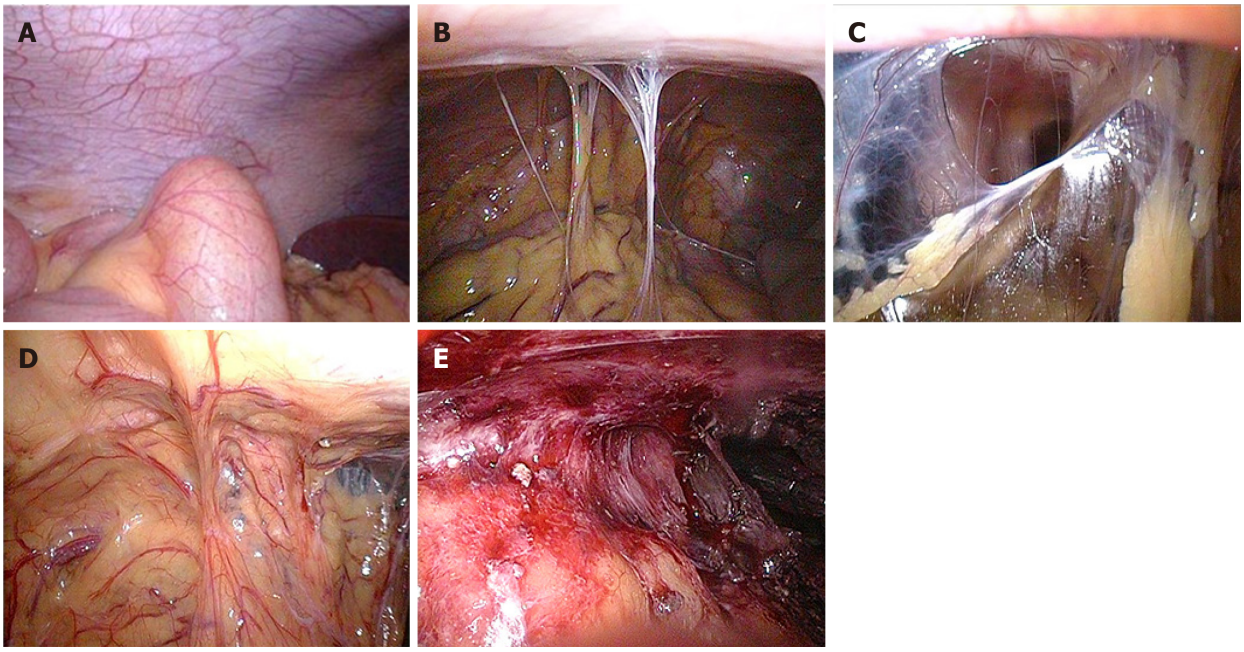

Figure 4 Levels of abdominal adhesion. A: Level 0, no adhesion; B: Level 1, slight adhesion (strip adhesion); C: Level 2, moderate adhesion (membrane adhesion or tight adhesion); D: Level 3, severe adhesion (fusion adhesion or complex adhesion); E: Level 4, extremely severe adhesion (wide compound adhesion).

combine scissors and an ultrasonic knife to separate adhesions and intestinal damage is often inevitable. We believe that levels 1 and 2 adhesions are simple adhesions because the separation of adhesions *via* laparoscopy usually does not cause intestinal damage or rupture. However, levels 3 and 4 adhesions are complex adhesions. In those cases, a large amount of blood oozing and rupture of intestinal injury often occur, and the injured intestines often need to be repaired or excised.

Another important preoperative imaging concern is whether abdominal adhesion affects other organs. If necessary, a gastric tube, ileus tube, anal tube and/or ureteral catheter may be inserted as intraoperative guidelines for protection[25]. Regarding temporary stoma, we will refer to the patient's condition and CDAI score, as well as a comprehensive assessment of the patient's psychological status and acceptance level. In addition, after mesenteric vasculature and bowel dissociation under laparoscopy, the diseased intestinal segment is pulled out through the stoma or an incision of 3-5 cm close to the trocar for further careful examination, resection, and anastomosis. This not only simplifies the surgical procedure, but also shortens the operation time and reduces the cost of hospitalization.

Perioperative management is also important for CD patients. Sometimes, laparoscopic surgery takes a long time and requires a high level of physical condition. The situation regarding enteric fistulas should be fully evaluated before the operation. For patients with severe infection, percutaneous drainage or double cannula flushing should be considered first, and the surgery should be performed after the infection and inflammatory edema are alleviated. At the same time, antibiotic therapy should be used rationally and both abdominal and pulmonary infections should be considered, which provides a prerequisite for surgery. In brief, preoperative management of malnutrition and coexisting disease should be performed as much as possible before surgical intervention[26]. Surgery can only have the desired effect if the nutritional status is improved, the disease is in remission, and the coexisting diseases are controlled. The principle of damage control surgery should also be given full consideration for the surgery of enteric fistulas[27]. For seriously ill patients, one-stage operation is not considered and a temporary stoma should be performed first. Further treatment should be commenced after the condition of the body stabilizes.

The disadvantage of this research is that it is not a randomized controlled study. Currently, many surgeons prefer laparoscopic surgery, inevitably leading to selection bias. At the moment, most studies demonstrated that laparoscopic ileocolonic resection in CD is available. But for complex or recurrent CD, there is insufficient evidence to recommend laparoscopic surgery as the preferred technique. In the future, we will continue to explore the long-term follow-up of patients with complex or recurrent CD undergoing laparoscopic resection.

CONCLUSION

The inflammatory properties of CD lead to a certain particularity and complexity of the intraperitoneal anatomy, making it subject to numerous changes. According to our experience, laparoscopy for CD is safe and feasible, conducive to the postoperative rehabilitation of patients, and worthy of further promotion. Laparoscopic surgery for CD requires surgeons not only to have rich CD treatment experience in open surgery, but also advanced laparoscopic surgical skills[28]. Most importantly, if the abdominal cavity is found to contain freezing-like adhesions during the operation, resulting in anatomical difficulties, the procedure should be transferred to laparotomy in a timely manner to try to avoid collateral damage, bleeding, infections, and other complications.

ARTICLE HIGHLIGHTS

Research background

Along with the unceasing progress of medicine, Crohn's disease (CD), especially complex CD, is no longer a taboo for minimally invasive surgery. However, considering its special disease characteristics, more clinical trials are needed to confirm the safety and feasibility of laparoscopic surgery for CD.

Research motivation

Although laparoscopic ileocolonic for CD is proved to be beneficial, for complex or recurrent CD, more minimally invasive surgical techniques need to be explored and applicated in laparoscopic surgery.

Research objectives

To investigate the safety and feasibility of laparoscopic enterectomy for CD, and to explore minimally invasive surgical techniques in complex CD.

Research methods

This study prospectively collected clinical data from patients with CD who underwent enterectomy from January 2017 to January 2020. Patients were divided into a laparoscopy group and a traditional laparotomy group according to the surgical method. The baseline characteristics, operative and pathologic data, and short-term (30-d) outcomes were compared between the two groups.

Research results

A total of 120 eligible patients were enrolled into the pre-standardized groups, including 100 in the laparoscopy group and 20 in the laparotomy group. Compared with the laparotomy group, the patients in the laparoscopy group recovered more quickly, but had fewer postoperative complications.

Research conclusions

Laparoscopic enterectomy combined with varieties of minimally invasive surgical techniques could promote the recovery of patients with CD.

Research perspectives

The inflammatory properties of CD lead to a certain particularity and complexity of the intraperitoneal anatomy, making it subject to numerous changes. It requires surgeons not only to have rich CD treatment experience in open surgery, but also advanced laparoscopic surgical skills. Most importantly, if the abdominal cavity is found to contain severe adhesions, the procedure should be transferred to laparotomy in a timely manner to avoid collateral damage, bleeding, infections, and other complications.

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ORIGINAL ARTICLE

Retrospective Study

Onodera's Prognostic Nutritional Index is a novel and useful prognostic marker for gastrointestinal stromal tumors

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Author contributions: Xu YY, Wang H, and Zong L designed the research; Wang H, You J, Hu WQ, Wang SF, and Chen P performed the research; Shi L, Yang F, and Zhao W analyzed the data; Xu YY and Wang H wrote the paper and contributed equally to this study.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Abstract

BACKGROUND

Immunoinflammatory markers such as the peripheral blood neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have gained considerable attention as prognostic markers in gastrointestinal stromal tumors (GISTs).

AIM

To assess the prognostic value of Onodera's Prognostic Nutritional Index (OPNI) for GISTs.

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Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

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METHODS

All patients who had undergone surgical resection for a primary, localized GIST from 2009 to 2016 at our cancer center were initially and retrospectively identified. Recurrence-free survival (RFS) was calculated by the Kaplan-Meier method and compared by the log-rank test. We used multivariate Cox proportional hazard regression models to identify associations with outcome variables.

RESULTS

A total of 235 GISTs were identified and included for analysis under our inclusion criteria. Univariate and multivariate analyses both identified the OPNI as an independent prognostic marker, and the OPNI was associated with the primary site, tumor size, mitotic index, tumor rupture, necrosis, and modified NIH risk classification. Low OPNI (< 51.30; hazard ratio = 5.852; 95% confidence interval: 1.072–31.964; P = 0.0414) was associated with worse RFS. The 2- and 5-year RFS rates of the patients with a low OPNI were 92.83% and 76.22%, respectively, whereas 100% and 98.41% were achieved by the patients with a high OPNI.

CONCLUSION

The preoperative OPNI is a novel and useful prognostic marker for GISTs.

Key Words: Gastrointestinal stromal tumor; Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Onodera's Prognostic Nutritional Index; Prognostic marker

Core Tip: Immunoinflammatory markers such as the peripheral blood neutrophil-to-lymphocyte ratio and the platelet-to-lymphocyte ratio have gained considerable attention as prognostic markers in gastrointestinal stromal tumors (GISTs). Here we conducted the first investigation of the prognostic value of Onodera's Prognostic Nutritional Index (OPNI) for GISTs. A total of 235 GISTs were identified and included for analysis under our inclusion criteria. Our study shown that the 2- and 5-year recurrence-free survival rates of the patients with a low OPNI were 92.83% and 76.22%, respectively, whereas 100% and 98.41% were achieved by the patients with a high OPNI, which demonstrated that the preoperative OPNI is a novel and useful prognostic marker for GISTs.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal (GI) tract; their estimated clinical incidence is nearly 1 per 100000 individuals per year[1,2]. The driving force of GISTs is thought to be mutation in *c-Kit* and minimally in the *PDGFRA* oncogene (platelet derived growth factor receptor alpha)[3,4]. GISTs can be malignant tumors arising anywhere in the GI tract or abdominal cavity[5]. Surgery remains the standard treatment for primary GISTs, and it has been the only potentially curative therapy.

GIST relapse is common even when the tumor undergoes R0 resection. The disease-free survival (DFS) of patients with GISTs has been markedly improved by the use of the molecularly-specific oral anticancer agent imatinib mesylate (IM), but its adverse reaction and resistance have some hindrance in the treatment of GISTs. Systemic adjuvant IM therapy needs more assurance to be beneficial for target patients. The four most important prognostic factors for GISTs are the tumor location, tumor size, mitotic index, and presence/absence of tumor rupture as suggested by the U.S. famous institutes (NIH, AFIP)[6-8]. Despite the use of these guidelines, even the latest risk

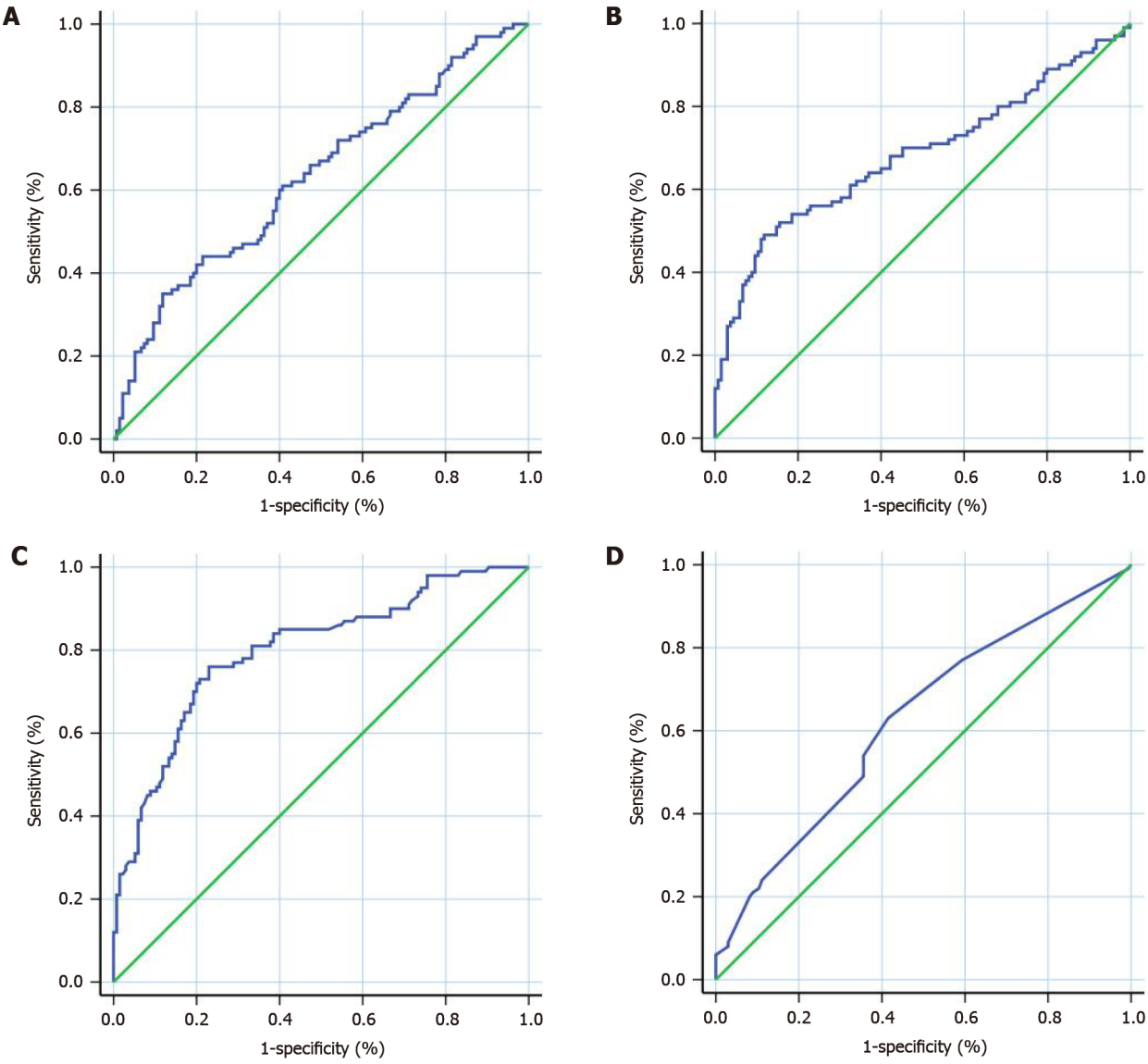

Figure 1 Receiver operator characteristic analysis of the neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, Onodera's Prognostic Nutritional Index, and Ki-67 index. A: Neutrophil-to-lymphocyte ratio; B: Platelet-to-lymphocyte ratio; C: Onodera's Prognostic Nutritional Index; D: Ki-67 index.

stratification system should be improved[9-11].

One of the components of the tumor microenvironment is tumor-associated inflammatory cells. These cells have important roles in both tumor development and progression, which can promote the proliferation, invasion, and metastasis of tumor cells[12]. Immunoinflammatory factors were shown to be associated with the oncogenesis, progression, and prognosis of GISTs. The peripheral blood neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR; an easily measured, reproducible and cost-effective systemic inflammatory marker) have been investigated as prognostic markers in patients with multiple solid tumors such as non-small-cell lung cancer, colorectal cancer, and gastric cancer[13-15].

Onodera's Prognostic Nutritional Index (OPNI) was useful for GI surgery patients to evaluate immune nutritional status[16]. The OPNI has been reported to be a useful prognostic marker in esophageal cancer[17], gastric cancer[18], colorectal cancer[19], and pancreatic cancer[20], but the prognostic value of the OPNI for GISTs has not been determined. We conducted the present study to evaluate the prognostic value of the OPNI for GIST.

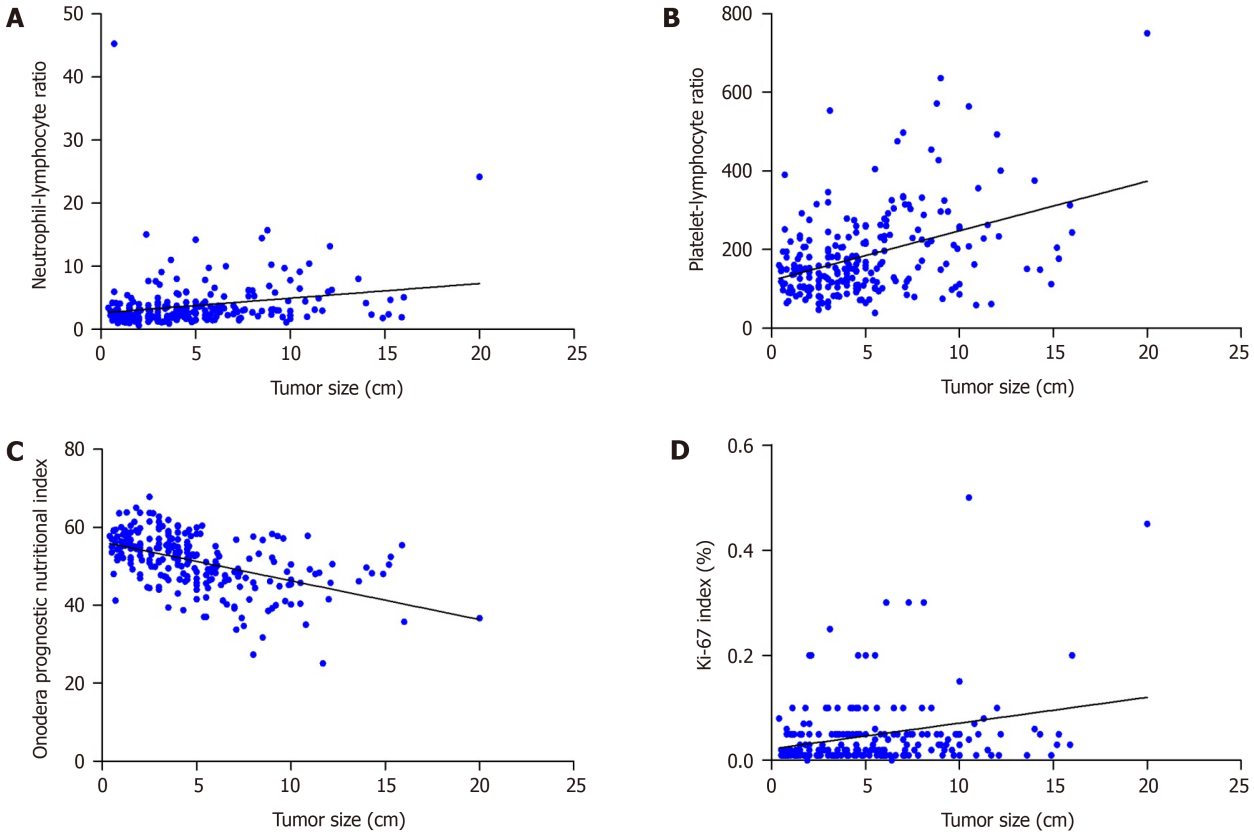

Figure 2 Correlation between gastrointestinal stromal gastrointestinal stromal tumor size and neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, Onodera's Prognostic Nutritional Index, and Ki-67 index. A: Neutrophil-to-lymphocyte ratio; B: Platelet-to-lymphocyte ratio; C: Onodera's Prognostic Nutritional Index; D: Ki-67 index.

MATERIALS AND METHODS

Patients

We retrospectively retrieved the data of the patients with GISTs treated at Northern Jiangsu People's Hospital (Yangzhou, China) from 2009 to 2016. The inclusion criteria were as follows: (1) R0 resection in GIST; (2) absence of coeval tumors; (3) no treatment or therapies (chemotherapy, radiotherapy, or imatinib); and (4) without signs of infection. A final total of 235 GISTs were included. This study was approved by the Ethics Committee of Northern Jiangsu People's Hospital, and written informed consent for their data to be used was obtained from all the patients.

Preoperative peripheral blood routine tests and OPNI evaluation

All the patients' preoperative peripheral blood routine tests had been performed within 7 d before surgery. The NLR value was calculated as the neutrophil count (10^9/L) divided by the lymphocyte count (10^9/L). The value of the PLR was calculated by the same method as the NLR. The OPNI was calculated as the serum albumin (g/L) + 5 × total lymphocyte count (10^9/L).

Clinicopathological features

All specimens were diagnosed as GI mesenchymal (non-epithelial) tumors by hematoxylin and eosin (H&E) staining, and further confirmed by positive immunohistochemical staining for CD117 and discovered on GIST 1(DOG-1) with or without CD 34, desmin, SMA, and S-100 positive expression. If the result was negative for both staining, then *c-Kit* gene exons 9, 11, 13, and 17 or *PDGFRA* gene exons 12 and 18 were analyzed for DNA mutation.

We obtained the patients' clinical data from their medical records: Age, gender, and basic clues like primary tumor location, tumor diameter, and rupture of tumor (preoperative/intraoperative). Pathologists measured tumor diameter before specimen fixation. The cell type, mitotic index, and necrosis of tumor were the histopathological markers for analysis. Tumor shape and size, mitotic index, tumor location, and rupture of tumor are four risk stratification factors. And the mitotic index was counted per 50

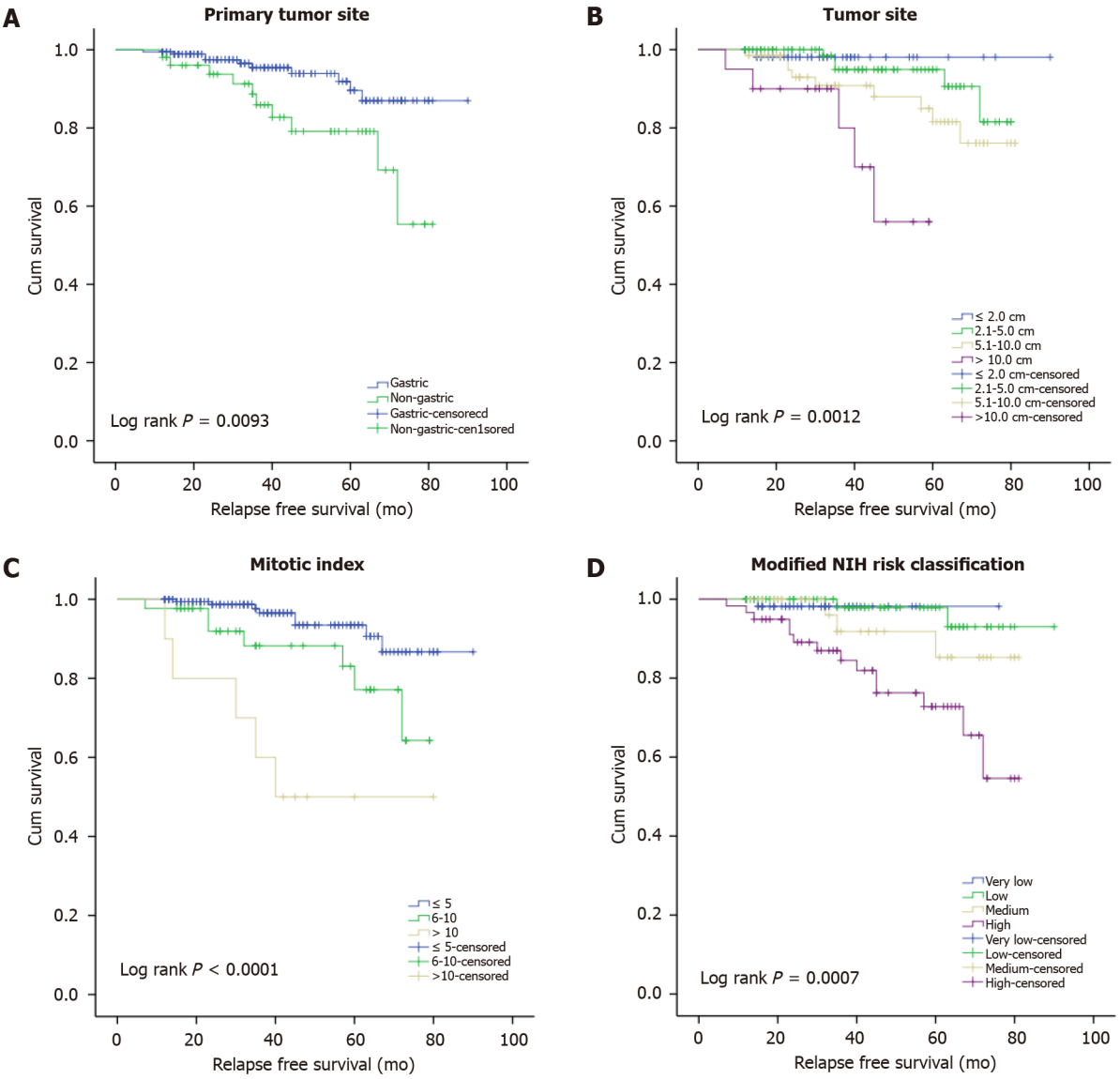

Figure 3 Recurrence-free survival analysis of 235 patients with primary gastrointestinal stromal tumors. The Kaplan-Meier curve analysis demonstrated worse recurrence-free survival rates for the patients presenting with (A) non-gastric origin, (B) larger tumor size, (C) higher mitotic index, or (D) high modified NIH risk.

randomly selected high-power fields by two pathologists.

Follow-up

After their surgeries, the patients were followed by endoscopy and computed tomography examinations every 6 mo to evaluate the presence/absence of tumor recurrence and distant metastasis. We obtained the patients' follow-up information from the hospital's records and tumor registry, or by contacting directly with the patients or their family member.

Patients with GISTs can live with the tumor for a relatively long time even if they recur/metastasize. We speculated that the most suitable event for survival analysis was relapse or metastasis, and use of IM treatment for relapse and metastasis of GISTs can affect overall survival. We calculated the duration of a patient's relapse free survival (RFS) from the surgery date for GIST, which was the study's primary outcome. And the study's secondary endpoints were receiver operator characteristic (ROC) analysis of NLR, PLR, OPNI, and Ki-67 index, and correlation between tumor size and NLR, PLR, OPNI, and Ki-67 index.

Statistical analysis

IBM SPSS Statistics were used to calculate all statistical analyses. Continuous variables are presented as the mean ± SD, and count data are summarized using frequencies and percentages. We calculated the correlation of continuous variables by obtaining the

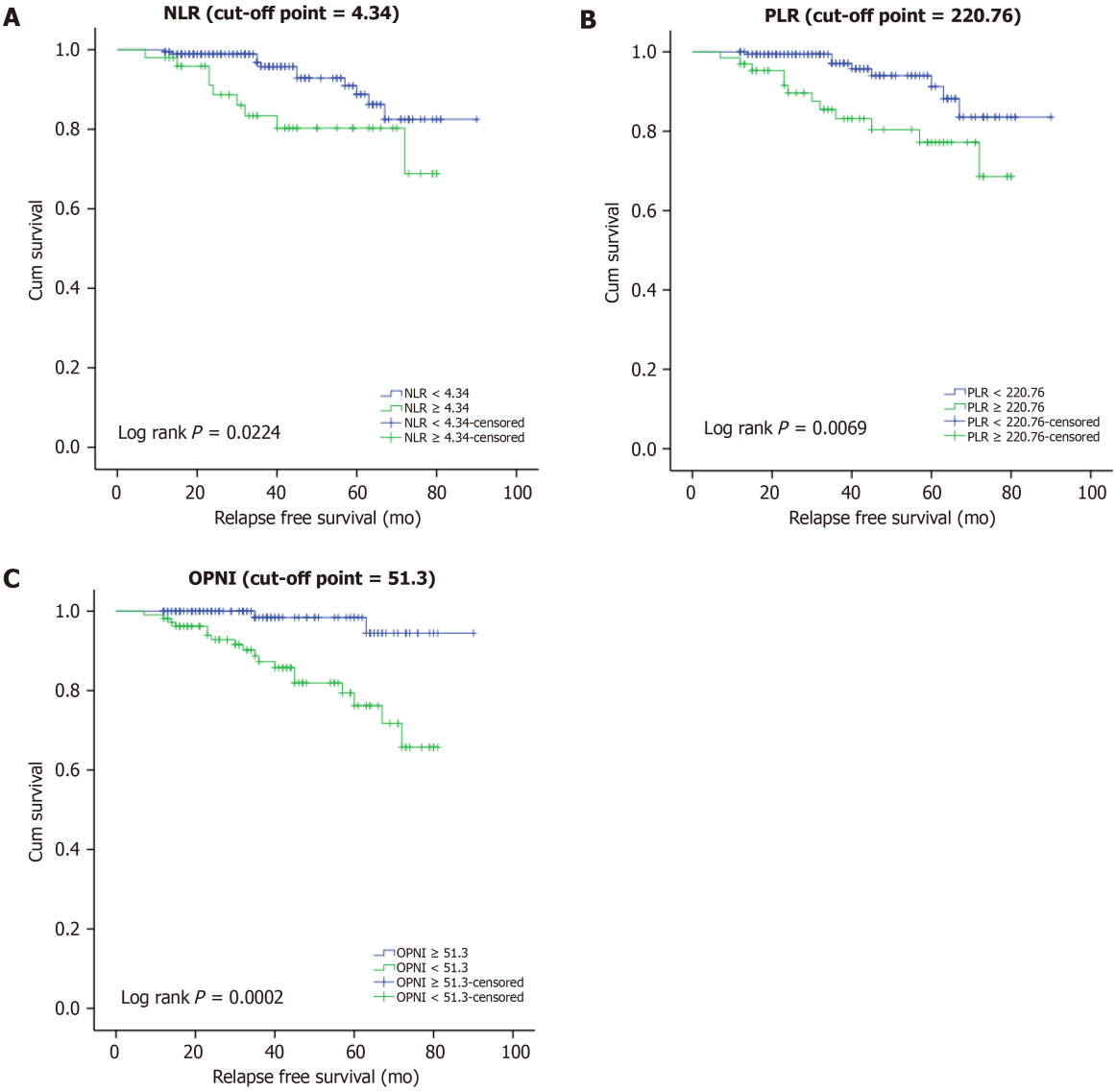

Figure 4 Recurrence-free survival analysis of 235 patients with primary gastrointestinal stromal tumors. The Kaplan-Meier curve analysis demonstrated worse recurrence-free survival rates for the patients presenting with (A) a higher neutrophil-to-lymphocyte ratio, (B) higher platelet-to-lymphocyte ratio, or (C) lower Onodera's Prognostic Nutritional Index. NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; OPNI: Onodera's Prognostic Nutritional Index.

Pearson correlation coefficient, and we calculated the correlation of discrete variables by obtaining Spearman's correlation coefficient. ROC analysis was used to determine the cut-off points of the NLR, PLR, OPNI, and Ki-67 index. Univariate analysis was performed using the Kaplan-Meier method, and the results were compared by the log-rank test. We conducted a multivariate analysis with the Cox proportional hazards model. A P value < 0.05 was accepted as significant.

RESULTS

Clinicopathological parameters

The median age of the 235 patients (118 men and 117 women) was 62 years (range, 30–86 years), along with 125 patients (53%) aged more than 60 years. The basic symptoms of the GIST patients were abdominal discomfort/pain (n = 104), GI bleeding and obstruction (n = 63 and 8), rupture of tumor (n = 2), weight loss (n = 7), and being asymptomatic (n = 51). The GISTs can be found in the stomach (n = 183), small intestine (n = 41), colorectum (n = 10), and intraperitoneum with unknown etiology. The tumor sizes varied from 0.4 to 20 cm (median, 4.3 cm). Histologically, the spindle-cell type was most common (n = 206), followed by the epithelioid-cell type (n = 16) and the mixed type (n = 13). The mitotic index, necrosis, and more detailed

Table 1 Clinicopathological features of 235 patients with primary gastrointestinal stromal tumors

Characteristic	*n* (%)
Gender	
Male	118 (50.2)
Female	117 (49.8)
Age (yr, mean SD)	60.09 ± 10.12
≤ 60	110 (46.8)
> 60	125 (53.2)
Clinical manifestation	
Abdominal discomfort or pain	104 (44.3)
Gastrointestinal bleeding	63 (26.8)
Obstruction	8 (3.4)
Perforation or rupture	2 (0.9)
Weight loss	7 (3.0)
Asymptomatic	51 (21.7)
Preoperative laboratory variables	
Hemoglobin (g/L, mean SD)	122.69 ± 29.94
White blood cell (10^9 /L, mean SD)	6.52 ± 2.70
Neutrophil count (10^9 /L, mean SD)	4.40 ± 2.35
Lymphocyte count (10^9 /L, mean SD)	1.42 ± 0.53
Platelet count (10^9 /L, mean SD)	230.11 ± 100.76
Albumin (g/L, mean SD)	44.19 ± 6.66
NLR (mean SD)	3.80 ± 3.95
PLR (mean SD)	184.83 ± 109.06
OPNI (mean SD)	51.27 ± 7.12
Primary tumor site	
Stomach	183 (77.9)
Small intestine	41 (17.4)
Colorectum	10 (4.3)
Intraperitoneally with unknown origin	1 (0.4)
Tumor size (cm, mean SD)	5.003 ± 3.5458
≤ 2.0	55 (23.4)
2.1-5.0	93 (39.6)
5.1-10.0	67 (28.5)
> 10.0	20 (8.5)
Predominant cell type	
Spindle	206 (87.7)
Epithelioid	16 (6.8)
Mixed	13 (5.5)
Mitotic index (per 50 HPFs)	
≤ 5	182 (77.4)
6-10	43 (18.3)
> 10	10 (4.3)

Necrosis	
Yes	66 (28.1)
No	169 (71.9)
Tumor rupture	
Yes	11 (4.7)
No	224 (95.3)
Risk classification	
Very low risk	58 (24.7)
Low risk	77 (32.8)
Intermediate risk	41 (17.4)
High risk	59 (25.1)
CD117	
(–)	4 (1.7)
(+)	169 (71.9)
(++)	18 (7.7)
(+++)	44 (18.7)
CD34	
(–)	11 (4.7)
(+)	165 (70.2)
(++)	12 (5.1)
(+++)	47 (20.0)
DOG-1	
(–)	3 (1.3)
(+)	211 (89.8)
(++)	12 (5.1)
(+++)	9 (3.8)
Ki-67 index (%, mean SD)	4.65 ± 6.37
Follow-up time (months, mean SD)	40.20 ± 20.18
Follow-up status	
Relapse-free survival	215 (91.5)
Relapse	15 (6.4)
Metastasis	5 (2.1)

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; OPNI: Onodera's Prognostic Nutritional Index.

clinicopathological variables are summarized in Table 1.

ROC analysis

We used the continuous variables of NLR, PLR, OPNI, and the Ki-67 index as test variables, and the RFS as the state variable. The areas under the ROC curves, cut-off points, sensitivities, specificities, and Youden indexes of the NLR, PLR, OPNI, and Ki-67 index are provided in Table 2 and Figure 1.

Correlation analyses

A lower OPNI was associated with the primary tumor location (P = 0.0004), tumor diameter (P < 0.0001), mitotic index (P < 0.0001), rupture of tumor (P = 0.0030), necrosis (P < 0.0001), and risk stratification by the modified NIH (P < 0.0001). A significant correlation was observed between the NLR and tumor size [Pearson

Table 2 Receiver operator characteristic analyses for neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, Onodera's Prognostic Nutritional Index, and ki-67 index

	NLR	PLR	OPNI	Ki-67 index
Cut-off point	4.34	220.76	51.30	2.5%
Sensitivity% (95%CI)	35.00 (25.73-45.19)	49.00 (38.86-59.20)	76.00 (66.43-83.98)	63.00 (52.76-72.44)
Specificity% (95%CI)	88.15 (81.47-93.07)	88.15 (81.47-93.07)	77.04 (69.02-83.83)	58.52 (49.73-66.93)
Youden Index	0.2315	0.3715	0.5304	0.2152
AUC (95%CI)	0.6308 (0.5584-0.7031)	0.6820 (0.6096-0.7545)	0.7999 (0.7420-0.8578)	0.6237 (0.5514-0.6960)
P value	0.0006	< 0.0001	< 0.0001	0.0012

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; OPNI: Onodera's Prognostic Nutritional Index; AUC: Area under the curve.

Table 3 Correlation analysis of tumor size and mitotic index with neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, Onodera's Prognostic Nutritional Index, and ki-67 index

	Tumor size		Mitotic index	
	Pearson *r*	*P* value	*Rs*	*P* value
NLR	0.2082	0.0013	0.1021	0.1185
PLR	0.4098	< 0.0001	0.2045	0.0016
OPNI	-0.4955	< 0.0001	-3.048	< 0.0001
Ki-67 index	0.2727	< 0.0001	0.2551	< 0.0001

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; OPNI: Onodera's Prognostic Nutritional Index.

correlation coefficient (r) = 0.2082, P = 0.0013]. Similarly, the PLR, OPNI, and Ki-67 index were each correlated strongly with tumor size (Table 3). There was a negative correlation between the OPNI and GIST tumor size, whereas the NLR, PLR, and Ki-67 index were positively correlated with GIST tumor size (Figure 2). Spearman's correlation test revealed that the PLR (Rs =0.2045, P = 0.0016), OPNI (Rs = −3.048, P < 0.0001), and Ki-67 index (Rs =0.2551, P < 0.0001) were correlated with the mitotic index (Table 3). Correlation analysis of clinicopathologic parameters with OPNI, NLR, PLR, and Ki-67 index are shown in the Supplementary Tables 1-4, which showed no significance difference.

Follow-up

Patients were followed for a median of 35 mo (range 7–90 mo), and 9.79% (23/235) of the patients were lost to follow-up. The number of relapse patients was, including 5.96% (14/235) with local recurrence in the abdominopelvic cavity and 3.83% (9/235) with liver metastasis (n = 9), and lymph metastasis was not seen. The Kaplan-Meier 1-, 2-, and 5-year RFS rates were 99.15% (95%CI: 96.64–99.7), 96.61% (95%CI: 92.97–98.38), and 86.87% (95%CI: 78.73–92.04), respectively.

Univariate survival analysis

The results of our univariate survival analysis demonstrated that the primary site (log-rank P = 0.0093), tumor size (log-rank P = 0.0012), mitotic index (log-rank P < 0.0001), modified NIH risk stratification (log-rank P = 0.0007), NLR (log-rank P = 0.0224), PLR (log-rank P = 0.0069), and OPNI (log-rank P = 0.0002) were specific prognostic markers for RFS of our GIST patient series. The correlations of clinicopathological factors with the RFS are shown in Table 4 and Figure 3. The univariate survival analysis shows no significance association between recurrence and albumin and lymphocyte count. And the results of ROC analysis for albumin and lymphocyte count are shown in Supplementary Table 5.

Multivariate survival analysis

The collinearity diagnostics of all the explanatory variables was performed to exclude

Table 4 Univariate analysis (Kaplan-Meier) of factors for recurrence-free survival in gastrointestinal stromal tumors

Factor	1-year RFS rate (95%CI)	2-year RFS rate (95%CI)	5-year RFS rate (95%CI)	Log-rank *P* value
Age (yr)				0.5441
≤ 60	99.09% (93.72-99.87)	96.92% (90.66-99.01)	91.20% (80.62-96.14)	
> 60	99.20% (94.46-99.89)	96.35% (90.49-98.62)	82.93% (69.26-90.91)	
Gender				0.2889
Male	98.31% (93.39-99.57)	95.19% (88.74-97.99)	84.07% (71.68-91.35)	
Female	100%	98.03% (92.30-99.51)	84.96% (66.88-93.61)	
GI bleeding				0.1877
Yes	98.41% (89.26-99.77)	98.41% (89.26-99.77)	82.02% (63.00-91.85)	
No	99.42% (95.94-99.92)	95.84% (90.90-98.12)	89.37% (80.44-94.36)	
Primary site				0.0093
Gastric	99.45% (96.18-99.92)	97.47% (93.30-99.04)	89.62% (79.32-94.94)	
Non-gastric	98.08% (87.12-99.73)	93.75% (81.78-97.95)	79.12% (61.86-89.21)	
Tumor size				0.0012
≤ 2.0 cm	100%	98.10% (87.12-99.73)	98.10% (87.12-99.73)	
2.1-5.0 cm	100%	100%	94.90% (84.98-98.33)	
5.1-10.0 cm	98.51% (89.87-99.79)	92.93% (82.17-97.30)	81.55% (65.45-90.65)	
> 10.0 cm	95.00% (69.46-99.28)	90.00% (65.59-97.40)	56.00% (20.71-80.77)	
Predominant cell type				0.7759
Spindle	99.51 % (96.60-99.93)	97.22 % (93.41-98.84)	88.47 % (79.83-93.55)	
Epithelioid	93.75 % (63.22-99.10)	93.75 % (63.22-99.10)	84.38 % (49.30-96.00)	
Mixed	100%	100%	76.39 % (30.91-94.01)	
Mitotic index				< 0.0001
≤ 5 per 50 HPFs	100%	98.67% (94.75-99.67)	93.47% (85.43-97.15)	
6-10 per 50 HPFs	97.67% (84.61-99.67)	91.93% (76.88-97.34)	77.13% (53.86-89.67)	
>10 per 50 HPFs	100%	80.00% (40.86-94.59)	50.00% (18.35-75.32)	
Necrosis				0.2676
Yes	98.48% (89.72-99.79)	98.48% (89.72-99.79)	83.69% (66.12-92.63)	
No	100%	95.79% (90.79-98.10)	89.58% (81.22-94.34)	
Tumor rupture				0.0695
Yes	100%	100%	63.49% (23.81-86.61)	
No	99.11% (96.48-99.78)	96.43% (92.62-98.29)	88.40% (79.94-93.44)	
Risk classification				0.0007
Very low risk	100%	98.18% (87.78-99.74)	98.18% (87.78-99.74)	
Low risk	100%	100%	97.92% (86.11-99.70)	
Intermediate risk	100%	100%	85.27% (59.66-95.20)	
High risk	96.61% (87.11-99.14)	89.10% (77.27-94.97)	72.82% (56.21-83.98)	
NLR				0.0224
< 4.34	99.46% (96.22-99.92)	98.89% (95.65-99.72)	88.76% (78.31-94.35)	
≥ 4.34	98.00% (86.63-99.72)	88.68% (74.82-95.15)	80.29% (64.11-89.73)	
PLR				0.0069
< 220.76	100%	99.39% (95.75-99.91)	91.24% (80.00-96.31)	

≥ 220.76	96.92% (88.25-99.22)	89.64% (78.27-95.23)	77.17% (61.76-86.99)	
OPNI				0.0002
≥ 51.30	100%	100%	98.41% (89.26-99.77)	
< 51.30	98.13% (92.73-99.53)	92.83% (85.49-96.53)	76.22% (62.51-85.48)	
Ki-67 index				0.0592
< 2.5%	100%	98.88% (92.29-99.84)	88.03% (68.96-95.72)	
≥ 2.5%	98.29% (93.34-99.57)	94.34% (87.79-97.43)	84.39% (74.22-90.79)	
Albumin				0.0589
< 38.95	99.86% (96.42-99.91)	98.79% (96.65-98.72)	89.74% (76.31-93.35)	
≥ 38.95	99.01% (89.63-99.82)	90.68% (86.52-96.45)	87.23% (75.11-89.63)	
Lymphocyte count				0.0524
< 0.975	99.46% (96.22-99.82)	96.89% (95.15-99.02)	88.76% (78.11-94.05)	
≥ 0.975	98.70% (89.93-99.62)	90.68% (86.82-95.15)	87.29% (74.11-93.53)	

GI: Gastrointestinal; RFS: Recurrence-free survival; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; OPNI: Onodera's Prognostic Nutritional Index.

the internal correlation. We selected only the factors that showed a significant correlation with RFS in the univariate survival analysis for inclusion in the Cox proportional hazards model in entry strategies. The results of the study are listed in Table 5. The only significant independent negative prognostic indicators for RFS were high mitotic index ($HR_{6–10/50\ HPFs\ vs\ 5/50\ HPFs}$ = 1.896, 95%CI: 0.518–6.949; $HR_{>10/50\ HPFs\ vs\ 5/50\ HPFs}$ = 6.791, 95%CI: 1.554–29.672; overall P = 0.0365) and low OPNI (HR = 5.852, 95%CI: 1.072–31.964; P = 0.0414) (Figure 4).

DISCUSSION

More precise risk classification criteria that can be used to predict the postoperative prognosis of patients with GIST - especially criteria that can be simply and feasibly measured and calculated by using clinicopathological data - have been required. Herein, we evaluated the prognostic value of the OPNI for patients with GISTs, and our analyses demonstrated that the OPNI was an independent prognostic marker that was associated with the GIST primary site, tumor size, mitotic index, tumor rupture, necrosis, and modified NIH risk classification in our patient series.

The AFIP criteria[7] and the modified NIH consensus criteria[8], which encompass the four factors tumor diameter, mitotic index, location, and rupture of tumor, are the most widely used criteria to evaluate the post-surgery or intra-surgery risk in GIST cases, and the accuracy of these four factors is generally similar for prognosis. A nomogram that can be used to estimate the RFS at 2 and 5 years after surgery for a primary GIST was developed by the Memorial Sloan-Kettering Cancer Center sarcoma team[22]. And more recently, a novel prognostic contour map was generated using the pooled data of 920 GIST patients who received no adjuvant therapy[21].

The OPNI, as a nutrition index, was initially established by Onodera and his colleagues in 1984. The OPNI has been used to divide patients with higher and lower OPNI values for prognostic evaluation, and it was reported that the prognoses of the patients with lower OPNI values were significantly worse than those of the patients with higher OPNI values[22]. Similar results regarding gastric carcinoma have also been reported[23]. In the present study, however, the cut-off value of the PNI was shown to be 51.30 in the ROC analysis. Our further analysis demonstrated that a lower OPNI was associated with the primary tumor site, tumor size, mitotic index, tumor rupture, necrosis, and the modified NIH risk classification. In the multivariate survival analysis, the OPNI was an independent prognostic indicator for GISTs.

A low OPNI may be the result of hypoproteinemia and/or lymphopenia, which can be explained by several potential phenomena: (1) The nutritional supplementation of branched-chain amino acids can improve a patient's hypoproteinemia and reduce tumor recurrence[24]; and (2) Lymphocytes have an important role in the host immune

Table 5 Multivariate analysis [Cox regression analysis (Enter method)] for recurrence-free survival

Factor	Hazard ratio	95%CI	*P* value
Primary tumor site			0.0878
Gastric	1.000	-	-
Non-gastric	2.641	0.866-8.053	-
Tumor size (cm)			0.4749
≤ 2.0	1.000	-	-
2.1-5.0	1.318	0.006-292.720	0.9201
5.1-10.0	1.612	0.006-445.888	0.8678
> 10.0	4.765	0.015-1515.961	0.5953
Mitotic index (/50 HPFs)			0.0365[1]
≤ 5	1.000	-	-
6-10	1.896	0.518-6.949	0.3341
>10	6.791	1.554-29.672	0.0109[1]
Tumor rupture			0.5202
No	1.000	-	-
Yes	0.589	0.117-2.957	-
NIH risk classification			0.9763
Very low risk	1.000	-	-
Low risk	0.283	0.001-64.779	0.6491
Intermediate risk	0.282	0.001-91.515	0.6681
High risk	0.277	0.001-101.508	0.6702
NLR			0.7613
< 4.34	1.000	-	-
≥ 4.34	0.838	0.268-2.620	-
PLR			0.6958
< 220.76	1.000	-	-
≥ 220.76	1.259	0.397-3.995	-
OPNI			0.0414[1]
≥ 51.30	1.000	-	-
< 51.30	5.852	1.072-31.964	-

[1]With statistical significance. NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; OPNI: Onodera's Prognostic Nutritional Index.

response, counteracting tumor formation and progression[25].

Because OPNI consists of albumin and lymphocyte count levels, low OPNI means hypoalbuminemia and lymphocytopenia, which may contribute to tumor development and progression[24]. Lower albumin levels in patients with lower OPNI reflect malnutrition and impaired protein synthesis ability especially those with large tumor size and high mitotic index. Lymphocytes have an important role in the host immune response, counteracting tumor formation and progression[25]. The present study also examined lymphocyte-related markers, such as NLR and PLR, but these markers were not identified as independent prognostic factors in the multivariate analysis. OPNI predicted the prognosis of GIST patients more precisely than NLR and PLR because the OPNI contains albumin and lymphocyte levels as nutritional and immune factors.

Our study has several limitations to address. This was a single-center retrospective study, and a multicenter study is needed to expand the sample size to compensate for this deficiency. The best cut-off value was determined by the highest Youden index by

plotting the ROC curve, but it is still unclear what cut-off value is the best for the clinical diagnosis of GISTs. An exploration of the best cut-off value and studies of its intrinsic molecular mechanism are future research topics.

CONCLUSION

In conclusion, our analyses demonstrated an association between immunoinflammatory and nutritional factors and the recurrence-free survival and clinicopathological features of patients with primary GISTs. The OPNI was shown to be an independent indicator for progression-free survival in GISTs, and it may be a valuable parameter for predicting a tumor's biological behavior using peripheral blood samples.

ARTICLE HIGHLIGHTS

Research background

Prognostic markers have gained considerable attention in gastrointestinal stromal tumors (GISTs).

Research motivation

To improve the prognostic prediction of GISTs, we designed this study.

Research objectives

We conducted the first investigation of the prognostic value of Onodera's Prognostic Nutritional Index (OPNI) for GISTs.

Research methods

In this study, the recurrence-free survival, and the receiver operator characteristic analysis of neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), OPNI, and Ki-67 index, and the correlation between tumor size and NLR, PLR, OPNI and Ki-67 index were detected.

Research results

Univariate and multivariate analyses both identified the OPNI as an independent prognostic marker.

Research conclusions

The preoperative OPNI could be a prognostic marker for GISTs.

Research perspectives

We hope that we could find a valuable parameter for predicting the prognosis of GISTs using peripheral blood samples.

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ORIGINAL ARTICLE

Retrospective Study

Utility of preoperative systemic inflammatory biomarkers in predicting postoperative complications after pancreaticoduodenectomy: Literature review and single center experience

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Abstract

BACKGROUND

The role of preoperative inflammatory biomarkers (PIBs) in predicting postoperative morbidity has been assessed in colorectal and otorhinolaryngeal surgery. However, data regarding the role that preoperative inflammatory biomarkers have on morbidity after pancreaticoduodenectomiy (PD) are less consistent.

AIM

To assess the utility of PIBs in predicting postoperative complications after pancreaticoduodenectomy.

METHODS

A database of 317 consecutive pancreaticoduodenectomies performed from April

informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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2003 to November 2018 has been retrospectively analyzed. Data regarding preoperative neutrophil-to-lymphocyte ratio (NLR), derived NLR and C-reactive protein (CRP), and postoperative complications of 238 cases have been evaluated. Exclusion criteria were: age < 18-years-old, previous neoadjuvant treatment, absence of data about PIBs, concomitant hematological disorders, and presence of active infections at the moment of the surgery. PIBs were compared using Mann-Whitney's test and receiver operating characteristic (ROC) analysis was performed to define the cutoffs. The positive predictive value (PPV) was computed to evaluate the probability to develop complication. *P*-values < 0.05 were considered statistically significant.

RESULTS

According to the literature findings, only four papers have been published reporting the relation between the inflammatory biomarkers and PD postoperative morbidity. A combination of preoperative and postoperative inflammatory biomarkers in predicting complications after PD and the utility of preoperative NLR in the development of postoperative pancreatic fistula (POPF) have been reported. The combination of PIBs and postoperative day-1 drains amylase has been reported to predict the incidence of POPF. According to our results, CRP values were significantly different between patients who had/did not have postoperative complications and abdominal collections ($P < 0.05$). Notably, patients with preoperative CRP > 8.81 mg/dL were at higher risk of both overall complications and abdominal collections (respectively $P = 0.0037$, PPV = 0.95, negative predictive value [NPV] = 0.27 and $P = 0.016$, PPV = 0.59, NPV = 0.68). Preoperative derived neutrophil-to-lymphocyte ratio (dNLR) (cut off > 1.47) was also a predictor of abdominal collection ($P = 0.021$, PPV = 0.48, NPV = 0.71). Combining CRP and dNLR, PPV increased to 0.67. NLR (cut off > 1.65) was significantly associated with postoperative hemorrhage ($P = 0.016$, PPV = 0.17, NPV = 0.98).

CONCLUSION

PIBs may predict complications after PD. During postoperative care, PIB levels could influence decisions regarding the timing of drains removal and the selection of patients who might benefit from second level diagnostic exams.

Key Words: Preoperative inflammatory markers; Pancreaticoduodenectomy; Complications; Neutrophil-to-lymphocyte ratio; Derived neutrophil-to-lymphocyte ratio

Core Tip: Inflammatory markers are involved in cancer's pathogenesis and growth. In addition, their role in predicting post-operative complications in colorectal and otorhinolaryngeal surgery has been reported. Here, the role of preoperative inflammatory biomarkers in predicting postoperative complication after pancreaticoduodenectomy has been investigated.

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INTRODUCTION

Periampullary tumors include cancers from the pancreatic head, distal bile duct, ampulla of Vater, and duodenum[1].Pancreaticoduodenectomy (PD) represents the gold standard of treatment for these malignancies. Even though its postoperative

mortality is drastically decreased in high-volume centers, postoperative morbidity remains high, affecting approximately 30%-45% of patients[2,3].

The most common complications of PD are postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), postoperative hemorrhage (PPH), biliary fistula (BF), abdominal collections, and infections[4-6]. POPF is considered the "queen" of these complications since it is often the leading cause of other complications[7].

While factors, such as the presence of a soft pancreas, the small size of the Wirsung, common bile duct stumps, and previous biliary drainage, have been recognized to increase the risk of PD morbidity[8,9], less is known about the role that systemic inflammatory factors play in the development of complications after PD.

Currently, inflammatory biomarkers [*e.g.*, C-reactive protein (CRP), neutrophil count, Glasgow Prognostic Score (GPS), and neutrophil-to-lymphocyte ratio (NLR)], are proven to have an independent prognostic role in the prediction of cancer-specific and postsurgical survival of different malignancies, including periampullary malignancies[10-12].Moreover, their efficacy in predicting postoperative morbidity in colorectal, esophageal, and otorhinolaryngeal surgery has been assessed. Specifically, NLR > 3 is associated with anastomotic failure in colorectal surgery, while decreased levels of albumin and lymphocytes are associated with a higher incidence of complications after esophageal surgery and NLR < 3.5 and platelet-lymphocyte ratio (PLR) < 160 are correlated with impaired wound healing in head and neck surgery[13-16].

Data regarding the role that preoperative inflammatory biomarkers (PIBs) have on morbidity after PD are less consistent to the best of our knowledge[17].This study aimed to carry out a literature review to analyze and report the role that PIBs have on developing complications after PD. Personal monocentric experience focused on this topic has also been reported.

MATERIALS AND METHODS

Review methods

Literature research was performed, and articles about randomized clinical trials, observational cohort studies, systematic reviews, and original articles focusing on the role of PIBs on postoperative complications after PD were all considered. Only articles written in English with available full text have been analyzed. The last literature review was carried out on December 1st, 2020.

Materials and methods for the center experience analysis

A database of consecutive PDs performed at the Department of General Surgery of the University Campus Bio-Medico of Rome from April 2003 to November 2018 was retrospectively analyzed. The local Ethical Committee approved the study (28/19 OSS ComEt CBM). Inclusion criteria were: Adult patients (≥ 18-years-old) affected by periampullary tumor who underwent PD. Exclusion criteria were: Age < 18-years-old, previous neoadjuvant treatment, absence of data about PIBs, concomitant hematological disorders, or presence of active infections at the moment of the surgery (Figure 1).

Data regarding preoperative NLR, derived neutrophil-to-lymphocyte ratio (dNLR), platelet-to-lymphocyte ratio (PLR), C-reactive protein (CRP), and postoperative complications have been analyzed. NLR, dNLR and PLR were defined and calculated as previously reported: NLR (neutrophil/Lymphocyte), dNLR (neutrophil count/(White blood cell count- Neutrophil count)), PLR (Platelet count/Lymphocyte count)[18].

CRP was measured by the Dimension Vista® 500 System (Siemens Healthcare Diagnostics, Germany).

POPF, DGE, and PPH have been defined according to the internationally recognized standard[4-6].

Statistical analysis

Continuous variables (Plasmatic levels of NLR, dNLR, PLR, CRP) have been reported as median (95%CI, confidence intervals) according to their distributions, and differences have been tested with the Mann-Whitney's test due to data distribution (*i.e.* non-parametric according to the Shapiro-Wilks test for Normality). Categorical variables have been reported as numbers and relative frequencies, and differences across groups were tested by the chi-squared test. Receiver operating characteristic (ROC) analysis was performed among independent variables to define the cutoff point for plasma NLR, dNLR, PLR, CRP values to predict postoperative complications. Odds

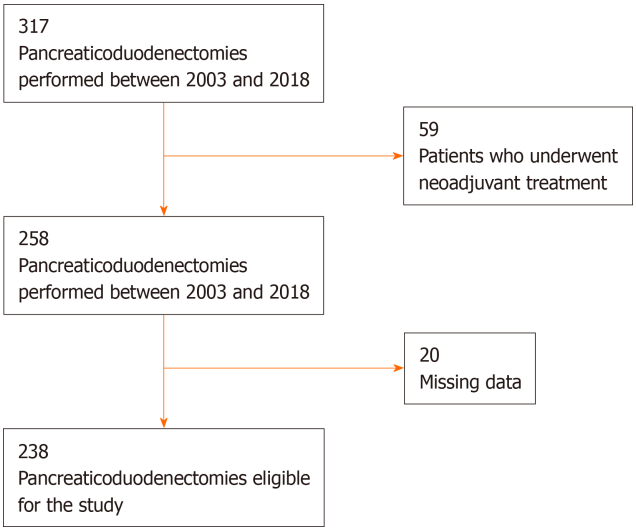

Figure 1 Flow diagram of patients' selection.

ratios (OR) and their 95%CI were calculated to evaluate the association between patients who underwent neoadjuvant treatment and postoperative complications. Chi-square and Fisher's exact test was used to confirm the statistical significance. All *P* values < 0.05 were considered statistically significant. Data have been analyzed using Med-Calc 18.11.3 statistical package (MedCalc Software, Mariakerke, Belgium).

RESULTS

To the best of our knowledge, only four papers investigated the role of PIBs, alone or in combination with postoperative inflammatory markers or other clinical parameters, on post-PD morbidity. Solaini *et al*[17] and, more recently, Zhang *et al*[19] investigated the combination of preoperative and postoperative inflammatory biomarkers in predicting complications after PD. Kumamoto *et al*[20] reported the role of preoperative NLR in the development of POPF, while Caputo *et al*[21] highlighted the utility of combining PIBs together with postoperative day 1-drains amylase (POD1-da) to predict the incidence of POPF.

Specifically, Solaini and colleagues, using a cohort of 378 patients who underwent to PD, demonstrated the role of preoperative white blood cell count (cut-off > 8.5 × 10^3 /mL, AUC 0.591, 95%CI: 10.53-0.64, *P* = 0.02), postoperative day 2 NLR (cut-off > 12.3, AUC 0.605, 95%CI: 0.55-0.66, *P* = 0.005) and CRP dosed on postoperative day 4 (cut-off > 188 mg/L, AUC 0.645, 95%CI: 0.58-0.7, *P* = 0.004) in predicting postoperative complications. The authors reported a higher accuracy and positive predictive value (PPV) (76.8% and 71.4%) combining the above-mentioned inflammatory markers. Nonetheless, according to this study's findings, increased NLR on postoperative day 2 and CRP > 272 mg/L on postoperative day 3 were significantly associated with POPF.

Zhang *et al*[19] analyzed the development of sepsis in 31 out of 138 PDs. The Authors studied inflammatory markers (IL-6, IL-2, IL-1, IL-10, tumor necrosis factor (TNF), and CRP) preoperatively and in POD1 in those who developed the complication and compared marker's levels with the group without sepsis. Preoperative IL-6, at the cutoff value of 5.26 pg/mL, resulted in an independent risk factor for sepsis, and was the only PIB significantly associated with a 3-fold higher risk of developing sepsis after PD (OR = 3.31, 95%CI :1.37-12.89, *P* = 0.044).

Kumamoto *et al*[20] reported the association between PIBs and post-PD Clavien-Dindo grade ≥ III complications. On a series of 84 PDs, 39 (46%) patients developed major postoperative complications. Higher neutrophil count (*P* < 0.05) and NLR (*P* < 0.01) were significantly able to predict complications as well as body mass index (BMI) (*P* < 0.01) did. The optimal cutoff values detected were neutrophil count 2.727/μL, NLR > 2.0 and BMI > 23.0 kg/m^2. Using multivariate logistic regression analysis, independent risk factors for major postoperative complications were NLR > 2.0 (OR = 6.77, 95.0%CI: 2.4421.13; *P* < 0.001) and BMI > 23.0 kg/m^2 (OR = 3.83, 95.0%CI: 1.3511.83; *P* = 0.011).

In Caputo *et al*[3,18,21], even though POD1-da levels were confirmed to be the main factor able to predict the risk of POPF, the combinations of PIBs with POD1-da levels allowed to improve POPF's PPV. Specifically, NLR > 3.2, dNLR > 3 and PLR > 137 increased up to 89% the POD1-da levels PPV for POPF development.

Centre experience results

Baseline demographic characteristics of the 238 PDs included in the study are reported in Table 1. The median age was 68 years (interquartile range [IQR] = 61-75 years). Male patients represented 57% of the cases and the median BMI was 24.1 kg/m^2 (IQR = 22.23-27.71 kg/m^2). At least one postoperative complication was observed in 78% of the cases. The main postoperative complications were: POPF 50.8% (121/238), DGE 30.6% (73/238), PPH 14.2% (34/238), abdominal collection 39.5% (94/238), and biliary fistula 14.2% (34/238). A biochemical leak occurred in 30.6% of POPF, while clinically relevant Grade B-C fistula was detected in 20% of these patients. PIBs values are listed in Table 2.

According to the Mann-Whitney's test, no relationship between PIBs and POPF occurrence was found. On the contrary, significant associations have been found between preoperative CRP and overall complications (P = 0.01) and between preoperative NLR and PPH (P = 0.03). Moreover, preoperative dNLR and CRP were significantly associated with abdominal collection (P = 0.026 and P = 0.017, respectively).

By ROC curve analysis, optimal cutoffs for PIBs and post-PD complications have been calculated. In detail, preoperative NLR at the cut off of > 1.65 was significantly associated with PPH (P = 0.016, PPV = 0.17, negative predictive value [NPV] = 0.98) (Figure 2A).

Preoperative CRP levels > 8.81 mg/dL have been found associated with higher rate of overall postoperative complications (P = 0.0037, PPV = 0.95, NPV = 0.27) and abdominal collections (P = 0.016, PPV = 0.59, NPV = 0.68) (Figure 3, Table 3). Preoperative levels of dNLR at the cut off of > 1.47 resulted significantly associated with abdominal collections (P = 0.021, PPV = 0.48, NPV = 0.71) (Figure 2B). Combining CRP and dNLR, PPV increased to 0.67.

DISCUSSION

Different studies demonstrated the role that inflammation plays in carcinogenesis. For example, the role of inflammation in pancreatic cancer patients has been investigated as well, and the association between inflammatory biomarkers and the prognosis of these patients was reported[22]. Cytokines and proangiogenic factors, whose production is regulated by white blood cells and platelets, have been mainly investigated[23].

The role that serum inflammatory biomarkers can play in the development of postoperative complications has been reported for surgery performed for different solid tumors. However, there is still a lack of data about the role that inflammation can play in developing complications after PD. Nonetheless, most of the literature on this topic focuses on inflammatory biomarkers dosed and calculated postoperatively[24].

The papers found in our literature research mainly reported data underlining the relationship between pre-operative and/or postoperative inflammatory markers and oncological outcomes, such as disease-free survival and overall survival in patients affected by periampullary tumors. Postoperative complications after PD were mainly related to postoperative inflammatory markers instead of PIBs.

According to Solaini *et al*[17], the combination of preoperative and postoperative levels of white blood cells, NLR, and CRP predict the development of postoperative complications after PD with particular regard to POPF. The association between preoperative NLR and the higher risk of POPF has also been reported by Kumamoto *et al*[20]. Zhang *et al*[19] has proposed preoperative IL-6 and postoperative PCT and CRP levels in a model to estimate the risk of sepsis after PD. Therefore, on this basis and considering the strong association between IL-6 and intestinal lipopolysaccharide, the authors suggested using preoperative immunonutrition to decrease the levels of IL-6 and, consequently, the risk of sepsis[21].

Even though POD1-da levels still represent the main indicator of the risk of POPF when compared to PIBs as reported by Caputo, the combination of preoperative NLR, NLR, and PLR with POD1-da levels was effective in predicting the increased risk of grade C POPF[21].

Table 1 Demographic characteristics of the study population median value and postsurgical infections characteristics

Demographic characteristics (*n* = 238) and postoperative complications	
Age	68 (59-74)
Median (IQR)	
Sex, *n* (%)	
Male	141 (59.2)
Female	97 (40.8)
BMI	
Median (kg/m^2)	24.9 (22.2-27.7)
Postoperative complications, *n* (%)	
Overall complications	191 (80.2)
Pancreatic fistula	121(50.8)
Pancreatic fistula Grade A	73 (30.6)
Pancreatic fistula Grade B-C	48 (20)
Hemorrhage	34 (14.2)
DGE	73 (30.6)
Abdominal collection	94 (39.5)
Biliary fistula	35 (14.7)
Sepsis	21 (8.8)
Infection of wound	23 (9.6)

BMI: Body mass index; DGE: Delayed gastric emptying; IQR: Interquartile range, 25th percentile to 75th percentile.

Table 2 Median levels of pre-operative inflammatory biomarkers

Preoperative inflammatory biomarkers	Median value
NLR (IQR)	227 (164-306)
dNLR (IQR)	1635 (117-21)
CRP (IQR)	53 mg/L (25-1633)

CRP: C-reactive protein; dNLR: Derived neutrophil-to-lymphocyte ratio; IQR: Interquartile range, 25th percentile to 75th percentile; NLR: Neutrophil-to-lymphocyte ratio.

Table 3 Statistical significance of preoperative inflammatory biomarkers

	Overall complications	Abdominal collection	PPH
NLR > 1.65	Ns	Ns	*P* = 0.016
dNLR > 1.47	Ns	*P* = 0.021	
CRP > 881 mg/L	*P* = 0.0037	*P* = 0.016	Ns

CRP: C-reactive protein; dNLR: Derived neutrophil-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio; Ns: Not significant; PPH: Postoperative hemorrhage.

In our present study, PIBs such as CRP, NLR, and dNLR was significantly associated with the development of surgical complications after PD, particularly abdominal collections and postoperative bleeding. Specifically, higher CRP levels significantly predict overall complications, while lower values of NLR and dNLR were associated with a lower risk of PPH and abdominal collection, respectively.

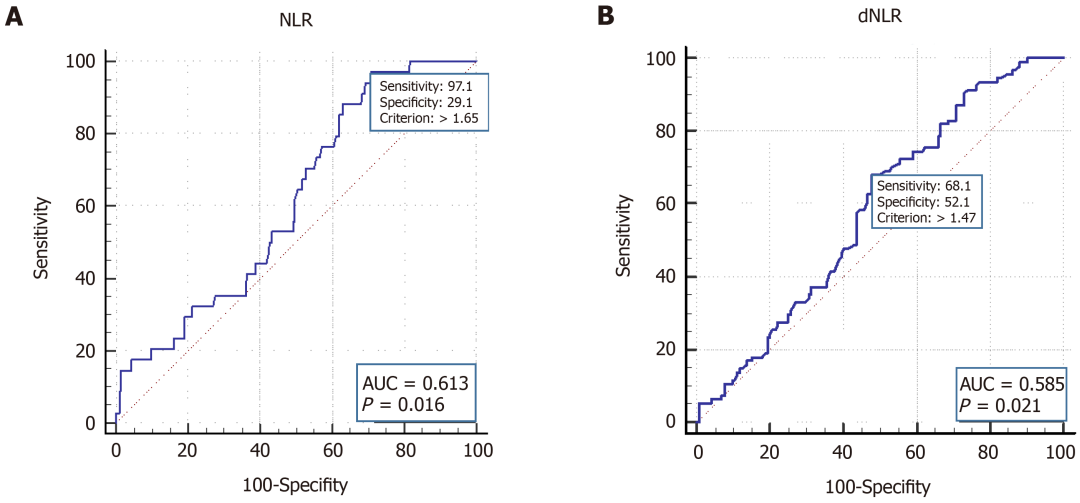

Figure 2 Receiver operating characteristic curves of preoperative neutrophil-to-lymphocyte ratio in postoperative hemorrhage and derived neutrophil-to-lymphocyte ratio in abdominal collections. A: Preoperative neutrophil-to-lymphocyte ratio in postoperative hemorrhage; B: Derived neutrophil-to-lymphocyte ratio in abdominal collections. AUC: Area under the curve; d-NLR: Derived neutrophil-to-lymphocyte ratio; NLR: Neutrophil-to-lymphocyte ratio;.

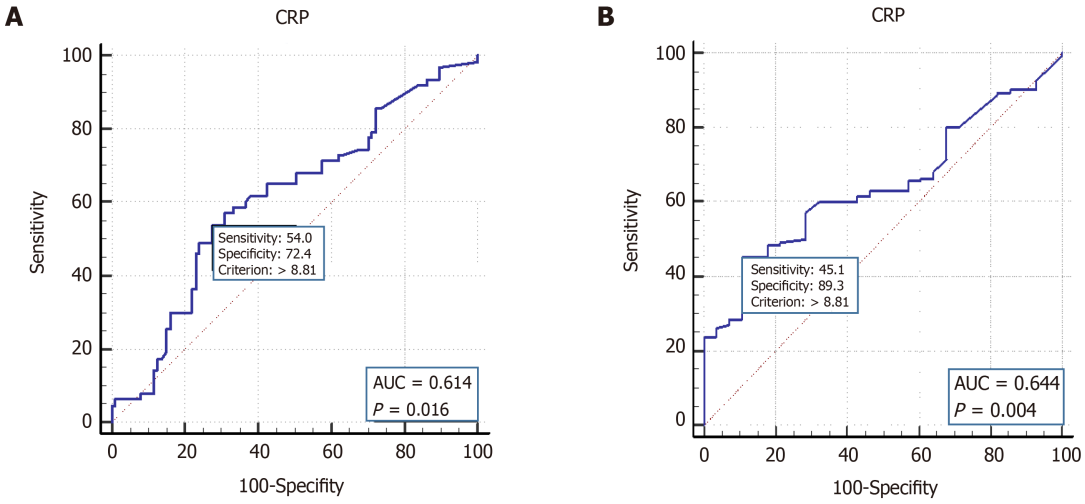

Figure 3 Receiver operating characteristic curves of preoperative C-reactive protein in abdominal collections and overall complications. A: C-reactive protein in abdominal collections; B: Overall complications. AUC: Area under the curve; CRP: C-reactive protein.

These findings are in part in agreement with Uchida and colleagues, who reported postoperative CRP's role in the prediction of the hemorrhage post PD. According to Uchida, patients with high CRP in POD3 are at higher risk of PPH since at higher risk of grade C POPF[25,26].From the literature and our findings, it is possible to establish the role of PIBs in predicting the development of complications after PD. However, as already highlighted by other authors, the rationale behind the association between preoperative inflammation and PD postoperative complications has yet to be fully defined.

Elevated NLR and PLR can distinguish spontaneous subarachnoid hemorrhage from acute headache[27] and were associated with gastrointestinal bleeding in patients with cerebral hemorrhage[28].

Moreover, an increased inflammatory state would generate a cytokine storm with consequent microvascular alterations responsible for impaired wound and anastomotic healing[29].

Nonetheless, according to Nakanishi, the systemic inflammatory response determines a dysfunction of the endothelium that loses its ability to produce prostacyclin and nitric oxide with a consequent decrease of dilatation and antithrombotic function inhibiting wound healing[30]

Based on what was highlighted in the literature and our findings, the routine use of anti-inflammatory drugs could be considered in patients with altered inflammatory status before PD, just as was done to prevent pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP)[31,32].

The present work is not without limitations. Our experience is retrospective, and there is a lack of direct evidence confirming the role of preoperative inflammatory status in PD complications development. Therefore, as already suggested by others, these findings must be interpreted with caution.

Our study's strengths are the homogeneity of the series; since we excluded patients who underwent neoadjuvant treatments that may have altered the inflammatory status and the analysis of only preoperative inflammatory biomarkers allowing to exclude the effect of the surgical trauma and of not yet clinically evident complications.

CONCLUSION

Although the role of inflammatory biomarkers has been assessed in predicting oncological outcomes of patients affected by periampullary tumors who underwent PD, the efficacy of PIBs in predicting postoperative morbidity has been marginally investigated. Despite the limited experiences published in the literature, the available data and results of our experience show that preoperative NLR, d-NLR, and CRP could predict the risk of complications after PD with particular regard to abdominal collections and hemorrhage. On this basis, PIBs may represent simple, cheap, and valuable tools to predict the risk of complications after PD and promote early interventions to reduce postoperative morbidity.

ARTICLE HIGHLIGHTS

Research background

Role of preoperative inflammatory biomarkers (PIBs) in predicting postoperative morbidity has been widely assessed in colorectal and otorhinolaryngeal surgery.

Research motivation

To date, little is known about the role of PIBs in predicting pancreaticoduodenectomy (PD) postoperative complications.

Research objectives

To exploit the utility of PIBs in predicting the postoperative course after PD.

Research methods

A literature research and a retrospective analysis of data from a prospective collected database of 317 consecutive pancreaticoduodenectomies have been performed. Data regarding preoperative neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR), platelet-lymphocyte ratio, C-reactive protein (CRP) and postoperative complications of 238 cases have been analyzed. PIBs were compared using MannWhitney's test and receiver operating characteristic (ROC) analysis was performed to define the cutoffs.

Research results

Patients with preoperative CRP > 8.81 mg/dL were at higher risk of both overall complications and abdominal collections (respectively $P = 0.0037$, PPV = 0.95, NPV = 0.27 and $P = 0.016$, PPV = 0.59, NPV = 0.68). _Preoperative dNLR (cut off > 1.47) was also predictor of abdominal collection ($P = 0.021$, PPV = 0.48, NPV = 0.71). Combining CRP and dNLR, PPV increased to 0.67. NLR (cut off > 1.65) was significantly associated with postoperative hemorrhage ($P = 0.016$, PPV = 0.17, NPV = 0.98).

Research conclusions

PIBS are cost-effective tools that may predict complications after pancreaticoduodenectomy and could be useful in the postoperative management.

Research perspectives

In clinical practice, PIBs could be used during the postoperative course of PD decisions

regarding timing of drains removal and selection of patients who can benefit from second level diagnostic exams (*e.g.*, CT scan).

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ORIGINAL ARTICLE

Retrospective Study

Low serum albumin may predict poor efficacy in patients with perforated peptic ulcer treated nonoperatively

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Abstract

BACKGROUND

Nonoperative management (NOM) is a promising therapeutic modality for patients with perforated peptic ulcer (PPU). However, the risk factors for poor efficacy and adverse events of NOM are a concern.

AIM

To investigate the factors predictive of poor efficacy and adverse events in patients with PPU treated by NOM.

METHODS

This retrospective case-control study enrolled 272 patients who were diagnosed with PPU and initially managed nonoperatively from January 2014 to December 2018. Of these 272 patients, 50 converted to emergency surgery due to a lack of improvement (surgical group) and 222 patients were included in the NOM group. The clinical data of these patients were collected. Baseline patient characteristics and adverse outcomes were compared between the two groups. Logistic regression analysis and receiver operating characteristic curve analyses were conducted to investigate the factors predictive of poor efficacy of NOM and adverse outcomes in patients with PPU.

RESULTS

Adverse outcomes were observed in 71 patients (32.0%). Multivariate analyses revealed that low serum albumin level was an independent predictor for poor efficacy of NOM and adverse outcomes in patients with PPU.

CONCLUSION

Low serum albumin level may be used as an indicator to help predict the poor efficacy of NOM and adverse outcomes, and can be used for risk stratification in patients with PPU.

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Core Tip: Risk factors are associated with a poor efficacy in patients with perforated peptic ulcer (PPU) treated by nonoperative management (NOM), and can be used for risk stratification in patients with PPU. Serum albumin level is an important predictor of the poor efficacy of NOM.

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INTRODUCTION

Perforation is a serious complication of peptic ulcer disease (PUD) with a morbidity rate between 6.2% and 27%[1-3]. Patients with perforated peptic ulcer (PPU) tend to be young male smokers residing in developing countries, while patients in developed countries tend to be elderly with associated use of steroid or non-steroidal anti-inflammatory drugs and multiple comorbidities[4]. The incidence of PPU has significantly decreased worldwide, especially in high-income countries[5], and only 2%-14% of PUD patients present with an acute abdominal perforation[6]. The reason for this overall progress is the introduction of new drugs (H2 receptor antagonists and proton pump inhibitors [PPIs]) and the diagnosis and management of *Helicobacter pylori* infection[4,7,8].

PPU is still one of the most common causes of abdominal pain in the emergency department and requires prompt diagnosis and treatment. Nonoperative treatment should be considered in patients with uncomplicated PPU, which prevents surgery and its resultant morbidity. Studies have demonstrated that approximately 40%-80% of patients with PPU will heal spontaneously, and most patients with uncomplicated PPU can benefit from nonoperative management (NOM)[5,9-11]. Prognostic factors that can enhance recovery, and reduce morbidity and mortality should be identified and investigated further.

The aim of this study was to evaluate the relationship between risk factors and clinical outcome, and identify which factors can be used for risk stratification in patients with PPU.

MATERIALS AND METHODS

Study population

This was a single-center retrospective case-control study. Patients who were diagnosed with PPU by computed tomography (CT) scan and treated by NOM on admission between January 2014 and December 2018 at Liaocheng People's Hospital (Shandong, China) were enrolled in the study. The following patients were considered suitable for NOM: Patients with an empty stomach at the time of perforation and who were in good general condition, patients with tolerable abdominal pain, limited peritonitis with no manifestations of shock on admission, or a CT scan of the abdomen revealed that free air or liquid was limited to 1-2 zones. Those who were accepted for emergency surgery on admission or had suspected gastric cancer were excluded. Patients with severe liver disease or renal disease were also excluded. The patients were divided into two groups based on whether vital parameters are normal and the findings of peritonitis or septic shock: The nonoperative management group (NOM group) and the surgical management group (surgical group). This study was approved by the Ethics Committee of Liaocheng People's Hospital. As it was a retrospective

study, signed informed consent was not necessary.

Data collection

All patient data were obtained from electronic charts. Demographic data such as gender and age were collected. A medical history of hypertension, diabetes mellitus, and smoking status was recorded. Clinical variables such as duration of abdominal pain, physical examinations, and vital signs were evaluated. Laboratory variables including leukocyte count, hemoglobin, serum albumin, procalcitonin (PCT) concentration, and C-reactive protein (CRP) were collected.

Nonoperative management

Nonoperative treatment of patients with PPU consisted of fasting, hemodynamic resuscitation, nasogastric suction, appropriate antibiotics, and antisecretory therapy with PPIs and somatostatin and repeated clinical assessment. If there was no significant improvement in the patient's condition within 12 h, operative treatment was considered. Clinical improvement was defined as a composition of improvements in vital signs and abdominal signs. They were managed by an experienced surgeon. Water-soluble contrast imaging was performed in all patients to determine whether the perforation had sealed. Gastroscopy and *Helicobacter pylori* examination were recommended within 1 mo after the patient had completely recovered.

Statistical analyses

Continuous variables are expressed as the mean ± SD or median (interquartile range) as appropriate. Categorical variables are expressed as the number and percentage. The Student's *t*-test or Mann–Whitney *U* test was used to compare the continuous data as appropriate. The χ^2 or Fisher's exact test was used to compare the categorical data. Logistic regression analyses were used to identify clinical data, which were independent predictors for clinical failure of NOM or adverse outcomes in patients with PPU. Unadjusted variables with a P value < 0.05 in the univariate analyses were subsequently included in the multivariate logistic regression model. To assess the predictive ability of clinical data, a receiver operating characteristic (ROC) curve was performed and the area under the curve (AUC) was calculated. All statistical tests were two-tailed, and differences were considered significant when $P < 0.05$.

RESULTS

Baseline characteristics of the study patients

Between January 2014 and December 2018, 306 patients with PPU were admitted to the Gastrointestinal Surgery Department of our hospital. A total of 272 patients with PPU who were initially managed nonoperatively were included in the analysis, and 50 of them were converted to surgery. Finally, 222 patients received nonoperative treatment. The baseline characteristics of the patients are summarized in Table 1. The proportion of patients older than 70 years, with pain duration prior to admission ≥ 12 h and body temperature ≥ 38 °C was higher in the surgical group than in the NOM group. The levels of PCT and CRP and the proportion of patients with serum albumin < 30 g/L were higher in the surgical group than in the NOM group.

Comparison of clinical adverse outcomes between the surgical group and NOM group

In this study, the incidence of adverse outcomes was 30% in the surgical group and 25.2% in the NOM group; there were no significant differences between the two groups ($P = 0.487$). However, the length of hospital stay in the surgical group was longer than that in the NOM group ($P < 0.001$; Table 2).

Logistic regression analyses of predictors of poor efficacy of NOM and adverse outcomes in patients with PPU

For the prediction of poor efficacy of NOM, variables including age ≥ 70 years, pain duration prior to admission ≥ 12 h, and serum albumin < 30 g/L were entered into the multivariate logistic regression model. The results showed that serum albumin < 30 g/L was an independent indicator for poor efficacy of NOM (adjusted odds ratio [OR]: 5.073, 95%CI: 2.527-10.184, $P < 0.001$). In addition, pain duration prior to admission ≥ 12 h independently predicted poor efficacy of NOM (Table 3).

Table 1 Comparison of baseline patient characteristics between the two groups, *n* (%)

Variables	Surgical group	NOM group	*P* value
	n = 50	*n* = 222	
Age in yr, average (median)	66.5 (15.8)	58.0 (21.3)	< 0.001
≥ 70 yr	19 (38.0)	44 (19.8)	0.006
Male, *n* (%)	32 (64.0)	162 (73.0)	0.205
Hypertension	16 (32.0)	45 (20.3)	0.072
DM	11 (22.0)	28 (12.6)	0.087
Smoking	26 (52.0)	83 (37.4)	0.057
Alcohol consumption	18 (36.0)	56 (25.2)	0.122
NSAIDs use	16 (32.0)	50 (22.5)	0.158
Pain duration prior to admission (median)	8.0 (9.0)	6.0 (6.0)	0.001
≥ 12 h	16 (32.0)	33 (14.9)	0.004
Heart rate (bpm) (median)	92.0 (24.0)	86.0 (18.0)	0.116
Body temperature (C) (median)	36.7 (1.2)	36.7 (0.7)	0.826
≥ 38 C	9 (18.0)	19 (8.6)	0.047
Hemoglobin (g/L)	116.8 22.7	126.5 22.2	0.006
< 90 g/L	7 (14.0)	15 (6.8)	0.090
WBC count (× 10^9/L) (median)	9.5 (6.6)	10.5 (3.3)	0.479
≥ 12 × 10^9/L	18 (36.0)	77 (34.7)	0.860
Procalcitonin (ng/mL) (median)	5.14 (10.03)	0.88 (3.96)	< 0.001
CRP (mg/L) (median)	151.28 (151.16)	68.46 (119.35)	< 0.001
Serum albumin (g/L)	27.5 4.65	33.7 6.79	< 0.001
< 30 g/L	32 (64.0)	54 (24.3)	< 0.001

CRP: C-reactive protein; DM: Diabetes mellitus; NOM: Nonoperative management; NSAIDs: Non-steroidal anti-inflammatory drugs; WBC: White blood cell.

Table 2 Adverse outcomes of patients with perforated peptic ulcer, *n* (%)

Complications	Surgical group, *n* = 50	NOM group, *n* = 222	*P* value
Wound infection	3 (6.0)	0	0.006
Respiratory infection	2 (4.0)	11 (5.0)	1.000
Urinary infection	4 (8.0)	9 (4.1)	0.415
Ascites	3 (6.0)	24 (10.8)	0.304
Pleural effusion	3 (6.0)	7 (3.2)	0.582
Abdominal abscess	0 (0)	5 (2.3)	0.588
Total complications	15 (30)	56 (25.2)	0.487
Length of hospital stay in d	12 (7)	9 (3)	< 0.001

NOM: Nonoperative management.

With regard to adverse outcomes, variables including age ≥ 70 years and serum albumin < 30 g/L were entered into the multivariate logistic regression model. The results showed that serum albumin < 30 g/L was also an independent indicator of adverse outcomes (adjusted OR: 2.945, 95%CI: 1.625-5.339, *P* <0.001) (Table 4). Thus,

Table 3 Logistic regression analysis for determining the independent predictors of poor efficacy of nonoperative management in patients with perforated peptic ulcer

Variable	OR	95%CI	*P* value	Adjusted OR	95%CI	*P* value
Age ≥ 70 yr	2.479	1.282-4.795	0.007	1.278	0.605-2.698	0.521
Male	0.658	0.344-1.260	0.207			
Hypertension	1.851	0.939-3.648	0.075			
Diabetes mellitus	1.954	0.898-4.253	0.091			
Smoking status	1.814	0.978-3.365	0.059			
Alcohol consumption	1.667	0.869-3.201	0.124			
NSAIDs use	1.619	0.826-3.171	0.160			
Pain duration prior to admission ≥ 12 h	2.695	1.339-5.427	0.005	2.495	1.163-5.352	0.019
Heart rate	1.018	0.998-1.037	0.071			
Body temperature ≥ 38 C	2.345	0.991-5.549	0.052			
Hemoglobin < 90 g/L	0.445	0.171-1.157	0.097			
WBC count ≥ 12 × 10^9/L	1.059	0.058-2.009	0.860			
Procalcitonin	1.027	1.000-1.056	0.052			
CRP	1.001	1.000-1.002	0.198			
Serum albumin < 30 g/L	5.331	2.876-10.635	< 0.001	5.073	2.527-10.184	< 0.001

CRP: C-reactive protein; NSAIDs: Non-steroidal anti-inflammatory drugs; PPU: Perforated peptic ulcer; WBC: White blood cell.

Table 4 Logistic regression analysis of predictors of clinical complications in patients with perforated peptic ulcer

Variables	OR	95%CI	*P* value	Adjusted OR	95%CI	*P* value
Age ≥ 70 yr	2.331	1.277-4.254	0.006	1.630	0.853-3.114	0.139
Male	1.390	0.777-2.488	0.268			
Hypertension	1.008	0.528-1.928	0.980			
Diabetes mellitus	1.729	0.842-3.550	0.136			
Smoking status	0.757	0.432-1.328	0.331			
Alcohol consumption	0.970	0.527-1.785	0.922			
NSAIDs use	0.977	0.519-1.839	0.941			
Pain duration prior to admission ≥ 12 h	1.316	0.667-2.594	0.428			
Heart rate	1.005	0.988-1.023	0.568			
Body temperature ≥ 38 C	0.586	0.214-1.606	0.299			
Hemoglobin < 90 g/L	0.590	0.236-1.471	0.257			
WBC count ≥ 12 × 10^9/L	0.787	0.441-1.405	0.418			
Procalcitonin	1.021	0.994-1.048	0.126			
CRP	1.000	0.999-1.001	0.933			
Serum albumin < 30 g/L	3.376	1.917-5.946	< 0.001	2.945	1.625-5.339	< 0.001

CRP: C-reactive protein; NSAIDs: Non-steroidal anti-inflammatory drugs; PPU: Perforated peptic ulcer; WBC: White blood cell.

serum albumin < 30 g/L was an independent risk factor for predicting the poor efficacy of NOM and adverse outcomes.

The performance of serum albumin in predicting the poor efficacy of NOM and adverse outcomes

The ROC curves for serum albumin in predicting poor efficacy of NOM and adverse outcomes are shown in Figure 1. The optimal cut-off value of serum albumin for predicting poor efficacy of NOM was 31.8 g/L, with 63% sensitivity and 82% specificity. The optimal cut-off value of serum albumin for predicting adverse outcomes was 29.9 g/L, with 76% sensitivity and 52% specificity. The AUC values for serum albumin for predicting poor efficacy of NOM and adverse outcomes was (0.774, 95%CI: 0.711–0.836) and (0.649, 95%CI: 0.572–0.727) ($P < 0.001$, respectively).

DISCUSSION

Our prediction models demonstrated the risk factors for poor efficacy of NOM and adverse outcomes in patients with PPU, and the AUC values verified their significance. Accumulating evidence has shown that serum albumin is not only a parameter of nutritional status but also a marker of acute inflammation and is associated with disease severity. Patients in the surgery group represented relatively serious infections. Therefore, the proportion of patients with serum albumin < 30 g/L was higher in the surgical group. Our results showed that serum albumin was an excellent risk predictor, not only for predicting poor efficacy of NOM but also for adverse outcomes. In addition, pain duration prior to admission ≥ 12 h was an independent risk factor for predicting poor efficacy of NOM.

In 1946, Taylor proposed the famous "Taylor method" in the NOM of PPU, and concluded that 28 PPU patients receiving NOM showed a lower mortality rate than patients receiving direct simple closure with an omental patch[12]. The first randomized trial performed by Crofts *et al*[10] revealed that 72% of patients treated by NOM had lower morbidity and mortality compared to the surgical group. Several retrospective studies have reported that the NOM technique has a higher success rate in well-selected patients[13]. Moreover, surgical treatment did not show an advantage with regard to morbidity and mortality compared to NOM[5,9,10]. According to World Society of Emergency Surgery guidelines, patients with PPU were suggested to avoid endoscopic treatment such clipping, fibrin glue sealing, or stenting. This approach needs further validation, as it may not be effective in perforated ulcer cases due to fibrotic tissue with loss of compliance. In our study, approximately 81.6% (222/272) of patients received NOM, and the incidence of non-fatal complications was similar to that for those who converted to surgery. These data are in accordance with previous studies and indicate that NOM is a feasible approach[9,14]. However, NOM for PPU is still controversial and has not been widely adopted. In many hospitals, surgical treatment is the preferred choice, and NOM is just an alternative for patients who are not suitable or unwilling to undergo surgery[6]. This study tried to determine the risk factors that will help clinicians select patients with PPU who will experience poor efficacy. Based on logistic regression analysis, two parameters were significantly correlated with poor efficacy of NOM: serum albumin < 30 g/L and pain duration prior to admission ≥ 12 h. With regard to adverse outcomes, only serum albumin < 30 g/L was an independent risk predictor. Furthermore, the AUC values showed that serum albumin had moderate power in predicting clinical outcomes.

Serum albumin has been used as a diagnostic marker for malnutrition in clinical practice for several years as it can reflect the nutritional status of patients[15]. The current evidence shows that serum albumin is not only a parameter of nutritional status, but also a marker of acute inflammation and is associated with disease severity [16]. In a prospective study including 2465 patients who were admitted to the emergency department, the mortality rate was higher in patients with low levels of serum albumin than those with normal serum albumin levels[17]. A previous study showed that PPU patients with low levels of serum albumin at presentation may predict the need for gastric resection, and elevated serum albumin levels can increase the success rate of NOM[18]. Consistent with a previous study, our findings showed that serum albumin < 30 g/L can predict the need for surgical management in patients with PPU who were initially treated nonoperatively. This study is the first to demonstrate that serum albumin is also an independent risk factor for adverse outcomes in patients with PPU. In patients with perforations, the production of acute phase proteins and inflammatory factors will lead to a further decline in serum albumin. Fluids leak slowly from intravascular to interstitial spaces causing local swelling, which induce difficult healing in patients with low levels of serum albumin. Routine measurement of serum albumin on admission, can be used for risk strati-

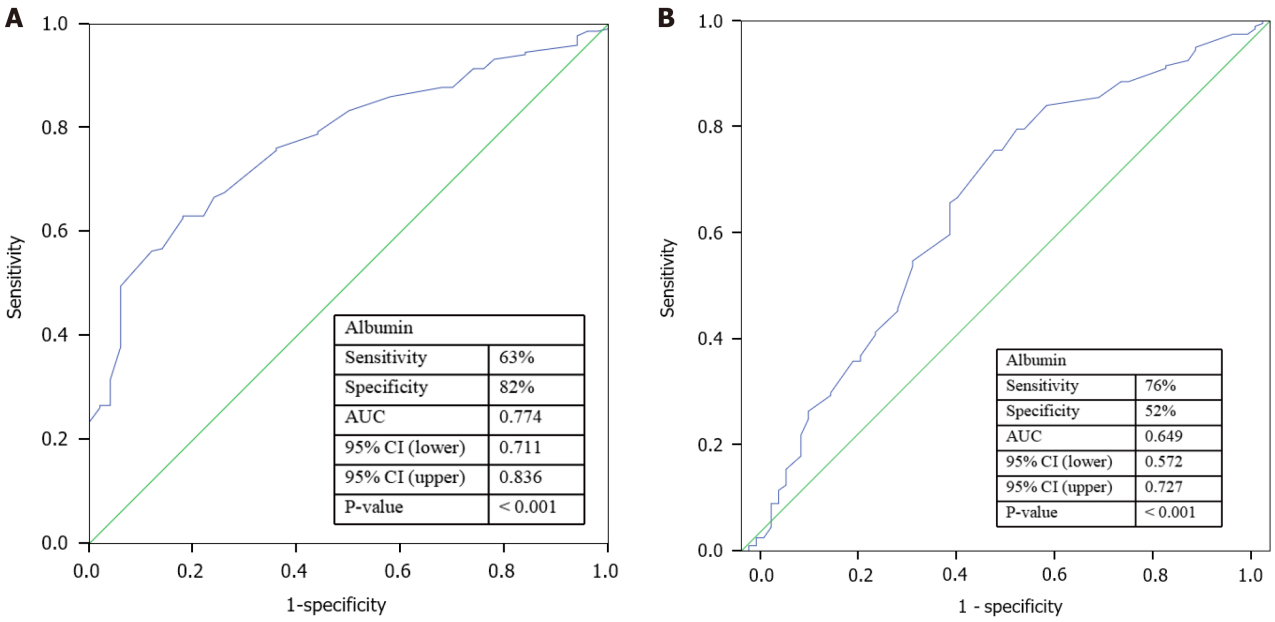

Figure 1 The receiver operating characteristic curves. A: The receiver operating characteristic (ROC) curves for serum albumin in predicting poor efficacy of nonoperative management (NOM); B: The ROC curves for serum albumin in predicting adverse outcomes of NOM. AUC: Area under the curve.

fication in patients with PPU.

When the onset time of abdominal pain prior to admission is more than 12 h, pyrexia, hypotension and abdominal distension with acute circulatory collapse may be evident[19]. In our study, pain duration prior to admission ≥ 12 h was an independent risk factor for predicting poor efficacy of NOM. The data from our study were consistent with those observed in a previous study[20].

In our analysis, 81.6% of cases (222/272) received NOM with a complication rate of 32%, and patients who converted to surgery had a morbidity rate of 30%. In addition, our study also demonstrated that hospital stay was shorter in the NOM group than in the surgical group. Taken together, these findings show that NOM was safe and effective in patients with PPU. In addition, several risk factors have been confirmed to be significantly associated with poor efficacy of NOM and can be used for risk stratification in patients with PPU.

This study had several limitations. First, this was a single-center retrospective study, and the patients were treated by different doctors. Second, relevant indicators were analyzed only when the patient was admitted to the hospital, and the various indicators during hospitalization were not included. Third, there is currently no uniform standard for uncomplicated upper gastrointestinal perforation; thus, biases in patient selection may exist.

CONCLUSION

The use of NOM for PPU may be debated for some time. The advantages of NOM are obvious. It is important to stratify patients into high and low risk on admission. NOM is recommended in patients who are in good general condition with an empty stomach at the time of perforation. Low serum albumin is an independent risk factor that may predict adverse consequences of NOM for PPU.

ARTICLE HIGHLIGHTS

Research background

Nonoperative management (NOM) is a promising therapeutic modality for patients with perforated peptic ulcer (PPU). However, the risk factors for poor efficacy and adverse events of NOM are a concern.

Research motivation

Prognostic factors that could enhance recovery, and reduce morbidity and mortality should be identified and investigated further in patients with PPU.

Research objectives

The aim of this study was to evaluate the relationship between risk factors and clinical outcome, and identify which factors can be used for risk stratification in patients with PPU.

Research methods

Total 272 patients who were diagnosed with PPU and initially managed nonoperatively from January 2014 to December 2018 were enrolled. The clinical data of these patients were collected. Baseline patient characteristics and adverse outcomes were compared between the two groups.

Research results

Multivariate analyses revealed that low serum albumin level was an independent predictor for poor efficacy of NOM and adverse outcomes in patients with PPU.

Research conclusions

Low serum albumin level may be used as an indicator to help us predict poor efficacy of NOM and adverse outcomes, and can be used for risk stratification in patients with PPU.

Research perspectives

Low serum albumin is an independent risk factor that may predict adverse consequences of NOM for PPU.

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ORIGINAL ARTICLE

Retrospective Study

Oesophageal adenocarcinoma: In the era of extended lymphadenectomy, is the value of neoadjuvant therapy being attenuated?

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Author contributions: Park JS contributed to manuscript drafting; Van der Wall H contributed to statistical analysis; Park JS and Kennedy C contributed to data collection, manuscript editing; Van der Wall H and Falk GL contributed to study conception, data collection, manuscript drafting, manuscript editing

Institutional review board statement: Data were extracted from a research database with current approval by the Sydney Local Health District Human Research Ethics Committee (reference: LNR/12CRGH/248).

Informed consent statement: Patients had given written informed consent for the study of data under the institutional ethics committee guidelines.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the

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Abstract

BACKGROUND

Neoadjuvant chemotherapy (NACT) and oesophagectomy is the standard of care for resectable oesophageal adenocarcinomas. Survival outcomes following resection have been improving over time while NACT remain largely unchanged. Indeed, a recent meta-analysis of randomized control trials did not demonstrate a survival benefit in adding NACT, raising the possibility that improved surgical techniques may be reducing the perceived effectiveness of NACT.

AIM

To compare the effect of addition of NACT to a standardized surgery and lymphadenectomy on overall and disease-free survival in patients undergoing curative oesophagectomy for oesophageal adenocarcinoma.

METHODS

Patient data were analysed from a prospectively maintained surgical survival database. Demographic, surgical, and survival outcomes were compared between groups according to treatment and nodal count.

RESULTS

The data of 243 consecutive patients were identified. 79 patients were given NACT and 162 had surgery only. The NACT group were younger, and there was less frequent stage I adenocarcinoma. Overall survival was similar between

corresponding author at jinsoo.park@health.nsw.gov.au. Participants gave informed consent for data sharing. No additional data are available.

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NACT and surgery only groups (5YS: 48.7% *vs* 42.5%; $P = 0.113$), as was disease-free survival (5YS: 40.6% *vs* 39.9%; $P = 0.635$). There were ≥ 30 nodes removed in 46 patients, and < 30 in 197 patients, but were otherwise similar. There was improved survival in patients with ≥ 30 nodes removed than those with < 30 nodes (5YS: 64.4% *vs* 40.7%; $P = 0.015$), and a better disease-free survival that neared significance (5YS: 54.9% *vs* 36.6%; $P = 0.078$).

CONCLUSION
NACT did not appear to affect overall or disease-free survival. However, an overall survival benefit was observed in patients with ≥ 30 lymph nodes removed, and a benefit in disease-free survival which was not significant.

Key Words: Oesophagectomy; Oesophageal adenocarcinoma; Neoadjuvant chemotherapy; Lymphadenectomy; Survival outcome; Surgical technique

Core Tip: This study aimed to compare the effect of neoadjuvant chemotherapy to a standardized surgery and lymphadenectomy on survival outcomes in curative oesophagectomy for cancer. Overall and disease-free survival were similar between neoadjuvant chemotherapy (NACT) and surgery only groups. There was improved survival in patients with ≥ 30 nodes harvested compared to those with < 30 nodes. The possibility that improved lymphadenectomy techniques, as opposed to NACT, improves survival outcomes in curative resection of oesophageal adenocarcinoma warrants further investigation.

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INTRODUCTION

Oesophagectomy and lymphadenectomy remain a mainstay in the curative treatment of oesophageal adenocarcinoma. Neoadjuvant chemotherapy (NACT) or combined neoadjuvant chemoradiotherapy (NACRT) preceding surgical resection is now the standard in multimodal therapy aimed at curing disease.

Multiple randomized control trials have found neoadjuvant regimens to increase long-term survival compared to surgery alone[1,2]. However, a meta-analysis of eleven randomized controlled trials did not demonstrate a survival benefit when comparing NACT plus surgery *vs* surgery alone[3]. There is uncertainty as to whether it is only neoadjuvant therapy that provides an improvement to overall survival, or other factors such as pre-operative staging, patient selection, or extent of resection and lymphadenectomy.

The value of extended lymphadenectomy after neoadjuvant therapy is uncertain. It has been reported that extended lymphadenectomy affects survival in various studies [4-6], but the extent to which it improves overall and disease-free survival after neoadjuvant therapy remains unclear. It has been argued that if there is no survival benefit in removing more lymph nodes, a less extensive lymphadenectomy may be more acceptable[7].

The present study aimed to assess the effect of NACT preceding surgery *vs* surgery alone, with standardized extensive mediastinal dissection, as well as the extent of lymph node removal, on overall- and disease free-survival in participants that underwent oesophageal resection with curative intent for adenocarcinoma in a consecutive cohort of patients.

MATERIALS AND METHODS

Patient selection and data collection

Data for adenocarcinoma were extracted from a prospective oesophageal cancer database maintained by the senior author (GLF). Patients who underwent curative oesophagectomy for oesophageal cancer between January 1990 to October 2019 were identified and included in this study. Patients were excluded if they underwent procedures in addition to oesophagectomy at the time of operation. Extracted data included baseline demographics, tumour location, histopathology, stage, perioperative outcomes and survival.

Curative surgery was offered if the patient treatment risk was considered reasonable and primary and nodal disease encompassed within the field of resection with expected clear (R0) margins. Neoadjuvant treatment was administered increasingly as evidence supporting its usage evolved, in the form of MAGIC protocol [8] chemotherapy for oesophageal adenocarcinoma in the form of epirubicin, cisplatin, and either fluorouracil or capecitabine. Patient demographics, clinicopathological data, and survival outcomes were compared amongst the study population. Patients were grouped and compared according to receipt of NACT, as well as whether they had ≥ 30 nodes resected in the pathologic specimen.

Surgical management

Surgery was performed 3-5 wk after completion of NACT. The standardized surgical management for mid-to-lower oesophageal and gastro-oesophageal junctional (GOJ) tumours was oesophageal resection performed with laparotomy with right thoracotomy in Ivor-Lewis fashion. Transthoracic, two-field lymphadenectomy was performed en bloc with the oesophageal resection. Figure 1 demonstrates an operative photograph of a representative oesophagectomy resection specimen, with en bloc lymphadenectomy of lesser sac lymph nodes. Oesophagectomy with the addition of a left cervical incision in McKeown fashion was infrequently utilized for adenocarcinomas in the middle third of the oesophagus.

Follow up was standardized, and was done through the senior surgeon (GF), or by proxy. Clinical history and examination was performed at three months for two years, then six months for the next three years, and then on an annual basis henceforth. Correspondence with the primary care doctor was performed when the patient was inaccessible or remote. Cross-sectional imaging was performed eighteen months post-operatively, or to assess the possibility of recurrences when clinically indicated. Pathologic staging was performed by specialist pathologists in accordance with the American Joint Committee on Cancer (AJCC, 8th edition)[9].

Statistical analysis

SPSS V24 (IBM Corp, NY) was utilized for statistical analysis. Data were expressed as medians and ranges. A post-hoc analysis of power was performed to ensure that the study number was sufficiently powered to provide statistical significance. Nominal and ordinal data were analyzed with the chi squared test. Non parametric continuous data were analyzed with the Mann-Whitney *U* test for dual variables, or Kruskal-Wallis test for multiple variables. Analyses of survival outcomes were assessed with the Kaplan-Meier method, and curves representing survival outcomes were assessed with the Breslow (Wilcoxon) test. Multivariate analyses were calculated with logistic regression modelling. A multivariable model tested various potential confounding variables: Age, sex, Barrett's oesophagus, tumour location, AJCC stage, and histological tumour grade. A statistical analysis with $P < 0.05$ was considered significant.

RESULTS

Clinicopathologic characteristics

Of 702 patients with oesophageal malignancy were managed by the senior author (GF) between June 1990 and October 2019. Curative oesophageal resection was performed in 395 of these patients. 39 patients had data unavailable due to loss to follow-up. 5 patients underwent operations in addition to oesophageal resection (for example, lung resection or colectomy), and were excluded from analysis. 243 patients had adenocarcinoma confirmed on histopathology of resected specimen, and formed the study cohort.

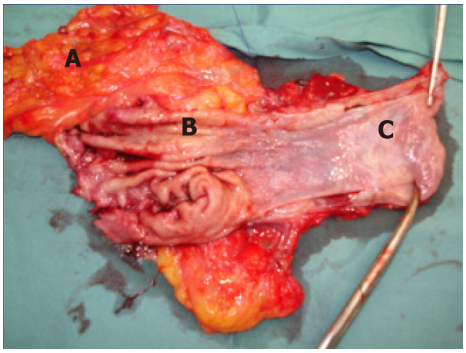

Figure 1 Operative photograph of a representative oesophagectomy resection specimen, with en bloc lymphadenectomy of lesser sac lymph nodes. A: Abdominal lymphadenectomy; B: Stomach; C: Oesophagus.

The cohort was analysed by whether they underwent oesophagectomy earlier in the series (1990-2004) or later in the series (2005-2019). 122 patients had surgery earlier in the series and 121 patients had surgery later in the series. These two groups were similar in terms of demographic features, sex, and age, and operative factors such as tumour location and number of lymph nodes harvested.

Comparison of groups (NACT and surgery alone)

Surgery only was performed in 162 patients, and 79 patients had NACT preceding surgery. Two patients had incomplete data on NACT regimen. The NACT group was younger, with a median age of 62 years (range: 42-75) compared to a median age in the surgery only group of 69 years (range: 37-87; $P < 0.001$). Between the NACT and surgery only groups, there were similar distributions of males ($P = 0.770$) and Barrett's oesophagus ($P = 0.279$) (Table 1).

The NACT group had less patients that were stage I adenocarcinoma on pathologic assessment of resected surgical specimen compared with the surgery only group (15.6% *vs* 27.7%; $P = 0.040$). Tumour location was similar between NACT and surgery groups amongst upper, middle, and lower parts of the oesophagus as well as the GOJ. Tumour differentiation was also similarly distributed between the two groups. More lymph nodes were counted in the NACT group, a median of 24 (range: 3-61), compared to the surgery only group with a median of 18 (range: 0-45; $P < 0.001$). The proportion of patients who had ≥ 30 lymph nodes removed was also greater in the NACT compared to the surgery only group (32.9% *vs* 12.3%; $P < 0.001$). There was no difference in the number of nodes that were positive between the two groups ($P = 0.344$).

Overall survival outcomes (NACT and surgery alone)

Median overall survival of the study cohort was 19.3 mo (range: 0.1-220.3). Overall survival at 1, 2, and 5 years was 75.7%, 58.2%, and 45%, respectively. 30-d mortality in the study cohort was 3.7%.

Median overall survival in the NACT group was 17.9 mo (range: 0.8-161.2), and in the surgery only group, 20.9 mo (range: 0.1-220.3). Kaplan-Meier analysis of overall-survival between NACT *vs* surgery-only groups is demonstrated in Figure 2A. There was no difference in overall survival between NACT and surgery-only populations. Overall survival at 1-, 2-, and 5-years in the NACT population was 81.5%, 64.8%, and 48.7%, respectively. Overall survival at 1-, 2-, and 5-years in the surgery-only population was 72.8%, 55.1%, and 42.5%, respectively ($P = 0.113$).

Disease-free survival outcomes (NACT and surgery alone)

Median disease-free survival of the study cohort was 14.5 mo (range: 0.1-220.3). Disease-free survival at 1, 2, and 5 years was 66.3%, 50.1%, and 40%, respectively.

Median disease-free survival in the NACT group was 13.3 mo (range: 0.8-161.2), and in the surgery only group, 16.7 mo (range: 0.1-220.3). Kaplan-Meier analysis of disease-free-survival between NACT *vs* surgery-only groups is demonstrated in Figure 2B. There was no difference in disease-free survival between NACT and surgery-only populations. Disease-free survival at 1-, 2-, and 5-years in the NACT population was 64.9%, 52.7%, and 40.6%, respectively. Disease-free survival at 1-, 2-, and 5-years in the surgery-only population was 66.5%, 49.2%, and 39.9%, respectively ($P = 0.635$).

Table 1 Characteristics between neoadjuvant chemotherapy groups

	NACT (*n* = 79)	Surgery only (*n* = 162)	*P* value
Age (median, range)	62 (42-75)	69 (37-87)	< 0.001[1]
Sex			
Male	67	135	0.770
Female	12	27	
Barrett's oesophagus	30 (38%)	73 (45.1%)	0.297
Tumour location			
Upper	1 (1.3%)	4 (2.5%)	0.562
Mid	0 (0%)	3 (1.9%)	0.233
Lower	29 (38.7%)	65 (40.6%)	0.775
GOJ	45 (60%)	88 (55%)	0.471
Tumour differentiation			
Poor	35 (46.1%)	76 (48.7%)	0.703
Mod	38 (50%)	67 (42.9%)	0.311
Well	3 (3.9%)	13 (8.3%)	0.216
Stage[1]			
I	12 (15.6%)	43 (27.7%)	0.040[1]
II	20 (26%)	27 (17.4%)	0.127
III	43 (55.8%)	80 (51.6%)	0.543
IV	1 (1.3%)	5 (3.2%)	0.384
Nodes positive	1 (0-20)	1 (0-22)	0.344

[1]American Joint Committee on Cancer (AJCC) 8th edition. NACT: Neoadjuvant chemotherapy; GOJ: Gastro-oesophageal junction.

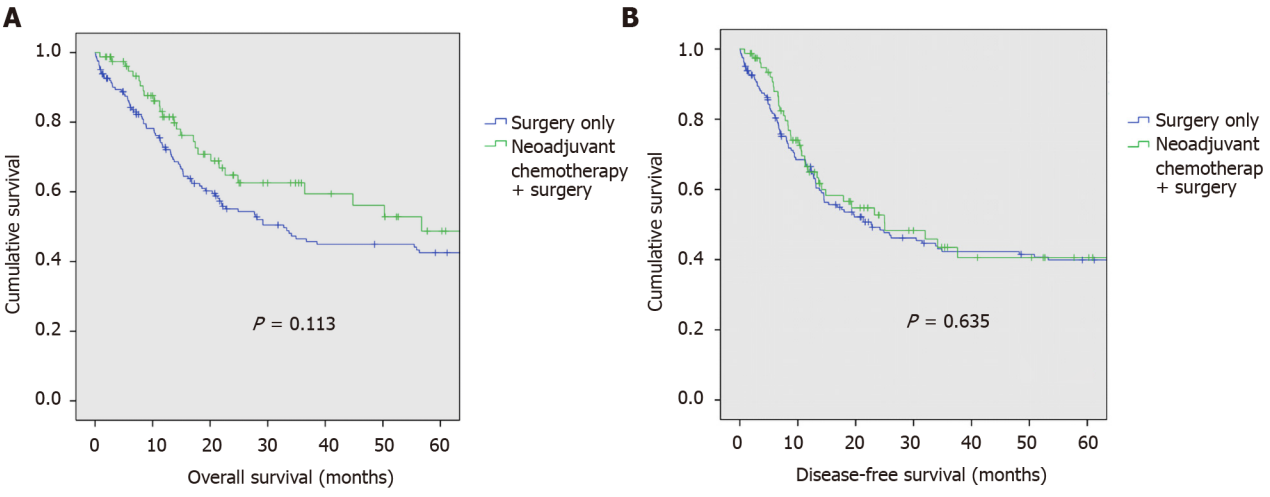

Figure 2 Kaplan-Meier survival curves between neoadjuvant chemotherapy and surgery only groups. A: Overall survival; B: Disease-free survival.

Comparison by nodes removed

The study cohort was then separated into two groups by the number of nodes removed. There were 46 patients with ≥ 30 nodes removed, and 197 patients had < 30 nodes removed. Their demographic and clinicopathologic data are summarized in Table 2. The two groups were otherwise similar in terms of age, sex, presence of Barrett's, NACT, tumour location, tumour grade, and pathologic AJCC 8th Edition

Table 2 Characteristics between node collection groups

	≥ 30 nodes (*n* = 46)	< 30 nodes (*n* = 197)	*P* value
Age (median, range)	66.5 (45-87)	66 (37-84)	0.970
Sex			
Male	40 (87%)	163 (82.7%)	0.488
Female	5 (13%)	34 (17.3%)	
Barrett's oesophagus	20 (43.5%)	85 (43.1%)	0.967
Tumour location			
Upper	1 (2.2%)	4 (2.1%)	0.953
Mid	0 (0%)	3 (1.6%)	0.399
Lower	14 (31.1%)	80 (41.7%)	0.193
GOJ	30 (66.7%)	105 (54.7%)	0.144
Tumour differentiation			
Poor	19 (41.3%)	93 (49.7%)	0.305
Mod	23 (50%)	82 (43.9%)	0.453
Well	4 (8.7%)	12 (6.4%)	0.584
Stage[1]			
I	11 (23.9%)	44 (23.5%)	0.956
II	11 (23.9%)	36 (19.3%)	0.480
III	23 (50%)	101 (54%)	0.625
IV	1 (2.2%)	5 (2.7%)	0.848

[1]American Joint Committee on Cancer (AJCC) 8th edition. GOJ: Gastro-oesophageal junction.

staging.

Overall survival outcomes by number of nodes removed

Median overall survival in patients who had ≥ 30 nodes removed was 31.4 mo (range: 0.8-176.5), and in patients who had < 30 nodes removed, 18 mo (0.1-220.3). The Kaplan-Meier survival curve for overall survival between patients with ≥ 30 nodes and < 30 nodes removed is shown in Figure 3A. Patients with ≥ 30 nodes had improved overall survival compared to those with < 30 nodes removed. Overall survival at 1, 2, and 5 years in the group of patients who had ≥ 30 nodes removed was 81%, 78%, and 64.4%, respectively. Overall survival at 1-, 2-, and 5-years in the population who had < 30 nodes removed was 74.5%, 53.9%, and 40.7%, respectively ($P = 0.015$).

Disease-free survival outcomes by number of nodes removed

Median disease-free survival in patients who had ≥ 30 nodes removed was 21.4 mo (range: 0.8-176.5), and in patients who had < 30 nodes removed, 13.7 mo (range: 0.1-220.3). The Kaplan-Meier survival curve for disease-free survival between patients with ≥ 30 nodes and < 30 nodes removed is shown in Figure 3B. There was no difference in disease-free survival between patients who had ≥ 30 nodes removed *vs* those that had less than 30 nodes removed. Disease-free survival at 1-, 2-, and 5-years in those who had ≥ 30 nodes removed was 71.6%, 63.7%, and 54.9%, respectively. In those with less than 30 nodes removed, disease-free survival was 65.1%, 47%, and 36.6%, respectively ($P = 0.078$).

By multivariate analysis, independent predictors for greater overall survival were AJCC stage ($P < 0.001$), histologic grade ($P < 0.001$), and more than 30 nodes removed ($P = 0.016$). Male sex ($P = 0.642$), age older than 75 years ($P = 0.369$), tumour location ($P = 0.057$), and Barrett's oesophagus ($P = 0.421$) did not predict overall survival on multivariate analysis.

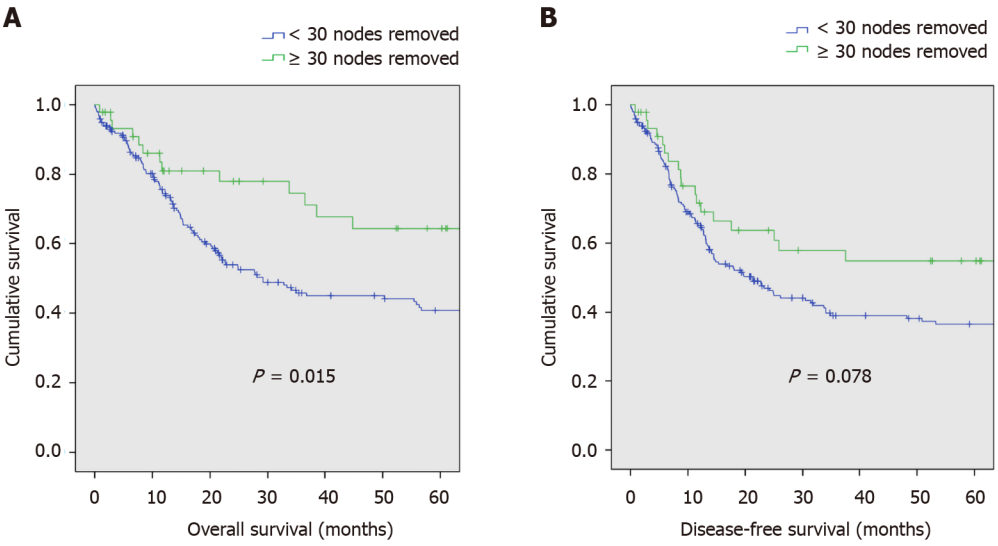

Figure 3 Kaplan-Meier survival curves for overall survival between ≥ 30 nodes and < 30 nodes removed. A: Overall survival; B: Disease-free survival.

DISCUSSION

In this cohort of 243 patients with oesophageal adenocarcinoma treated with curative oesophagectomy and two-field lymphadenectomy, NACT plus surgery did not appear to affect overall (P = 0.113) or disease-free survival (P = 0.206). Instead, an overall survival benefit was observed in patients who had ≥ 30 lymph nodes removed (P = 0.015), and a benefit in disease-free survival neared significance (P = 0.078).

The apparent failure of NACT to improve overall and disease-free survival was surprising, but not without precedent. The Medical Research Council OEO2 trial, which reported 5-year survival of 23% in the NACT and surgery group compared to 17.1% in their surgery only group (P = 0.03), was pivotal in gaining acceptance of NACT. However, 9.4% of overall patients had unresectable disease at surgery and 15.2% had macroscopically involved (R2) margins. The proportion of patients with involved margins or unresectable tumours was considerably higher in the surgery only group, and may have biased results (26.4% *vs* 14.3%)[2] Resectability may also have been affected by NACT, so this may have been an instrumental difference in the OEO2 study. OEO2 contained a high number of squamous carcinoma which is likely to behave differently from adenocarcinoma, making direct comparison uncertain.

There is a trend in most published retrospective data showing that surgery has improved over time. Fontana *et al*[10] reported an improvement in survival outcomes following radical resection of oesophageal and gastric cancers over a decade, identifying a larger number of resected lymph nodes as a possible factor affecting survival[10]. Similarly, analysis of the SEER database has identified that survival of local oesophageal cancer has improved dramatically over the past 3 decades[11]. This has followed advances in the management of oesophageal adenocarcinoma such as improved staging with positron emission tomography, endoscopic ultrasound and later-generational thoracoabdominal computer tomography. Consequently, the survival data in the OEO2 trial is significantly worse than most current series.

Data from the Swedish population registry of oesophago-gastric resections published by Klevebro *et al*[12] did not demonstrate a survival benefit in patients with adenocarcinoma who underwent NACT and surgery compared with surgery alone [12]. Subgroup analysis of only fit patients without co-morbidities showed a strong trend towards improving survival with NACT and surgery, ultimately concluding that the benefit of NACT was reproducible only for fit and healthy patients. The North American intergroup study by Kelsen *et al*[13] randomized 440 patients to pre-operative chemotherapy preceding surgery or surgery only. They did not report a difference in overall survival between the two groups for adenocarcinoma or epidermoid cancer of the oesophagus[13].

Mariette *et al*[14] randomised 195 patients to NACRT plus surgery or surgery alone in treating locally advanced oesophageal cancer. When comparing NACRT plus surgery with surgery alone, they did not report a difference in overall survival (5 year survival 41.1% and 33.8%, respectively) or disease-free survival (5 year survival 35.6%

and 27.7%, respectively) between the two groups. They also reported a significantly higher in-hospital post-operative mortality in the neoadjuvant arm (11.1% *vs* 3.4%; P = 0.049). The possibility is raised that higher quality surgery (complete microscopic (R0) resection rates, a high number of lymph nodes retrieved, and a low 30-d postoperative mortality rate) in the surgery-only group may have contributed to the apparent diminished effectiveness of neoadjuvant therapy[14]. The study however contained a large cohort of squamous cell carcinoma (SCC).

The present study demonstrates a survival benefit in patients who had ≥ 30 nodes removed, with a 5 year survival rate of 64.4% *vs* 40.7% in those with less nodes removed. Whether extended lymphadenectomy affects long-term survival following oesophagectomy remains controversial.

Several studies report that extended lymphadenectomy improves long-term survival. Kang *et al*[5] examined 233 patients who underwent oesophagectomy for oesophageal SCC without neoadjuvant therapy. In comparing three groups with varying degree of lymphadenectomy, they reported no difference in overall or disease-free survival[5]. Similarly, Koen Talsma *et al*[15] compared the effect of resected nodes on survival in patients with and without NACRT. They reported that the total number of resected nodes was significantly associated with survival for patients in the surgery-only arm when compared with NACRT only[15]. Kelty *et al*[16] showed improved survival according to the ratio of positive to negative nodes removed confirming the effectiveness of increasing nodal retrieval[16]. Multiple studies have examined the extent of lymphadenectomy needed for a survival benefit. The estimate for a minimum lymph node harvest to confer a survival benefit have ranges from 18 to 30[4,6].

Conversely, Lagergren *et al*[7] reported that the extent of lymphadenectomy did not influence survival following surgery for oesophageal cancer. They did not demonstrate a dose-response association between varying degrees of lymphadenectomy and 5-year overall survival. However, there were three surgeons conducting operations, with no consensus about the preferred extent of lymphadenectomy[7]. The issue of heterogenous operative technique is addressed by Phillips *et al*[17], who reported that the absolute number of lymph nodes removed did not improve survival in a cohort of patients who underwent transthoracic oesophagectomy and a standardized two-field lymphadenectomy[17].

Similarly, both NACT and NACRT have been shown to have variable efficacy when an extensive lymphadenectomy is performed[14]. Data from the CROSS trial confirms that the extent of lymphadenectomy has not been shown to make a difference after NACRT. It was noted by investigators that patients that did not receive NACRT had a significant survival benefit for every 10 lymph nodes harvested[15]. The authors speculated that micrometastases in patients not treated with NACRT may be controlled with lymphadenectomy. This would suggest a complimentary effect of lymphadenectomy and neoadjuvant therapy on involved lymph nodes. A meta-analysis of NACRT and surgery compared against surgery alone showed a smaller benefit than previously demonstrated in the CROSS study (8.7%)[18]. This may reflect improved surgical techniques, including lymphadenectomy, contributing to improved survival outcomes, reducing the effect of neoadjuvant therapies.

The main disadvantage of the present study is that it was simply a cohort study with prospective data storage and not randomized, and a long duration of data collection. An advantage is that adenocarcinoma only was examined and results pertain to this tumour type only. Additionally there was no difference between the first half of the series and the second half of the series in staging or for lymph node count, indicating a standardized operative technique throughout the cohort, and no variation in harvested lymph node count over time, meaning that the effect of NACT as an independent variable was more precisely observed.

CONCLUSION

NACT did not appear to affect overall or disease-free survival in our cohort. Instead, an overall survival benefit was observed in patients who had ≥ 30 lymph nodes removed, and a benefit in disease-free survival which neared significance. Such mixed data in multiple studies suggests the need for further randomised controlled trials of neoadjuvant therapy and surgery with lymphadenectomy compared with surgery with lymphadenectomy alone, in adenocarcinoma of the oesophagus and GOJ. Ideally, surgeons should aim to harvest more than 30 lymph nodes in the contemporary era.

ARTICLE HIGHLIGHTS

Research background

A meta-analysis of eleven randomized controlled trials did not demonstrate a survival benefit when comparing neoadjuvant chemotherapy (NACT) plus surgery *vs* surgery alone. There is uncertainty as to whether it is only neoadjuvant therapy that provides an improvement to overall survival, or other factors such as pre-operative staging, patient selection, or extent of resection and lymphadenectomy.

Research motivation

Techniques in oesophagectomy are improving, but the regimen for neoadjuvant therapies has largely remained static.

Research objectives

The authors aimed to assess the effect of addition of NACT to a standardized surgery and lymphadenectomy on overall and disease-free survival in patients undergoing curative oesophagectomy for oesophageal adenocarcinoma.

Research methods

Survival data in a prospectively maintained surgical database were interrogated to review demographic, surgical, and survival outcomes. These were compared between groups according to treatment and nodal count.

Research results

The authors found that overall and disease-free survival were similar between patients that had undergone NACT preceding surgery and surgery only groups. There was improved survival in patients with ≥ 30 nodes removed than those with < 30 nodes and a better disease-free survival that neared significance.

Research conclusions

NACT did not appear to affect overall or disease-free survival in our cohort. Instead, an overall survival benefit was observed in patients who had ≥ 30 lymph nodes removed, and a benefit in disease-free survival which neared significance. Ideally, surgeons should aim to harvest more than 30 lymph nodes in the contemporary era.

Research perspectives

Conflicting results and mixed data in multiple studies suggests the need for further randomised controlled trials of neoadjuvant therapy and surgery with lymphadenectomy compared with surgery with lymphadenectomy alone.

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ORIGINAL ARTICLE

Retrospective Study

Outcomes of reduction hepatectomy combined with postoperative multidisciplinary therapy for advanced hepatocellular carcinoma

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Author contributions: Asahi Y analyzed and interpreted the patient data, was involved in the data acquisition, made substantial contributions to the study conception and design, and was a major contributor during the writing of the manuscript; Kamiyama T participated in drafting and critically revising the article; Kakisaka T, Orimo T, Shimada S, Nagatsu A, Aiyama T, Sakamoto Y and Kamachi H revised the draft manuscript by adding intellectual insights and providing critical advice; Taketomi A provided critical comments to improve the manuscript and gave final approval for its submission; all of the authors have read and approved the final manuscript.

Institutional review board statement: This research was

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Abstract

BACKGROUND

The prognosis of advanced hepatocellular carcinoma (HCC) that is not indicated for curative hepatectomy remains poor, despite advances in the treatment of HCC, including the development of tyrosine kinase inhibitors (TKIs). The outcomes of reduction hepatectomy and multidisciplinary postoperative treatment for advanced HCC that is not indicated for curative hepatectomy, including those of recently treated cases, should be investigated.

AIM

To examine the outcomes of combination treatment with reduction hepatectomy and multidisciplinary postoperative treatment for advanced HCC that is not indicated for curative hepatectomy.

METHODS

Thirty cases of advanced HCC that were not indicated for curative hepatectomy, in which reduction hepatectomy was performed between 2000 and 2018 at the Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, were divided into postoperative complete remission (POCR) (+) and POCR (-) groups, depending on whether POCR of all evaluable lesions was achieved through postoperative treatment. The cases in the POCR (-) group were subdivided into POCR (-) TKI (+) and POCR (-) TKI (-) groups, depending on whether TKIs were administered postoperatively.

RESULTS

The 5-year overall survival rate and mean survival time (MST) after reduction hepatectomy were 15.7% and 28.40 mo, respectively, for all cases; 37.5% and 56.55

approved by the institutional review board of Hokkaido University Hospital.

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mo, respectively, in the POCR (+) group; and 6.3% and 14.84 mo, respectively, in the POCR (-) group (P = 0.0041). Tumor size, major vascular invasion, and the number of tumors in the remnant liver after the reduction hepatectomy were also found to be related to survival outcomes. The number of tumors in the remnant liver was the only factor that differed significantly between the POCR (+) and POCR (-) groups, and POCR was achieved significantly more frequently when ≤ 3 tumors remained in the remnant liver (P = 0.0025). The MST was 33.52 mo in the POCR (-) TKI (+) group, which was superior to the MST of 10.74 mo seen in the POCR (-) TKI (-) group (P = 0.0473).

CONCLUSION
Reduction hepatectomy combined with multidisciplinary postoperative treatment for unresectable advanced HCC that was not indicated for curative hepatectomy was effective when POCR was achieved *via* multidisciplinary postoperative therapy. To achieve POCR, reduction hepatectomy should aim to ensure that ≤ 3 tumors remain in the remnant liver. Even in cases in which POCR is not achieved, combined treatment with reduction hepatectomy and multidisciplinary therapy can improve survival outcomes when TKIs are administered.

Key Words: Hepatocellular carcinoma; Reduction hepatectomy; Multidisciplinary therapy; Tyrosine kinase inhibitors; Postoperative complete remission

Core Tip: This was a retrospective study examining the outcomes of combination treatment with reduction hepatectomy and multidisciplinary postoperative treatment for advanced hepatocellular carcinoma (HCC). When reduction hepatectomy is performed for unresectable advanced HCC that is not indicated for curative hepatectomy, achieving postoperative complete remission (POCR) *via* postoperative multidisciplinary therapy is the key to success, with the 5-year overall survival rate and mean survival time for the POCR (+) group being 37.5% and 56.55 mo, respectively. To achieve POCR, reduction hepatectomy should be performed with the aim of reducing the number of tumors in the remnant liver to ≤ 3. Even in cases in which POCR is not achieved, tyrosine kinase inhibitor treatment might improve the prognosis of advanced HCC after reduction hepatectomy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant hepatic tumor, accounting for 85%-90% of primary malignant hepatic tumors[1]. Advanced HCC is defined as progressive malignant HCC, which is hard to treat in a single hepatectomy procedure[2,3]. This is one reason for the poor prognosis of advanced HCC because hepatectomy is an important curative option. In fact, it is more effective at achieving local control of advanced HCC than any other treatment[4]. Local ablation therapy (LAT), including radiofrequency ablation (RFA) and microwave coagulation therapy (MCT), can also result in long survival periods; however, LAT is designed to treat less advanced HCC than hepatectomy[5]. Other treatment options include transarterial infusion (TAI) therapies, such as transarterial chemoembolization (TACE) and intraarterial chemotherapy (IAC), and the systemic administration of tyrosine kinase inhibitors (TKIs); however, the outcomes of these treatments are unsatisfactory. For instance, the survival period after TKI treatment ranges from 10 to 11 mo for advanced HCC[6,7].

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Postoperative multidisciplinary therapy for HCC can include additional surgery, LAT (RFA or MCT), TAI (TACE or IAC), and TKI treatment. A retrospective study reported mean survival times (MSTs) of 31.8 and 18.6 mo for Barcelona Clinic Liver Cancer (BCLC) stage B and C HCC after reduction hepatectomy followed by postoperative local therapy targeting the liver, such as additional hepatectomy, LAT, and TAI[8]. In another retrospective study, the prognosis of patients who exhibited remnant extrahepatic lesions after reduction hepatectomy was reported to be poor (3-year overall survival [OS] rate: 0%)[9]. However, the latter study only included 6 cases of HCC with extrahepatic lesions, and postoperative TKI treatment was not mentioned. Although there are various treatment options for HCC, there are few reports about reduction hepatectomy followed by multidisciplinary postoperative therapy for cases of advanced HCC that are not indicated for curative hepatectomy, and the utility of this treatment strategy should be evaluated.

In the present study, we evaluated the efficacy of combination treatment involving reduction hepatectomy followed by multidisciplinary therapy, including TKI treatment, for unresectable advanced HCC that was not indicated for curative hepatectomy.

MATERIALS AND METHODS

Patients

Of 828 hepatectomies performed for HCC between 2000 and 2018 at our department, the clinical data for 30 patients who underwent reduction hepatectomy for BCLC stage B or C advanced HCC that was not indicated for curative hepatectomy were retrospectively analyzed. The preoperative investigations and hepatectomy were carried out according to the method described in our previous report[10]. Major vascular invasion, major portal vein invasion, and major hepatic vein invasion were found in 17, 15, and 2 cases, respectively. All 30 patients were preoperatively evaluated using 3-phase dynamic contrast-enhanced computed tomography (CT). The preoperative whole-liver volume and tumor volume, the estimated volume of the remnant liver, and the effective resection ratio of the liver were calculated preoperatively using a 3D workstation. Liver function was evaluated through blood tests, the indocyanine green retention rate at 15 min (ICGR15), and technetium-99m diethylenetriamine pentaacetic acid galactosyl human serum albumin (Tc-GSA) scintigraphy. HCC was considered to not be indicated for curative hepatectomy if resection of all of the evaluable lesions was not possible, or the predicted remnant liver volume after reduction hepatectomy was considered to be insufficient, according to the Hokkaido University algorithm for hepatic resection[10]. This algorithm indicates: (1) If the ICGR15 is < 15%, the effective resection ratio of the liver has to be < 60% for hemihepatectomy or extended hemihepatectomy to be performed; (2) If the ICGR15 ranges from 15% to 20%, sectionectomy can be performed; (3) If the ICGR15 ranges from 20% to 25%, segmentectomy can be performed; (4) If the ICGR15 ranges from 25% to 40%, a limited resection can be performed; and (5) If the ICGR15 is > 40%, hepatectomy is contraindicated. Reduction hepatectomy was performed for patients with unresectable advanced HCC that 1) were not indicated for curative hepatectomy, 2) were in a good general condition, and 3) were considered to be eligible for postoperative treatment, providing that it was considered that reduction hepatectomy of the main tumor would eliminate the most important poor prognostic factor (even if residual tumors remained in the liver), according to the Hokkaido University algorithm for hepatic resection. In all 30 cases, residual tumor (s) were present in the remnant liver after hepatectomy, and 3 patients had extrahepatic metastases (in the lungs in 2 cases and in the bone in 1 case). The pre- and postoperative treatments employed after the reduction hepatectomy, OS, prognostic factors for OS, and whether the postoperative treatments resulted in postoperative complete remission (POCR) of all evaluable lesions were also examined. POCR was considered to have been achieved when no evaluable lesions were detected during the imaging study performed to evaluate the effects of treatment.

This research was approved by the institutional review board of Hokkaido University Hospital (approval number: 019-0115), and all analyses of the clinical data were carried out according to the ethical guidelines of Hokkaido University.

Evaluation of POCR

During the first 1 to 2 mo after treatment, imaging studies were performed with contrast-enhanced CT or gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic

acid-enhanced magnetic resonance imaging (EOB-MRI) to evaluate the effects of LAT or TAI treatment. All cases were divided into two groups, according to whether POCR was achieved at least once in the postoperative period. The cases in which POCR was achieved were included in the POCR (+) group, and those in which POCR was not achieved were included in the POCR (-) group.

Statistical analyses

Some clinical data were converted to categorical variables. Pearson's chi-square test was used for the statistical analyses, except for variables with expected counts of ≤ 5, for which Fisher's exact test was used instead. OS was calculated using the Kaplan-Meier method and compared between the groups using the Wilcoxon test in the univariate analyses. Two-sided p-values of < 0.05 were considered significant. All analyses were performed with the software JMP (JMP Pro, version 14; SAS Institute Inc., Cary, NC).

RESULTS

Clinicopathological characteristics

Table 1 summarizes the clinical data for the 30 cases. The in-hospital and 90-day mortality data were excluded from Table 1 because no deaths occurred in hospital or within 90 days. The subjects' mean age was 62.8 ± 11.8 years old (44-89 years old). The mean serum levels of alpha-fetoprotein (AFP), protein induced by vitamin K absence/antagonist-II (PIVKA-II), total bilirubin (T-Bil), and albumin (Alb) were 10228.33 ± 7287.26 ng/mL (35-217390), 52534.8 ± 22566.31 mAU/mL (17-664680), 0.88 ± 0.08 mg/dL (0.4-1.9), and 3.71 ± 0.08 g/dL (2.9-4.6), respectively; the mean prothrombin time (PT) was 90.19% ± 2.75% (69.8-115.8); and the mean ICGR15 was 17.34% ± 1.96% (2.6-43.8). The mean size of the largest tumor was 10.13 ± 1.02 cm (2.0-24.0). Anatomical hepatectomy was conducted in 27 cases, and non-anatomical hepatectomy (partial resection of the liver) was carried out in the remaining 3 cases. The median surgical time was 340 min (188-911), and the median amount of intraoperative blood loss was 690 mL (0-35820). The median follow-up time was 17.41 mo (1.02-111.04).

Peri-surgical treatment

Table 2 summarizes the peri-surgical treatments, including both the preoperative and postoperative treatments, employed in the 30 cases. Preoperative treatment was performed in 6 cases. Postoperative treatment was employed in 28 cases. In one case, postoperative treatment was not employed, as the patient's general condition deteriorated due to a postoperative cerebral infarction. In another case, clinical information was lacking after a follow-up period of 1.01 mo because the postoperative treatment was not performed at our institution. POCR was and was not achieved during the postoperative period in 8 cases [26.7%; POCR (+) group] and 22 cases [73.3%; POCR (-) group], respectively. POCR was achieved in the following cases: 1 of 1 cases that were treated with a second hepatectomy, partial lung resection, TAI therapy, and chemotherapy after the reduction hepatectomy; 1 of 1 cases that were treated with a second hepatectomy, TAI therapy, chemotherapy, and external beam radiotherapy (ERT) for palliative purposes after the reduction hepatectomy; 1 of 1 cases that were treated with partial lung resection, LAT, TAI therapy, chemotherapy, and ERT after the reduction hepatectomy; 2 of 2 cases that were treated with LAT and TAI therapy with/or without ERT after the reduction hepatectomy; 1 of 6 cases that were treated with TAI therapy and chemotherapy with/or without ERT after the reduction hepatectomy; and 2 of 9 cases that were treated with TAI therapy with/or without ERT after the reduction hepatectomy. All 6 patients that received postoperative TKI treatment were included in the POCR (-) group.

Prognostic factors for OS

Among all 30 cases, the 1-year, 3-year, and 5-year OS rates after reduction hepatectomy were 72.4%, 31.3%, and 15.7%, respectively, and the MST after reduction hepatectomy was 28.40 mo. In the POCR (+) group, the 1-year, 3-year, and 5-year OS rates were 100%, 75.0%, and 37.5%, respectively, and the MST was 56.55 mo, whereas in the POCR (-) group the 1-year, 3-year, and 5-year OS rates were 61.9%, 12.6%, and 6.3%, respectively, and the MST was 14.84 mo (P = 0.0041, Figure 1). Univariate analyses revealed significant intergroup differences in the Child-Pugh class (P <

Table 1 Clinical and surgical data

Clinical data			Surgical data		
Age (yr)	62.8 ± 11.8		Anatomical hepatectomy	-	3
				+	27
Sex	Male	28	Operation time (min)	340	
	Female	2			
HBV/HCV	-	6	Blood loss (mL)	690	
	+	24			
Alb (g/dL)	3.71 ± 0.08		Number of tumors in the remnant liver	1-3	12
				≥ 4	18
T-Bil (mg/dL)	0.88 ± 0.08		POCR	+	8
				-	22
PT (%)	90.19 ± 2.75				
ICGR15 (%)	17.34 ± 1.96				
AFP (ng/mL)	102288 ± 7287				
PIVKA-II (AU/mL)	52534 ± 22566				
Child-pugh class	A	27			
	B	3			
Number of tumors	St	0			
	Mt	30			
Tumor size (cm)	10.13 ± 1.02				
Differentiation	Wel	1			
	Mod	16			
	Por	13			
pN	-	28			
	+	2			
Macrovascular invasion	-	5			
	+	25			
BCLC stage	B	12			
	C	18			
Distant metastasis	-	27			
	+	3			

PT: Prothrombin time; ICGR15: Indocyanine green retention rate at 15 min; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence/antagonist-II; BCLC: Barcelona Clinic Liver Cancer.

0.0001), tumor size (P = 0.0485), the frequency of major vascular invasion (P = 0.0053), the number of tumors in the remnant liver (P = 0.0283), and the frequency of POCR (P = 0.0041) (Table 3).

Comparison between the POCR (+) and POCR (-) groups

The clinical data for the POCR (+) and POCR (-) groups are shown in Table 4. Only the number of tumors in the remnant liver exhibited significant intergroup differences. The proportion of cases in which ≤ 3 tumors were seen in the remnant liver was higher in the POCR (+) group than in the POCR (-) group (P = 0.0025).

The cases in the POCR (-) group were subdivided into two groups according to whether postoperative TKI treatment was administered. Cases involving TKI treatment were included in the POCR (-) TKI (+) group, and those that did not involve

Table 2 Peri-surgical treatment

Preoperative treatment		
No treatment	24	
TAI	4	
TAI + ERT	1	
TAI + TKI[1] + ERT	1	
Postoperative treatment	**Total**	**POCR (+)**
TAI + hepatectomy + lung resection + chemo	1	1
Hepatectomy + chemo + TAI + ERT	1	1
Lung resection + LAT + TAI + chemo + ERT	1	1
Lung resection + LAT	1	0
Brain tumor resection + TAI + TKI[2] + chemo + ERT	1	0
LAT + TAI + ERT	2	2
TAI + TKI[3] + chemo (+ ERT)	3	0
TAI + TKI[4]	2	0
TAI + chemo (+ ERT)	6	1
TAI (+ ERT)	9	2
ERT	1	0
No treatment	1	0
Unknown	1	0
Total	30	8

[1]TKI: Sorafenib (n = 1).
[2]TKI: Sorafenib (n = 1).
[3]TKI: Sorafenib (n = 1), lenvatinib (n = 1), sorafenib + lenvatinib (n = 1).
[4]TKI: Sorafenib (n = 1), sorafenib + lenvatinib (n = 1). TAI: Transarterial infusion; ERT: External beam radiotherapy; TKI: Tyrosine kinase inhibitors; LAT: Local ablation therapy.

TKI treatment were included in the POCR (-) TKI (-) group. In the POCR (-) TKI (+) group, the 1-year, 3-year, and 5-year OS rates after reduction hepatectomy were 100%, 31.3%, and 0%, respectively, and the MST was 33.52 mo, whereas in the POCR (-) TKI (-) group the 1-year, 3-year, and 5-year OS rates after reduction hepatectomy were 46.7%, 6.7%, and 6.7%, respectively, and the MST was 10.74 mo (P = 0.0473, Figure 2). There were no significant differences between the clinicopathological data of the POCR (-) TKI (+) and POCR (-) TKI (-) groups (Table 5).

DISCUSSION

In the present study, the survival rate of the POCR (+) group was better than that of the POCR (-) group (P = 0.0041), suggesting that achieving POCR after reduction hepatectomy could have an important impact on survival in patients with advanced HCC that is not indicated for curative hepatectomy. Moreover, even in the cases in which POCR was not achieved the administration of TKIs resulted in an improvement in survival outcomes; *i.e.*, the survival rate of the POCR (-) TKI (+) group was better than that of the POCR (-) TKI (-) group (P = 0.0473). Thus, reduction hepatectomy could be effective against advanced HCC that is not indicated for curative hepatectomy, especially when POCR is achieved *via* postoperative multidisciplinary therapy. Even in cases in which POCR is not achieved, the administration of TKIs should be considered in the postoperative period.

In ovarian carcinoma, the maximal resection of any primary or metastatic carcinoma followed by postoperative chemotherapy has become the standard treatment strategy [11]. However, there are only a limited number of reports about reduction hepate-

Table 3 Univariate analyses

Clinicopathological data					Surgical data				
	Category	*n*	MST (m)	*P* value		Category	*n*	MST (m)	*P* value
Age (yr)	≥ 60	18	17.9	0.9267	Anatomical hepatectomy	-	3	39.0	0.2162
	< 60	12	29.7			+	27	16.9	
Sex	Male	28	17.9	0.1584	Operation time (min)	< 340	15	28.4	0.4177
	Female	2	-			≥ 340	15	14.8	
HBV/HCV	-	6	15.0	0.2674	Blood loss (mL)	< 690	15	29.7	0.6355
	+	24	29.7			≥ 690	15	16.4	
Alb (g/dL)	≥ 3.7	15	33.5	0.3444	Number of tumors in the remnant liver	1-3	12	56.5	0.0283[a]
	< 3.7	15	17.4			≥ 4	18	14.8	
T-Bil (mg/dL)	≤ 0.8	19	28.4	0.5131	POCR	+	8	56.6	0.0041[a]
	> 0.8	11	16.5			-	22	14.8	
PT (%)	≥ 90	17	17.9	0.7839					
	< 90	13	28.4						
ICGR15 (%)	≥ 15	12	29.7	0.6790					
	< 15	18	16.5						
AFP (ng/mL)	< 200	16	29.7	0.5569					
	≥ 200	14	17.9						
PIVKA-II (AU/mL)	< 100	3	73.2	0.0584					
	≥ 100	27	16.9						
Child-pugh class	A	27	29.7	< 0.0001					
	B	3	6.4						
Tumor size (cm)	≥ 10 cm	15	12.2	0.0485					
	< 10 cm	15	29.7						
Differentiation	wel/mod	17	17.9	0.5449					
	por	13	28.4						
pN	-	28	17.9	0.2335					
	+	2	56.5						
Macrovascular invasion	-	5	9.5	0.0053					
	+	25	30.0						
BCLC stage	B	12	33.8	0.7652					
	C	18	16.9						
Distant metastasis	-	27	28.4	0.6013					
	+	3	12.1						

[a]*P* < 0.05. MST: Mean survival time; PT: Prothrombin time; ICGR15: Indocyanine green retention rate at 15 min; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence/antagonist-II; BCLC: Barcelona Clinic Liver Cancer.

ctomy for HCC[9,12-14]. In the latter studies, it was reported that the OS rate after reduction hepatectomy for HCC ranged from 52%-67.7% at 1 year, from 20.0-40.6% at 3 years, and from 10%-21.7% at 5 years[9,13,14]. As different patients were selected and different treatment options were employed in different eras, it is hard to simply compare OS rates, although the OS rates described in previous reports were similar to those obtained in the present study.

Table 4 Comparison between the postoperative complete remission (+) and postoperative complete remission (-) groups

	Category	POCR (+)	POCR (-)	*P* value
Age	< 60/≥ 60	1/7	11/11	0.0994
Sex	Male/female	7/1	21/1	0.4690
HBV and/or HCV	-/ +	0/8	6/16	0.1550
Alb (g/dL)	< 3.7/≥ 3.7	5/3	10/12	0.6817
T-Bil (mg/dL)	≤ 0.8/> 0.8	6/2	13/9	0.6722
PT (%)	< 90/≥ 90	4/4	9/13	0.6976
ICGR15 (%)	< 15/≥ 15	4/4	14/8	0.6779
AFP (ng/mL)	< 200/≥ 200	4/4	12/10	1.0000
PIVKA-II	< 100/≥ 100	2/6	1/21	0.1655
Child-pugh class	A/B	8/0	19/3	0.5448
Tumor size (cm)	< 10/≥ 10	5/3	10/12	0.6817
Differentiation	wel or mod/por	5/3	12/10	1.0000
pN	-/ +	7/1	21/1	0.4690
Macrovascular invasion	-/ +	0/8	5/17	0.2868
Distant metastasis	-/ +	8/0	19/3	0.5448
BCLC stage	B/C	3/5	9/13	1.0000
Anatomical hepatectomy	-/ +	2/6	1/21	0.1665
Number of tumors in the remnant liver	1-3/≥ 4	7/1	5/17	0.0025[a]

[a]*P* < 0.05. POCR: Postoperative complete remission; PT: Prothrombin time; ICGR15: Indocyanine green retention rate at 15 min; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence/antagonist-II; BCLC: Barcelona Clinic Liver Cancer.

The potential prognostic factors identified in the univariate analyses in the current study were the Child-Pugh class, tumor size, major vascular invasion, the number of tumors in the remnant liver, and whether POCR was achieved. The Child-Pugh class was the only independent prognostic factor that exhibited significance in the multivariate analysis (data not shown). However, we decided to focus on POCR, as it can be set as an aim of multidisciplinary therapy after reduction hepatectomy.

Achieving POCR using postoperative multidisciplinary treatment had an important impact on survival in the current cases. When the cases were limited to those in which POCR was achieved, the 1-year, 3-year, and 5-year OS rates after reduction hepatectomy were 100%, 75.0%, and 37.5%, respectively, and the MST was 56.55 mo. This suggests that reduction hepatectomy followed by postoperative treatment that aims to achieve POCR could be an effective treatment strategy for advanced HCC that is not indicated for curative hepatectomy.

The postoperative treatments employed after reduction surgery for HCC are different from those used to treat other malignancies. Firstly, the recovery of the remnant liver after hepatectomy enables further treatment for tumors in the remnant liver, which is considered to affect prognosis in most cases of HCC[15]. In fact, tumors were detected in the remnant liver after reduction hepatectomy in all of the present cases, but extrahepatic metastases were only detected in 3 cases. Secondly, there are established additional non-surgical treatments for HCC localized in the liver, such as LAT and TAI therapy. RFA is indicated for cases of HCC involving ≤ 3 tumors and a maximum tumor size of ≤ 3 cm and is sometimes employed as an alternative to hepatectomy[5]. TACE is indicated for cases of unresectable HCC involving large or multifocal tumors without major vascular invasion or extrahepatic metastases[5]. R0 resection is the first-choice treatment for some advanced malignancies, even in cases involving distant metastasis. For distant metastases from HCC, there are not enough data supporting the validity of this approach, and the efficacy of surgical resection for lung metastases[16,17], adrenal gland metastases[18], and brain metastases[19] is disputed.

Table 5 Comparison between the postoperative complete remission (-) tyrosine kinase inhibitors (+) and postoperative complete remission (-)tyrosine kinase inhibitors (-) groups

	Category	POCR (-)/TKI (+)	POCR (-)/TKI (-)	*P* value
Age	< 60/≥ 60	4/2	7/9	0.6351
Sex	Male/female	6/0	15/1	1.0000
HBV and/or HCV	-/ +	2/4	4/12	1.0000
Alb (g/dL)	< 3.7/≥ 3.7	1/5	9/7	0.1619
T-Bil (mg/dL)	≤ 0.8/> 0.8	4/2	9/7	1.0000
PT (%)	< 90/≥ 90	2/4	7/9	1.0000
ICGR15 (%)	< 15/≥ 15	4/2	10/6	1.0000
AFP (ng/mL)	< 200/≥ 200	4/2	8/8	0.6462
PIVKA-II	< 100/≥ 100	0/6	1/15	1.0000
Child-pugh class	A/B	6/0	13/3	0.5325
Tumor size (cm)	< 10/≥ 10	4/2	6/10	0.3476
Differentiation	Wel or mod/por	4/2	8/8	0.6462
pN	-/ +	5/1	16/0	0.2727
Macrovascular invasion	-/ +	0/6	5/11	0.2663
Distant metastasis	-/ +	5/1	14/2	1.0000
BCLC stage	B/C	2/4	7/9	1.0000
Anatomical hepatectomy	-/ +	0/6	1/15	1.0000
Number of tumors in the remnant liver	1-3/≥ 4	0/6	5/11	0.2663

POCR: Postoperative complete remission; TKIs: Tyrosine kinase inhibitors; PT: Prothrombin time; ICGR15: Indocyanine green retention rate at 15 min; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence/antagonist-II; BCLC: Barcelona Clinic Liver Cancer.

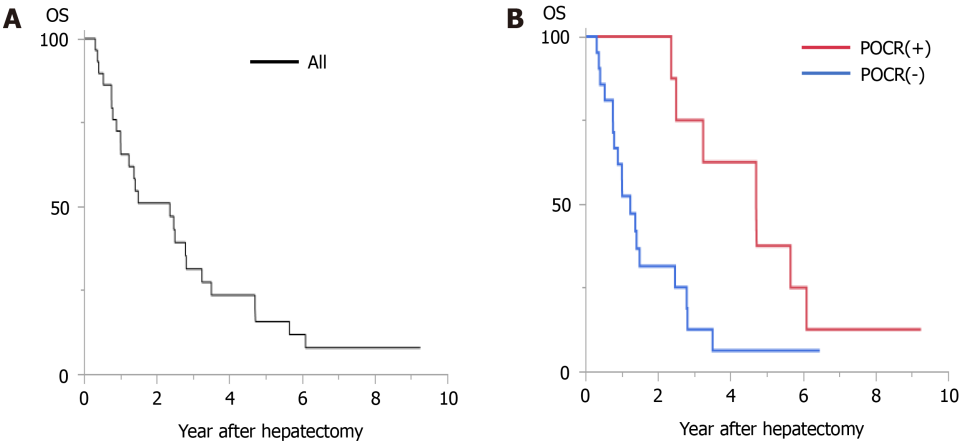

Figure 1 The survival curves obtained after reduction hepatectomy. A: The survival curve for all 30 cases of unresectable advanced hepatocellular carcinoma after reduction hepatectomy; B: The survival curves of the postoperative complete remission (POCR) (+) (red line) and POCR (-) (blue line) groups after reduction hepatectomy. POCR: Postoperative complete remission of evaluable lesions induced by multidisciplinary treatment after reduction hepatectomy.

In the present study, the number of tumors in the remnant liver after reduction hepatectomy was the only factor that differed significantly between the POCR (+) and POCR (-) groups. This indicates that it is important that reduction hepatectomy is performed with the aim of reducing the number of tumors in the remnant liver to ≤ 3, which agrees with the conclusion of the study by Hai *et al*[9]. According to the present study, POCR might not need to be achieved *via* surgery alone, and even patients in whom POCR is achieved using LAT or TAI therapy can be good candidates for reduction surgery. Furthermore, the findings of the current study suggest that some

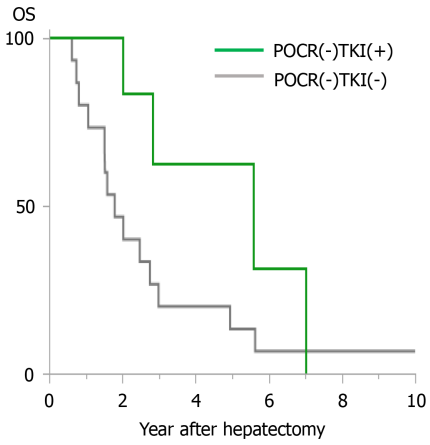

Figure 2 The survival curves of the postoperative complete remission (-), tyrosine kinase inhibitors (TKIs) (+) and postoperative complete remission (-),tyrosine kinase inhibitors (-) groups after reduction hepatectomy. The cases in which postoperative complete remission (POCR) was not achieved despite tyrosine kinase inhibitors (TKIs) treatment being administered in the postoperative period were included in the POCR (-) TKI (+) group (green line). The cases in which POCR was not achieved and TKIs were not administered in the postoperative period were included in the POCR (-) TKI (-) group (gray line).

patients would benefit from reduction hepatectomy even if POCR is not achieved. Patients that are likely to benefit from TKI treatment can also be good candidates for reduction hepatectomy.

In the current study, there were only 6 cases in which TKIs were orally administered. Two reasons are considered as possible explanations for the low frequency of TKI treatment. The first is the small number of cases included in the present study; *i.e.*, only 30. Second, the treatment options for HCC changed during the study period. The most important change was the introduction of TKIs as a treatment option. Sorafenib, a TKI, was reported to improve the prognosis of HCC in 2008[20], and it started to be used in the clinical setting in Japan in 2009. Moreover, lenvatinib, another TKI, was reported to be non-inferior to sorafenib in the REFLECT trial in 2018 [6]. In the present study, TKIs were only administered in the cases in which POCR was not achieved. This might have been due to the fact that TKIs were mainly administered when surgery, LAT, and TAI therapy were not indicated; *i.e.*, TKIs were used when the abovementioned treatments were not expected to be effective. The MST of the POCR (-) TKI (+) group was 33.52 mo, which is superior to the outcomes described in other studies in which unresectable HCC was treated with TKIs alone[6, 20].

Some cases that were successfully converted to downstaging hepatectomy after the preoperative administration of the TKIs sorafenib and lenvatinib have been reported [21-23]. Although these cases were successfully treated with conversion hepatectomy, the actual conversion rate due to the downstaging effects of TKIs remains unknown, and the response rate of HCC to TKI therapy (a complete response rate of 2% and a partial response rate of 38% can be achieved with lenvatinib[6]) is still insufficient to enable TKIs to be used for downstaging purposes as part of the standard treatment strategy for advanced HCC.

This study had several limitations. The first is the inevitable selection bias caused by the study's retrospective and single-center design, although one of the most important processes in reduction hepatectomy for advanced HCC that is not indicated for curative hepatectomy is the selection of cases that would benefit from such treatment. Two of the inclusion criteria for reduction hepatectomy for advanced HCC employed in the present study were similar to criteria reported by Komatsu *et al*[8]. The first was that it must be considered that reduction hepatectomy of the main tumor would eliminate the most important poor prognostic factor, and the second was that the patient's condition must be good enough to make them eligible for postoperative treatment. In the study by Komatsu *et al*[8], postoperative local treatment produced an obvious survival benefit. Surgical safety also has an important impact on whether postoperative multidisciplinary treatment can be performed. In the present study, postoperative treatment could not be performed in one case due to the deterioration of the patient's general condition because of a postsurgical complication. At the same time, the safety of surgery should be considered to be the most important factor from an ethical viewpoint. There were no surgery-related deaths in the present study. Other limitations of this study include the small number of cases and the short follow-up periods in some of the cases. Another limitation of the present study was the small

number of cases it included; therefore, a study involving more cases from multiple institutions should be performed in the future.

CONCLUSION

When reduction hepatectomy is performed for unresectable advanced HCC that is not indicated for curative hepatectomy, achieving POCR *via* postoperative multidisciplinary therapy is the key to success, with the 5-year OS rate and MST for the POCR (+) group being 37.5% and 56.55 mo, respectively. To achieve POCR, reduction hepatectomy should be performed with the aim of reducing the number of tumors in the remnant liver to ≤ 3. Even in cases in which POCR is not achieved, TKI treatment might improve the prognosis of advanced HCC after reduction hepatectomy.

ARTICLE HIGHLIGHTS

Research background

Reduction hepatectomy combined with multidisciplinary postoperative treatment should be considered as a treatment option for unresectable advanced hepatocellular carcinoma (HCC) that is not indicated for curative hepatectomy. A well designed and/or larger cohort study is required to further evaluate this treatment strategy.

Research motivation

Reduction hepatectomy combined with multidisciplinary postoperative treatment for unresectable advanced HCC that was not indicated for curative hepatectomy was effective when postoperative complete remission (POCR) was achieved through multidisciplinary postoperative therapy. To achieve POCR, reduction hepatectomy should aim to ensure that ≤ 3 tumors remain in the remnant liver. In cases in which POCR is not achieved, tyrosine kinase inhibitors (TKIs). can improve survival outcomes when administered as part of postoperative multidisciplinary therapy after reduction hepatectomy.

Research objectives

The 5-year overall survival rate and mean survival time (MST) for all cases after reduction hepatectomy were 15.7% and 28.40 mo, respectively. POCR, tumor size, major vascular invasion, and the number of tumors in the remnant liver after the reduction hepatectomy were found to be related to survival outcomes. In the POCR (+) and POCR (-) groups, the MST was 56.55 mo and 14.84 mo, respectively (P = 0.0041). POCR was achieved significantly more frequently when ≤ 3 tumors remained in the remnant liver (P = 0.0025). The MST was 33.52 mo in the POCR (-) TKI (+) group, which was superior to the MST of 10.74 mo seen in the POCR (-) TKI (-) group (P = 0.0473).

Research methods

Thirty cases of advanced HCC, in which reduction hepatectomy was performed between 2000 and 2018 at the Department of Gastroenterological Surgery I, Hokkaido University Graduate School of Medicine, were retrospectively investigated. These 30 cases were divided into two groups, the POCR (+) and POCR (-) groups, according to whether postoperative complete remission (POCR) of the evaluable lesions was achieved through postoperative treatment. Further analyses were performed after dividing the POCR (-) cases into two groups, the POCR (-) TKI (+) and POCR (-) TKI (-) groups, depending on whether TKIs were administered postoperatively.

Research results

To investigate the outcomes of combination treatment with reduction hepatectomy and multidisciplinary postoperative treatment for advanced HCC that is not indicated for curative hepatectomy.

Research conclusions

To date, few studies have evaluated combination treatment with reduction hepatectomy and multidisciplinary postoperative treatment for advanced HCC that is not indicated for curative hepatectomy.

Research perspectives

The prognosis of advanced HCC that is not indicated for curative hepatectomy remains poor, despite advances in the treatment of HCC including the development of tyrosine kinase inhibitors.

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ORIGINAL ARTICLE

Retrospective Study

Development and validation of a prediction model for deep vein thrombosis in older non-mild acute pancreatitis patients

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Abstract

BACKGROUND

Deep vein thrombosis (DVT) may cause pulmonary embolus, leading to late deaths. The systemic inflammatory and hypercoagulable state of moderate and severe acute pancreatitis (non-mild acute pancreatitis, NMAP) patients may contribute to the development of venous thromboembolism. Accurate prediction of DVT is conducive to clinical decisions.

AIM

To develop and validate a potential new prediction nomogram model for the occurrence of DVT in NMAP.

METHODS

NMAP patient admission between 2013.1.1 and 2018.12.31 at the West China Hospital of Sichuan University was collected. A total of 220 patients formed the training set for nomogram development, and a validation set was constructed using bootstrapping with 100 resamplings. Univariate and multivariate logistic regression analyses were used to estimate independent risk factors associated with DVT. The independent risk factors were included in the nomogram. The accuracy and utility of the nomogram were evaluated by calibration curve and decision curve analysis, respectively.

RESULTS

A total of 220 NMAP patients over 60 years old were enrolled for this analysis. DVT was detected in 80 (36.4%) patients. The final nomogram included age, sex, surgery times, D-dimer, neutrophils, any organ failure, blood culture, and classification. This model achieved good concordance indexes of 0.827 (95%CI: 0.769-0.885) and 0.803 (95%CI: 0.743-0.860) in the training and validation sets,

additional data are available.

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respectively.

CONCLUSION

We developed and validated a prediction nomogram model for DVT in older patients with NMAP. This may help guide doctors in making sound decisions regarding the administration of DVT prophylaxis.

Key Words: Acute pancreatitis; Deep vein thrombosis; Prediction model; Bootstrap; Nomogram; Discrimination and calibration

Core Tip: Deep vein thrombosis (DVT) may cause pulmonary embolus, leading to late death. Few studies have focused on DVT in moderate and severe acute pancreatitis. We identified eight predictors and developed and established a prediction nomogram model for DVT in older patients with moderate and severe acute pancreatitis. This model achieved good concordance indexes and may help guide doctors in the administration of DVT prophylaxis.

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INTRODUCTION

Acute pancreatitis (AP) is a common and potentially lethal disease with a rising incidence. The incidence of AP is 34 cases per 100,000 people in the general population per year worldwide[1]. Among gastrointestinal diseases, AP is one of the most common reasons for hospitalization in the United States, and the disease accounts for $2.6 billion health care dollars per year[2-4]. According to the 2012 Atlanta classification, most AP patients have mild acute pancreatitis. However, 20% of patients develop moderate or severe acute pancreatitis (non-mild acute pancreatitis, NMAP). Furthermore, the mortality of NMAP can reach 35%, which is significantly higher than that of mild acute pancreatitis[5]. Researchers usually focus on complications such as organ failure and infection in NMAP[6,7]. However, few of studies have paid attention to venous thromboembolism in NMAP. A previous study showed that the incidence of venous thromboembolism in hospitalized patients was approximately 0.4% to 1.3%[8]. NMAP usually requires a long hospital stay. The systemic inflammatory and hypercoagulable state of NMAP patients may contribute to the development of venous thromboembolism[9-11]. Deep vein thrombosis (DVT), a kind of venous thromboembolism, commonly develops in the lower extremities. It can cause acute pulmonary embolism (PE) when it falls and flows to the lung[12,13]. A recent study showed that the rate of DVT in AP patients could reach 38%[14]. Older patients more easily develop venous thromboembolism. This may increase the difficulty of treatment in older NMAP patients. However, there is a lack of a scoring model for predicting develop of DVT in NMAP patients. The existing scores for DVT are not suitable for critically ill patients[15-17]. In the past, nomograms were used as a graphical calculation to help solve engineering problems. As a statistical tool, nomograms have a unique advantage in visualizing the relationships of involved parameters. This approach enables users to calculate the overall probability of clinical outcome for an individual patient[18,19]. Recently, it has been widely used in clinical prediction models[20,21]. Thus, the aim of this study was to develop a prediction model for DVT in older NMAP patients.

MATERIALS AND METHODS

Study design and participants

Medical records of older NMAP patients admitted to West China Hospital from 2013.1.1 to 2018.12.31 were retrospectively collected. Included criteria were as follows: 1. AP was diagnosed in West China Hospital and classified as moderate or severe; 2. More than 60 years old. Pancreatic tumors are one of the causes of AP and are also a risk factor for DVT development[22]. Thrombosis development in other places may be a confounding factor in this study. Thus, patients who had the following diagnoses were excluded from this study: (1) Pancreatic tumor; and (2) Thromboses in other locations. This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.

Data collection and definition

AP was diagnosed through a combination of clinical manifestations and signs (i.e., sudden onset of upper abdominal pain), laboratory tests (amylase or lipase levels were three times higher than normal limits), and imaging examinations (abdominal ultrasound, abdominal computed tomography (CT), and magnetic resonance imaging) [23]. AP was classified according to the revised Atlanta Classification[23]. The definition of non-mild acute pancreatitis (NMAP) is acute pancreatitis classified as moderate or severe. Acute pancreatitis patients aged over 60 years old were defined as older acute pancreatitis patients. The diagnosis of DVT was based on the results of color Doppler ultrasonography when patients presented swelling or pitting edema, redness, and leg tenderness. Organ failure (OF) was defined as a patient who had at least one failure of respiratory function, cardiovascular function, or renal function. Respiratory failure was defined as PaO_2 < 60 mmHg, despite FiO_2 of 0.30, or a need for mechanical ventilation. Cardiovascular failure was defined based on circulatory systolic blood pressure < 90 mmHg, despite adequate fluid resuscitation, or a need for inotropic catecholamine support. Renal failure was defined as creatinine level > 177 μmol/L after rehydration or the need for hemofiltration or hemodialysis.

The following variables were recorded for the study population: Age, sex, etiology, smoking, drinking, surgery times, any organ failure, respiratory failure, renal failure, cardiovascular failure, severity classification, onset time to diagnosis of DVT, and blood index. In DVT patients, all variables were collected until the time of DVT diagnosis. In NDVT patients, all variables were collected throughout the whole hospital stay. Repeated measurements of continuous variables are shown on average.

Statistical analysis

Continuous variables are described as the mean (SD) or median and binary variables are expressed as counts (%). Statistical analysis was performed using R software. (Version 3.6.1)

Prediction model development

Relevant predictors included age, sex, surgery times, any organ failure, respiratory failure, cardiovascular failure, renal failure, blood culture, C-reactive protein, neutrophils, serum albumin, D-dimer, severity classification of DVT in patients with AP identified from a previous study[24,25] and advice of pancreatologists. Patients with more than 30% of the preselected predictors missing were excluded from model development.

In this study, 80 patients were identified with DVT, and more than ten times patients with NDVT were identified. Due to the imbalance between the DVT and NDVT groups, undersampling was performed to adjust the number between the two groups. A total of 10% NDVT patients were randomly selected compared with DVT patients. Finally, 140 NDVT patients were selected. Thus, training data included 80 DVT and 140 NDVT patients.

Logistic regression was used to identify the variables that were significantly correlated with DVT in the training group. Variables with a *P*-value less than 0.05 and more than 0.05 but suggested by pancreatologists were fed to a multivariate logistic regression model. Stepwise selection was used to further eliminate redundant variables. The resulting multivariate logistic regression model was used to build the prediction model.

Prediction model validation

The bootstrap method was used to evaluate the performance of the prediction model. In the bootstrap method, 100 random samples were drawn with replacement from the

original data set and the coefficients were recalculated.

To validate the prediction model, two criteria were used to evaluate the prediction performance. On the one hand, the concordance index (c-index) was calculated to estimate the discrimination of the prediction model. On the other hand, calibration curves were plotted to evaluate the consistency between predicted DVT probability and actual DVT proportion. Values of 1 and 0.5 indicate perfect discrimination and no discrimination, respectively. The C-index and calibration results presented are an average of the bootstrapped samples.

RESULTS

Baseline clinical characteristics

Medical records of NMAP patients over 60 years admitted to West China Hospital from 2013.1.1 to 2018.12.31 were collected. DVT was diagnosed in 80 patients. Due to the imbalance of the data, undersampling was performed on selected NDVT patients. Finally, 140 NDVT patients were randomly selected for analysis. The baseline characteristics of the patients, including demographics, clinical indexes, and blood indexes, in the two groups are shown in Table 1. There are 81 and 49 females in the NDVT group and DVT group, respectively. The DVT group included patients aged between 60 and 88 years (mean age: 70.16 years), and the NDVT group included patients aged 69.81 years. Biliary was the most common etiology in both groups. There were 37 (26.4%) and 33 (23.6%) NDVT patients who smoked and drank, respectively. Seventeen (21.2%) and 15 (18.8%) DVT patients smoked and drank, respectively. All organ failure in the DVT group was significantly higher than that in the NDVT group. Respiratory failure accounted for the largest proportion in OF. In total, 65% of patients were classified as severe. However, 67% of patients in the NDVT group were classified as moderate. Blood culture, D-dimer, and serum albumin in the DVT group were significantly different between the two groups. Table 2 shows the thrombus location of the DVT patients. The most common location of vein thrombosis was both lower limbs, which were detected in 31 (38.8%) patients. Only 3 (3.7%) patients were found to have vein thrombosis in the left upper limb, and 12 (15%) patients had vein thrombosis detected in more than two locations.

Prediction model development

Univariate and multivariate analyses were performed to select potential predictors. A nomogram model was constructed based on the results of the multivariate logistics regression analysis and the suggestions of pancreatologists. Finally, 8 potential predictors based on 220 patients were selected. These features included sex, age, surgery times, renal failure, classification, D-dimer, blood culture, and neutrophils. Figure 1 shows the nomogram in which sex, age, surgery times, renal failure, classification, D-dimer, blood culture, and neutrophils defined the individual risk of DVT in NMAP patients. In this nomogram, D-dimer is a continuous variable and every 5 unit increase in D-dimer results in an approximately 0.8-point increase in risk points. The nomogram maps the predicted probability of DVT on a scale of 0 to 220. For each covariate, a vertical line is drawn upwards, and the corresponding points are noted. This is repeated for each covariate ending with a total score that corresponds to a predicted probability of morbidity at the bottom of the nomogram. The odds ratios of the nomogram variables are summarized in Table 3.

Validation prediction model

The C-index for the prediction nomogram was 0.827 (95%CI: 0.769-0.885). It was confirmed to be 0.803 (95%CI: 0.743-0.860) through bootstrapping validation, which suggested the model's good discrimination. The calibration curve in Figure 2 shows good concordance between the estimated risk of DVT and the actual presence of DVT.

DISCUSSION

Using data from a retrospective study including older NMAP patients with DVT, we developed and internally validated a potential new prediction model for DVT. This is the first model for predicting DVT in older NMAP patients. The performance of the prediction model was adequate. This nomogram, based on routinely available demographic and blood indexes, predicts the probability of DVT in NMAP patients.

Table 1 Demographic characteristics

Variables	NDVT	DVT	*P* value
N	140	80	
Age	69.81 (7.52)	70.16 (7.84)	0.745
Gender: Female	81 (57.9)	49 (61.3)	0.726
Etiology			
Biliary	65 (47.4)	39 (48.8)	
Alcohol	3 (0.21)	5 (0.62)	
Hyperlipidemia	23 (16.4)	10 (12.5)	
Others	49 (35.0)	26 (32.5)	
Smoking	37 (26.4)	17 (21.2)	0.507
Drink	33 (23.6)	15 (18.8)	0.487
Surgery times			< 0.001
0	114 (81.4)	47 (58.8)	
1	24 (17.1)	23 (28.7)	
2	2 (1.4)	6 (7.5)	
3	0 (0.0)	4 (5.0)	
Any organ failure	72 (51.4)	67 (83.8)	< 0.001
Respiratory failure	61 (43.6)	58 (72.5)	< 0.001
Renal failure	15 (10.7)	31 (38.8)	< 0.001
Cardiovascular failure	23 (16.4)	37 (46.2)	< 0.001
Classification			< 0.001
Moderate to severe	95 (67.9)	28 (35.0)	
Severe	45 (32.1)	52 (65.0)	
Blood index			
Blood culture positive	8 (5.7)	20 (25.0)	< 0.001
D-dimer	5.87 (5.48)	8.78 (6.47)	0.002
CRP	120.77 (84.66)	124.51 (86.79)	0.796
WBC	11.09 (4.37)	11.74 (4.63)	0.312
Neutrophils	9.05 (4.08)	9.87 (4.48)	0.177
Serum albumin	32.90 (4.13)	31.25 (4.31)	0.006

NDVT: None deep vein thrombosis; DVT: Deep vein thrombosis; CRP: C-reactive protein; WBC: White blood cell.

The recent criteria of AP classification were put forward in 2012. Non-mild acute pancreatitis patients have a poorer prognosis, and they stay in the hospital for a long time. Hospitalization has been considered a significant risk factor for VTE[26]. Furthermore, older patients usually have slow blood flow. These factors all contribute to DVT development. However, doctors usually pay attention to DVT when patients have clinical manifestations, such as calf swelling. In trauma patients, occult DVT may cause pulmonary embolus, leading to late deaths due to fatality[27]. Early detection of DVT results in decreased rates of pulmonary embolus and mortality[28]. Therefore, accurate prediction of DVT is invaluable to provide treatment for each NMAP patient.

Our findings are essentially in line with previous venous thromboembolism studies. In the present study, we found that DVT mostly develops in both lower limbs at the same time. However, isolated left upper limbs only accounted for 3.7% of patients. A previous study showed that upper limb DVT is less than 10% of all DVT[22]. In this study, more than 16.2% of patients had upper limb DVT.

Table 2 The location of deep vein thrombosis

Location of the thrombosis	Number of patients (*n* = 80)
Left upper limb isolated	3 (3.7%)
Right upper limb isolated	6 (7.5%)
Both upper limbs	4 (5.0%)
Left lower limb isolated	14 (17.5%)
Right lower limb isolated	10 (12.5%)
Both lower limbs	31 (38.8%)
More than two locations	12 (15.0%)

Table 3 Odds ratio and 95% confidence interval of nomogram parameters

Variables	OR (95%CI)	*P* value
Age	1.02 (0.983-1.066)	0.257
Gender	1.23 (0.625-2.431)	0.546
Surgery times	2.70 (1.566-4.651)	0.000
Renal failure	0.35 (0.166-0.728)	0.005
Classification	2.17 (1.133-4.164)	0.020
D-dimer	1.02 (0.971-1.081)	0.382
Blood culture	0.53 (0.218-1.267)	0.152
Neutrophils	1.01 (0.930-1.087)	0.887

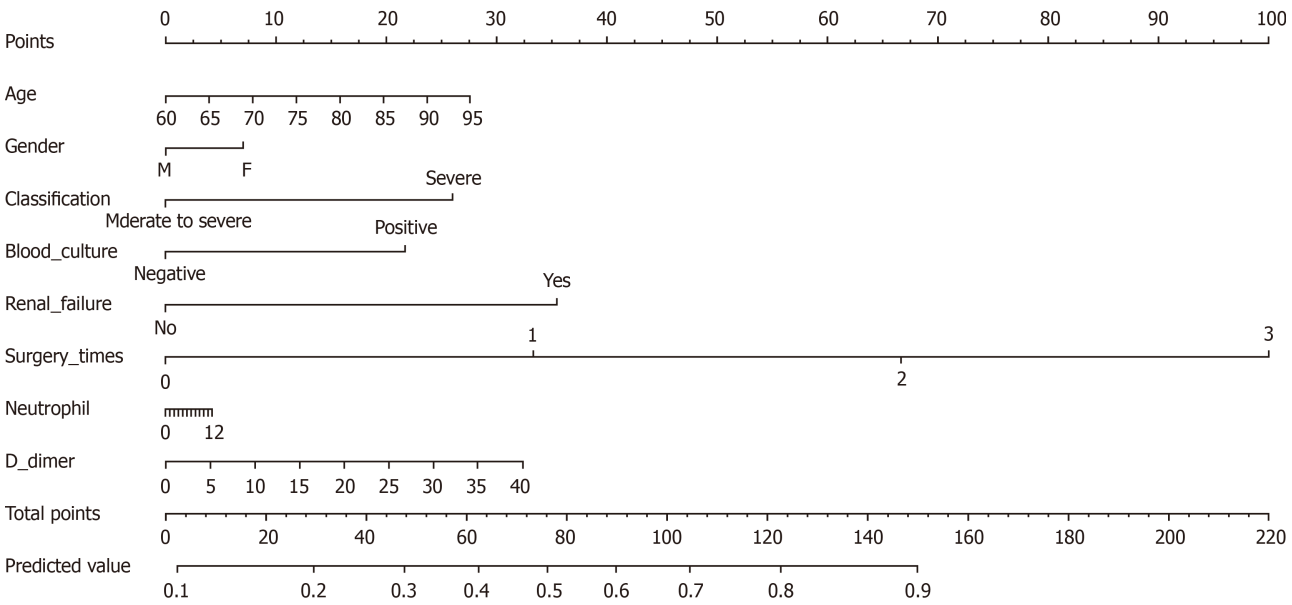

Figure 1 Nomogram for predicting deep vein thrombosis in non-mild acute pancreatitis patients. The nomogram maps the predicted probability of deep vein thrombosis (DVT) on a scale of 0 to 220. For each covariate, draw a vertical line upwards and record corresponding points. Repeated it and added the points. A total score corresponds to a predicted probability of DVT at the bottom of the nomogram.

Some predictors were already confirmed in other studies. D-dimer is the most well validated and widely used biomarker of venous thromboembolism excluded[25]. It is usually combined with the Wells score in practice. In this study, D-dimer was an important predictor of DVT. OF is regarded as one of the most important parameters of AP patients in the course of the early phase[23]. The main causes of OF are cytokine cascades resulting in systemic inflammatory response syndrome (SIRS)[29].

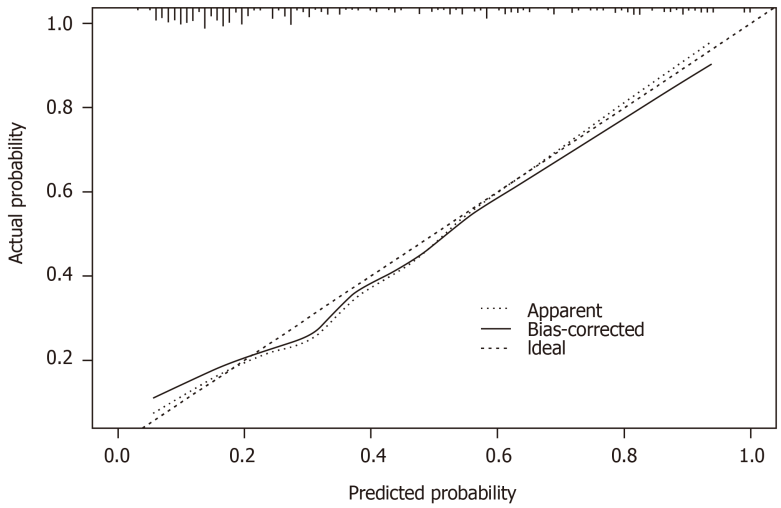

Figure 2 Calibration curve for deep vein thrombosis on the nomogram. The ideal line represents a perfect match between predicted and observed occurrence of deep vein thrombosis; Apparent line, prediction capability of the model obtained after data analysis; Bias-corrected line, prediction capability of the model obtained after bootstrap correction.

Respiratory failure, renal failure, and cardiovascular failure commonly take place in the clinical. OF can lead to long term bed rest and immobilization. Both of these contribute to DVT development[14]. However, in this study, only renal failure was in the final prediction model for DVT development. This factor was validated in a previous study[30]. Vascular endothelium is activated by proinflammatory cytokines in severe acute pancreatitis. This promotes the activation of coagulation cascades and circulating neutrophils[31]. Furthermore, neutrophils promote coagulation by inhibiting anticoagulant factors and releasing neutrophil extracellular traps[32]. These further promote thrombogenesis. Currently, mechanistic research shows that neutrophil extracellular traps hold promise for novel clinical treatment of DVT[32]. Patients with positive blood cultures have more severe inflammation than others. Additionally, infection has been thought to be a risk factor for venous thromboembolism[24]. Surgery is also a risk factor for venous thromboembolism[24]. Some NMAP patients need reoperation several times. More surgery times mean patients experience more frequent and longer bed rest.

Overall, our study first focused on the development of DVT in older NMAP patients, which has never been studied before. We analyzed the risk factors for DVT and built a nomogram model to predict the probability of developing DVT for NMAP patients. Proper use of this model can help physicians identify patients with a high risk of developing DVT.

There are several limitations in this study. First, this was a retrospective study, and the examination of DVT was not performed routinely. Thus, the diagnosis of DVT may have been missed in some patients. In addition, this was a single-center study, and validation was only performed in internal data. The results could be more convincing if external validation is performed. Moreover, due to the limitation of the sample size, potential bias may exist in the present study.

CONCLUSION

In this study, a nomogram model was built by combining eight independent risk factors for DVT. This nomogram score is a reliable and effective tool that can predict DVT in older patients with NMAP. This may help guide doctors in making sound decisions regarding the administration of DVT prophylaxis.

ARTICLE HIGHLIGHTS

Research background

Deep vein thrombosis (DVT) may cause pulmonary embolus leading to late deaths. The systemic inflammatory and hypercoagulable state of moderate and severe acute

pancreatitis (non-mild acute pancreatitis, NMAP) patients may contribute to the development of venous thromboembolism. Accurate prediction of DVT is conducive to clinical decisions.

Research motivation

There is a lack of a scoring model for predicting the development of DVT in NMAP patients.

Research objectives

We aimed to develop a prediction model for DVT in old NMAP patients.

Research methods

Univariate and multivariate logistic regression analyses were used to select independent risk factors associated with DVT. The selected risk factors were included in the nomogram. A validation set was constructed using bootstrapping with 100 resamplings. The accuracy and utility of the nomogram were evaluated by calibration curve and decision curve analysis, respectively.

Research results

Eighty DVT patients and 140 non-DVT patients were included in this study. Eight factors including age, sex, surgery times, D-dimer, neutrophils, any organ failure, blood culture, and classification constitute the prediction model. This model achieved good concordance indexes of 0.827 (95%CI: 0.769-0.885) and 0.803 (95%CI: 0.743-0.860) in the training and validation set, respectively.

Research conclusions

A reliable and effective nomogram model that can predict DVT in old patients with NMAP was constructed.

Research perspectives

The usability of the new model needs further validation by other center data.

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SCIENTOMETRICS

Immunotherapy after liver transplantation: Where are we now?

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Abstract

BACKGROUND

There is limited evidence on the safety of immunotherapy use after liver transplantation and its efficacy in treating post-liver transplant hepatocellular carcinoma (HCC) recurrence.

AIM

To assess the safety of immunotherapy after liver transplant and its efficacy in treating post-liver transplant HCC recurrence.

METHODS

A literature review was performed to identify patients with prior liver transplantation and subsequent immunotherapy. We reviewed the rejection rate and risk factors of rejection. In patients treated for HCC, the oncological outcomes were evaluated including objective response rate, progression-free survival (PFS), and overall survival (OS).

RESULTS

We identified 25 patients from 16 publications and 3 patients from our institutional database (total n = 28). The rejection rate was 32% (n = 9). Early mortality occurred in 21% (n = 6) and was mostly related to acute rejection (18%, n = 5). Patients who developed acute rejection were given immunotherapy earlier after transplantation (median 2.9 years *vs* 5.3 years, P = 0.02) and their graft biopsies might be more frequently programmed death ligand-1-positive (100% *vs* 33%, P = 0.053). Their PFS (1.0 ± 0.1 mo *vs* 3.5 ± 1.1 mo, P = 0.02) and OS (1.0 ± 0.1 mo *vs* 19.2 ± 5.5 mo, P = 0.001) compared inferiorly to patients without rejection. Among the 19 patients treated for HCC, the rejection rate was 32% (n = 6) and the overall objective response rate was 11%. The median PFS and OS were 2.5 ± 1.0 mo and 7.3 ± 2.7 mo after immunotherapy.

CONCLUSION

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Rejection risk is the major obstacle to immunotherapy use in liver transplant recipients. Further studies on the potential risk factors of rejection are warranted.

Key Words: Liver transplant; Hepatocellular carcinoma; Recurrence; Immunotherapy; Rejection; Survival

Core Tip: A literature review was performed to identify patients with prior liver transplantation and subsequent immunotherapy. Among the 28 included patients, the rejection rate was 32% (n = 9). Patients who developed acute rejection were given immunotherapy earlier after transplantation (median 2.9 years *vs* 5.3 years, P = 0.02) and their graft biopsies might be more frequently programmed death ligand-1 positive (100% *vs* 33%, P = 0.053). Among the 19 patients treated for hepatocellular carcinoma (HCC), the overall objective response rate was 11%. Rejection risk is the major obstacle to immunotherapy for post-liver transplant HCC recurrence.

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INTRODUCTION

Post-liver transplant hepatocellular carcinoma (HCC) recurrence represents a therapeutic challenge. Prognosis is generally poor while tumor progression is unrestrained with suppressed host immunity. Thanks to recent advances in oncological treatment and improved immunosuppression, the outlook of these patients has improved[1,2], and long-term survival is no longer impossible. Nevertheless, reduced immune surveillance remains the Achilles heel for tumor control.

Over the last decade, immunotherapy has revolutionized cancer treatment. By disengaging immune checkpoints pathways, host immune response is augmented and directed towards the tumor. Immunotherapy is also characterized by a favorable side-effect profile compared to targeted therapy, which has been extensively investigated for post-transplant HCC recurrence. Modest efficacy was observed, but significant adverse effect has often led to dose reduction or discontinuation[3-6]. While immunotherapy has demonstrated satisfactory outcomes in patients with advanced primary HCC[7,8], its role in post-transplant HCC recurrence has not been investigated. There are two major obstacles to immunotherapy use in this setting. First, the possibility of enhancing alloimmunity and inducing rejection has raised safety concern. Second, efficacy is also questionable because concomitant immunosuppression potentially interferes with the immunomodulatory pathways involved. Given these concerns, liver transplant patients have been excluded from cancer immunotherapy trials, and limited data exist on the role of immune checkpoint inhibitors for post-liver transplant HCC recurrence.

In this study, we reviewed the literature for the record of patients who had undergone prior liver transplantation and received immunotherapy. In addition, we reviewed the liver transplant recipients who had been treated with immunotherapy in our institution. The objective was to summarize the existing experience and provide further insights on safety and efficacy of immunotherapy for post-transplant HCC recurrence.

MATERIALS AND METHODS

Patients

A literature search was performed on PubMed (United States National Library of

Medicine, National Institutes of Health, United States) for relevant English articles with a combination of keywords: "liver transplantation" with "immunotherapy" or "checkpoint inhibitors" or "programmed cell death 1" or "PD-1" or "cytotoxic T lymphocyte associated 4" or "CTLA-4." The full text of potentially relevant articles was reviewed. Original case reports, case series, observation studies, and review articles were included if they described immune checkpoint inhibitor therapy in a patient with prior liver transplantation. Laboratory studies without clinical subjects were excluded. References in the included studies were reviewed for additional relevant articles. Patient data was extracted including demographics, timing and indication of immunotherapy, concomitant immunosuppression, programmed death ligand-1 (PD-L1) status, adverse events, treatment response, and survival. Subjects were cross-checked to ensure no individual patient was included twice. In addition, we reviewed the records of liver transplant recipients who underwent immunotherapy in Queen Mary Hospital, the University of Hong Kong during the period from January 2016 to December 2020. Patient data were retrieved from a prospectively maintained institutional database.

Methods and statistics

We assessed the safety of immunotherapy by reviewing the rejection rate and mortality in all identified patients treated for various indications. We also looked into patients treated for recurrent HCC after liver transplantation to investigate the efficacy of immunotherapy in this setting. We reviewed the best treatment response, rate of early mortality, progression-free survival (PFS), and overall survival (OS) after immunotherapy. Early mortality was defined as mortality within 30 d from immunotherapy. Treatment response was defined according to the Response Evaluation Criteria in Solid Tumors 1.1[9]. Data was summarized with descriptive statistics. Continuous variables were expressed with medians and interquartile ranges (IQRs). Parametric and non-parametric variables were compared with the Student's *t*-test and Mann-Whitney *U* test where appropriate. Categorical variables were expressed in frequencies and percentages and were compared with the chi-square test. Survival data was analyzed with the Kaplan-Meier method and compared using the log-rank test. Data were analyzed using Statistical Package for the Social Sciences 16.0 (SPSS) for Windows (SPSS Inc., Chicago, IL, United States). Statistical significance was defined by $P < 0.05$.

RESULTS

Using PubMed, we identified 16 publications describing 25 patients who had a prior liver transplantation and subsequently received immunotherapy[10-25]. From the institutional database, there were 3 patients fulfilling the same inclusion criteria. These 28 patients formed the basis of this study (Table 1).

Patient characteristics

The descriptive characteristics are shown in Table 2. There was a male predominance (79%), and the median age was 61 (IQR 53-66). Nineteen patients (68%) were treated for recurrent HCC, 8 (29%) for *de novo* melanoma, and 1 (4%) for squamous cell carcinoma of the lung. Most received immunotherapy after failure of prior systemic therapy (median line of systemic treatment 2, IQR 1-3). Twenty-five patients (89%) received a programmed cell death protein-1 (PD-1) inhibitor (nivolumab 54%; pembrolizumab 36%). Four patients (14%) received cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitor (ipilimumab) and they were all indicated for melanoma. One patient received ipilimumab followed by pembrolizumab.

Seven graft liver and eight tumor tissues were tested for PD-L1 status. Among the tested samples, the rates of positive PD-L1 staining were 71% for graft liver and 50% for tumor. Ten patients (36%) received tacrolimus monotherapy as immunosuppression. Six patients (21%) received a mammalian target of rapamycin (mTOR) inhibitor as single agent while 5 patients (18%) received combination therapy with tacrolimus and an mTOR inhibitor.

Graft rejection and associated factors

The rate of acute rejection following immunotherapy was 32% ($n = 9$). Early mortality occurred in 21% ($n = 6$), and most were related to acute rejection (18%, $n = 5$). Patients who developed acute rejection were given immunotherapy earlier after transplantation (median 2.9 years *vs* 5.3 years, $P = 0.02$). Among the patients with

Table 1 Patients with prior liver transplantation and subsequent immunotherapy

Ref.	Drug	No. of cycles	Sex	Age	Indication	Year from transplant	Line of therapy	Rejection	Early mortality	PD-L1 status		Immunosuppression	Best response	PFS (mo)	OS (mo)
										Graft	Tumor				
De Toni and Gerbes[10]	Nivolumab	15	M	41	HCC	NA	1	No	No	NA	0%	Tacrolimus	PD	3.5	7
Friend *et al*[11]	Nivolumab	2	M	20	HCC	4	2	Yes	Yes	Pos	Pos	Sirolimus	NA	1	1
Friend *et al*[11]	Nivolumab	1	M	14	HCC	3	3	Yes	Yes	Pos	Pos	Tacrolimus	NA	1	1
Varkaris *et al*[12]	Pembrolizumab	NA	M	70	HCC	8	NA	No	No	NA	NA	Tacrolimus	PD	NA	NA
Munker and De Toni[13]	Nivolumab	NA	M	57	HCC	2.7	3	No	No	NA	10%	Tacrolimus	PD	2.2	1.2 (surviving)
Munker and De Toni[13]	Nivolumab	NA	M	56	HCC	7.8	4	No	No	5%	NA	Sirolimus/MMF	PD	0.7	1.1 (surviving)
Munker and De Toni[13]	Nivolumab	NA	F	35	HCC	3.7	5	No	No	0%	0%	Tacrolimus	PD	1.3	1.3 (surviving)
Munker and De Toni[13]	Nivolumab	NA	M	64	HCC	1.2	2	No	Yes	NA	0%	Tacrolimus	NA	0.3	0.3
Munker and De Toni[13]	Nivolumab	NA	M	68	HCC	1.1	2	Yes	Yes	30%	0%	Sirolimus	NA	0.9	0.9
Al Jarroudi *et al*[14]	Nivolumab	4	M	70	HCC	2.75	3	Yes	No	NA	NA	Tacrolimus	NA	4	4
Al Jarroudi *et al*[14]	Nivolumab	5	F	62	HCC	1	4	No	No	NA	NA	Tacrolimus	PD	2.5	NA
Al Jarroudi *et al*[14]	Nivolumab	6	M	66	HCC	5	4	No	No	NA	NA	Tacrolimus	SD	3	NA
Rammohan *et al*[15]	Pembrolizumab	14	M	57	HCC	4.3	2	No	No	NA	NA	Tacrolimus/mTOR inhibitor	CR	10 (no progression)	10 (surviving)
Gassmann *et al*[16]	Nivolumab	1	F	53	HCC	3	2	Yes	Yes	NA	NA	Everolimus	NA	0.8	0.8
Nasr *et al*[17]	Pembrolizumab	35	M	63	HCC	4.6	2	No	No	NA	NA	Tacrolimus/MMF	CR	25 (no progression)	25 (surviving)
Wang *et al*[18]	Pembrolizumab	1	M	48	HCC	1	1	Yes	No	NA	NA	Tacrolimus/Everolimus	NA	NA	8 (surviving)
Au (current research)	Nivolumab	4	M	62	HCC	2.2	3	No	No	NA	NA	Tacrolimus/Everolimus	PD	4.0	7.3

Au (current research)	Nivolumab	6	M	53	HCC	6.0	2	No	No	NA	NA	Sirolimus	PD	2.8	10.6
Au (current research)	Pembrolizumab	16	M	77	HCC	32	1	No	No	NA	NA	Tacrolimus/Everolimus	SD	12.4	19.2
Ranganath and Panella[19]	Ipilimumab	4	F	59	Melanoma	8	NA	No	No	NA	NA	Sirolimus	PR	5	9 (surviving)
Morales *et al*[20]	Ipilimumab	4	M	67	Melanoma	8	2	No	No	NA	NA	Sirolimus/MMF	PR	4 (no progression)	14 (surviving)
Munker and De Toni[13]	Pembrolizumab	NA	M	55	Melanoma	5.5	2	No	No	0%	5%	Everolimus/MMF	CR	21.1 (no progression)	21.1 (surviving)
Munker and De Toni[13]	Pembrolizumab	NA	M	64	Melanoma	3.1	2	Yes	No	25%	NA	MMF/Prednisolone	NA	NA	0.7 (surviving)
Kuo *et al*[21]	Ipilimumab/Pembrolizumab	4/25	M	62	Melanoma	6	NA	No	No	NA	NA	Sirolimus	PR	24 (no progression)	24 (surviving)
Dueland *et al*[22]	Ipilimumab	1	F	67	Melanoma	1.5	1	Yes	No	NA	NA	Prednisolone	PD	3 (no progression)	4
Schvartsman *et al*[23]	Pembrolizumab	2	M	35	Melanoma	20	1	No	No	NA	NA	Tacrolimus	CR	6	6 (surviving)
Tio *et al*[24]	Pembrolizumab	1	F	63	Melanoma	NA	NA	Yes	Yes	NA	NA	Ciclosporin	NA	NA	NA
Biondani *et al*[25]	Nivolumab	3	M	54	SCC lung	13	1	No	No	NA	NA	Tacrolimus/Everolimus	PD	2.25	15

CR: Complete response; F: Female; HCC: Hepatocellular carcinoma; M: Male; NA: Not available; OS: Overall survival; PD: Progressive disease; PFS: Progression-free survival; PR: Partial response; SCC: Squamous-cell carcinoma; SD: Stable disease.

acute rejection, graft PD-L1 positivity was possibly more frequent but not statistically evident (100% *vs* 33%, $P = 0.053$). Otherwise, patients with and without rejection were comparable in terms of age (63 *vs* 59, $P = 1.00$), indication of immunotherapy ($P = 0.93$), proportion of PD-1 *vs* CTLA-4 blockade ($P = 1.00$), and immunosuppressive therapy received ($P = 0.29$-0.48). Excluding one patient who received both PD-1 and CTLA-4 blockade, the rejection rate was similar between patients receiving PD-1 (8/24) and CTLA-4 blockade (1/3) (both 33%, $P = 1.00$).

Patients with acute rejection suffered from more early mortalities (56% *vs* 5%, $P = 0.002$). Their PFS (1.0 ± 0.1 mo *vs* 3.5 ± 1.1 mo, $P = 0.02$) and OS (1.0 ± 0.1 *vs* 19.2 ± 5.5 mo, $P = 0.001$) compared inferiorly to patients without rejection (Figures 1 and 2).

Efficacy in treating recurrent HCC

Patients who received immunotherapy for HCC recurrence were treated with immunotherapy earlier after transplant than those treated for *de novo* malignancies (median time from transplant 3.3 years *vs* 7 years, $P = 0.03$). They received immuno-

Table 2 Descriptive characteristics of all patients with prior liver transplantation and subsequent immunotherapy

	All	Rejection	No rejection	*P* value
Total (%)	28	9 (32)	19(68)	
Gender (M/F; %M)	22/6 (79)	6/3 (67)	16/3 (84)	0.29
Age	61 (53-66)	63 (34-67.5)	59 (54-64)	1.00
Year after transplant	3.9 (2.5-6.5)	2.9 (1.2-3.1)	5.3 (2.7-8.0)	0.02
Indication (%)				0.93
HCC	19 (68)	6 (67)	13 (68)	
Melanoma	8 (29)	3 (33)	5 (26)	
SCC of lung	1 (4)	0 (0)	1 (5)	
Line of systemic therapy	2 (1-3)	2 (1-3)	2 (1-4)	0.52
Immunotherapy by drug (%)				0.92
Nivolumab	15 (54)	5 (56)	10 (53)	
Pembrolizumab	10 (36)	3 (33)	7 (37)	
Ipilimumab	4 (14)	1 (11)	3 (16)	
Immunotherapy by class (%)				1.00
PD1/PD-L1	24 (86)	8 (89)	16 (84)	
CTLA-4	3 (11)	1 (11)	2 (11)	
Both	1 (4)	0 (0)	1 (5)	
PD-L1 positivity (%)				
Graft	5/7 (71)	4/4 (100)	1/3 (33)	0.053
Tumor	4/8 (50)	2/3 (67)	2/5 (40)	0.47
Immunosuppression (%)				
Single agent tacrolimus	10 (36)	2 (22)	8 (42)	0.31
Single agent mTOR-inhibitor	6 (21)	3 (33)	3 (16)	0.29
Tacrolimus with mTOR-inhibitor	5 (18)	1 (11)	4 (21)	0.52
Others	7 (25)	3 (33)	4 (21)	0.48
Acute rejection (%)	9 (32)			
Mortality in 30 d (%)	6 (21)	5 (56)	1 (5)	0.002
Progression-free survival	3 ± 0.6	1.0 ± 0.1	3.5 ± 1.1	0.02
Overall survival	10.6 ± 5.3	1.0 ± 0.1	19.2 ± 5.5	0.001

CTLA-4: Cytotoxic T-Lymphocyte antigen-4; F: Female; HCC: Hepatocellular carcinoma; M: Male; mTOR: Mammalian target of rapamycin; PD-1: Programmed cell death protein-1; PD-L1: Programmed death ligand-1; SCC: Squamous-cell carcinoma.

therapy as a median of second-line systemic therapy (IQR 1-3) (Table 3). Six patients (32%) suffered rejection and one patient (5%) suffered early mortality unrelated to rejection. Treatment response was not evaluated for these patients. The proportion of patients with complete response, partial response, stable disease, and progressive disease were 11% (n = 2), 0% (n = 0), 11% (n = 2), and 42% (n = 8) respectively. The overall objective response rate was 11%. The median PFS and OS were 2.5 ± 1.0 and 7.3 ± 2.7 mo after immunotherapy.

We compared the relative efficacy of nivolumab and pembrolizumab for recurrent HCC after liver transplantation. Pembrolizumab was used as an earlier line of therapy (median third line *vs* second line, P = 0.03). Pembrolizumab was associated with a higher complete response (0% *vs* 40%, P = 0.03), less progressive disease (50% *vs* 20%, P = 0.03), and better PFS (1.3 ± 1.1 *vs* 12.4 mo, P = 0.004) and OS (4.0 ± 3.4 *vs* 19.2 mo, P = 0.006). Pembrolizumab was potentially associated with fewer early mortalities but this was not statistically evident (36% *vs* 0%, P = 0.12).

Table 3 Descriptive characteristics of patients with immunotherapy for post-transplant hepatocellular carcinoma recurrence

	All	Nivolumab	Pembrolizumab	*P* value
Total (%)	19	14 (74)	5 (26)	
Rejection (%)	6 (32)	5 (36)	1 (20)	0.52
Early mortality (%)	5 (26)	5 (36)	0 (0)	0.12
Line of systemic therapy	2 (1-3)	3 (2-4)	2 (1-2)	0.03
Tumour PD-L1 positivity (%)	3/7 (43)	3/7 (43)	0/0 (-)	
Best treatment response (%)				
Complete response	2 (11)	0 (0)	2 (40)	0.03
Partial response	0 (0)	0 (0)	0 (0)	0.64
Stable disease	2 (11)	1 (7)	1 (20)	0.58
Progressive disease	8 (42)	7 (50)	1 (20)	0.03
Progression-free survival	2.5 ± 1.0	1.3 ± 1.1	12.4	0.004
Overall survival	7.3 ± 2.7	4.0 ± 3.4	19.2	0.006

PD-L1: Programmed death ligand-1.

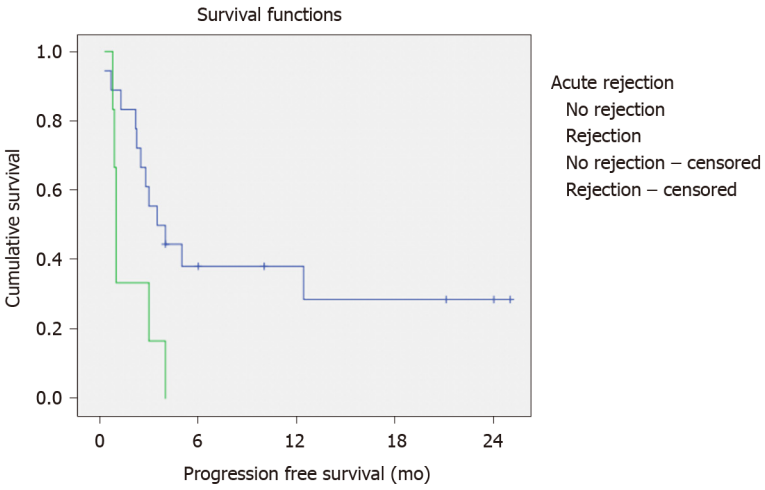

Figure 1 Progression-free survival of all patients stratified by the presence of rejection (*P* = 0.02).

DISCUSSION

We found that immunotherapy could be associated with fatal graft rejection. The rejection rate was relatively high (32%), and more importantly, was associated with a high rate of organ failure and early mortality (56% in patients with rejection). A more malignant clinical course was observed opposed to spontaneous acute rejection, which was usually treatment responsive and seldom resulted in irreversible consequences [26-28]. To optimize patient selection, we investigated the potential clinical factors associated with acute rejection in the identified patient sample. These factors included the timing of immunotherapy, the role of PD-1 *vs* CTLA-4 blockade, the effect of PD-L1 positivity on the liver graft biopsy, and the strength of the immunosuppressive regimen during immunotherapy.

We observed that patients with long-term liver transplantation were less liable to rejection when treated with immunotherapy. From our cohort, patients with rejection received immunotherapy earlier after transplantation (median time from transplant 2.9 years *vs* 5.3 years, $P = 0.02$). After transplant, immune tolerance towards the liver graft increases with time[29,30]. The underlying mechanism is the dissemination and persistence of donor leukocytes from the liver graft to the recipient, leading to systemic chimerism[31]. This explains why most spontaneous acute rejection occurs

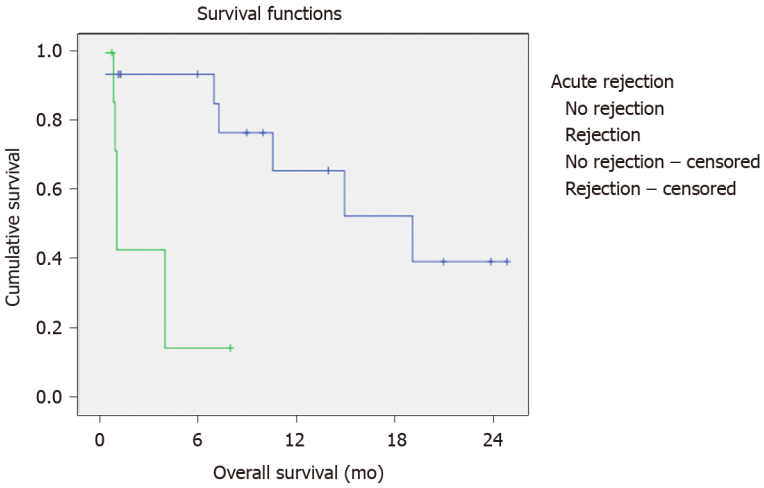

Figure 2 Overall survival of all patients stratified by the presence of rejection (*P* = 0.001).

early after liver transplant[32], allowing immunosuppression to be tapered with time. The protective effect of time was consistently observed in the setting of immunotherapy, however to a lesser extent. While the risk of spontaneous rejection is largely reduced beyond the first year after transplant[32], the risk of post-immunotherapy rejection persists further. Patients who developed post-immunotherapy rejection were given immunotherapy at a median time of 2.9 years after transplant. Existing data are too limited to conclude the safe time interval before immunotherapy that can safely be used. However, it appears that the risk of rejection cannot be neglected in the first few years after transplantation.

Most HCC recurrence occurs early after liver transplantation[33]. From the current series, patients who received immunotherapy for HCC recurrence were treated with immunotherapy earlier after transplant than those treated for *de novo* malignancies (median time from transplant 3.3 years *vs* 7 years, $P = 0.03$). From our experience, patients with early HCC recurrence also have a poorer prognosis[1]. While the use of immunotherapy for post-transplant HCC recurrence is investigational, it is reasonable to reserve immunotherapy to patients with late recurrence. With reduced rejection risk and better tumor biology, better outcomes can be expected.

Researchers have proposed that PD-1 inhibition is potentially associated with a higher risk of rejection and graft loss compared to CTLA-4 blockade[34]. In a cohort of 12 transplant recipients, rejection occurred in 4 of the 8 patients receiving anti-PD-1 therapy but in none of the 4 patients receiving anti-CTLA-4 treatment[35]. It is hypothesized that the PD-1 pathway plays a more integral role in allograft immune tolerance[35,36]; however, our data did not support this hypothesis. In the current cohort, patients who received anti-PD-1 agents had a rejection rate that was very similar to those receiving CTLA-4 blockade (33% *vs* 33%, $P = 1.00$). In comparison, our study was characterized by inclusion of liver transplant recipients only, and a better sample size ($n = 28$). Though insufficient to indicate the relative safety profile of both classes of immune checkpoint inhibitor, our observation showed that CTLA-4 blockade is not without risk of liver graft rejection. Given its established efficacy in primary HCC, anti-PD-1 agents should remain the agent of choice when immunotherapy is contemplated for treatment of post-transplant HCC recurrence[7,8].

Allograft PD-L1 staining was evaluated in 7 patients treated with immunotherapy. Patients with rejection were more frequently observed to have positive graft PD-L1 staining, though statistical significance was not reached. Our data are suggestive of a potential role of graft PD-L1 positivity predicting rejection. However, many of these allograft biopsies were taken during rejection. To allow risk stratification before commencement of therapy, a baseline allograft biopsy may be more valuable. In our institution, protocolled graft biopsy is taken during transplant after implantation. To better study the significance of graft PD-L1 status, these implant biopsies could be reviewed for PD-L1 status when immunotherapy is contemplated.

Immunosuppression is usually tapered upon diagnosis of cancer to preserve anti-tumor immunity[33]. Upon recurrence, some patients had calcineurin inhibitors weaned off and were maintained on an mTOR-inhibitor. In these patients, we did not observe a higher rejection rate following immunotherapy. However, the current study was underpowered to compare heterogenous immunosuppressive regimens. Dosage

and drug level information was also incomplete for evaluation. The ideal immunosuppression for patients undergoing immunotherapy requires extensive investigation into the interaction between anti-tumor immunity and alloimmunity, which warrants future laboratory and clinical studies.

In non-organ transplant recipients, mild immune-related adverse events can often be observed or treated with steroids while continuing immunotherapy[37]. Although antagonizing mechanisms between immune checkpoint inhibitor and steroid have been described in cellular models[38], clinical studies have not consistently concluded a nefarious interaction between them[39]. In contrast, liver transplant recipients often suffer irreversible liver failure after immunotherapy induces graft rejection, despite high doses of steroid and prompt withdrawal of immunotherapy. Given the serious consequences of graft rejection, continuation of immunotherapy could not be recommended based on the current experience.

The overall response rate for immunotherapy for post-transplant HCC recurrence was low (11%). A significant proportion of patients developed rejection (32%), leading to mortality or premature discontinuation of treatment. These results suggest that safety of immunotherapy must be addressed before its potential efficacy can be fully assessed. Of note, the 5 patients who received pembrolizumab had a better overall response rate and survival. The comparably lower rate of rejection (36% *vs* 20%, P = 0.52) could have partly contributed. However, pembrolizumab was commenced earlier in the course of disease, while nivolumab was usually given after failure of multiple lines of systemic therapy. The disease status of these patients was not available for comparison. Their potential confounding effects should be considered when interpreting the outcomes. In the current series, patient numbers were too limited to assess the relationship between tumor PD-L1 status and treatment response. In future studies, explant tumor PD-L1 status can be reviewed when patients are contemplated for immunotherapy.

The current study was limited by its methodology. Subjects were sampled from individual case reports and series with low homogeneity, and data analysis is vulnerable to publication bias. Patients with extreme outcomes were preferentially reported and the rejection rate could have been overestimated. The included patients had heterogenous immunosuppressive regimen, which potentially affect rejection and tumor response. The small sample size largely limited the analytical power.

CONCLUSION

From the limited experience in the literature, we conclude that rejection remains the major obstacle to immunotherapy use in the setting of post-liver transplant HCC recurrence. It is associated with considerable risk of organ failure and mortality. Before immunotherapy can be recommended for post-transplant HCC recurrence, it is essential to determine which patients are at risk of developing rejection. We have identified a short duration from transplant and graft PD-L1 positivity as potential risk factors. We suggest establishing an international registry to allow information regarding immunotherapy for post-liver transplant HCC recurrence to be systemically collected. With better understanding and insights, we could better select the suitable patients and achieve more desirable outcomes.

ARTICLE HIGHLIGHTS

Research background

Evidence on the safety of immunotherapy in liver transplant recipient is limited. Its efficacy on treating post-liver transplant hepatocellular carcinoma (HCC) recurrence is unknown.

Research motivation

To study the potential role of immunotherapy in the setting of post-liver transplant HCC recurrence.

Research objectives

To assess the safety of immunotherapy after liver transplantation and to assess its efficacy on treating post-liver transplant HCC recurrence.

Research methods

A review of current literature describing immune checkpoint inhibitor therapy in a patient with prior liver transplantation. Patients from our institution were included for review.

Research results

There were 28 patients identified. The rejection rate was 32% (n = 9). Early mortality occurred in 21% (n = 6) and were mostly related to acute rejection (18%, n = 5). Patients with acute rejection were given immunotherapy earlier after transplantation (median 2.9 years *vs* 5.3 years, P = 0.02). Their progression-free survival (1.0 ± 0.1 *vs* 3.5 ± 1.1 mo, P = 0.02) and overall survival (1.0 ± 0.1 *vs* 19.2 ± 5.5 mo, P = 0.001) compared inferiorly to patients without rejection. Among the 19 patients treated for HCC, the rejection rate was 32% (n = 6) and the overall objective response rate was 11%.

Research conclusions

Rejection risk is the major obstacle to immunotherapy use in liver transplant recipients.

Research perspectives

Further studies on the potential risk factors of rejection are warranted.

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CASE REPORT

Hodgkin lymphoma masquerading as perforated gallbladder adenocarcinoma: A case report

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Author contributions: Manesh M, Henry R, Gallagher S and Zielsdorf S were the patient's surgeons, reviewed the literature and contributed to manuscript drafting; Greas M performed the pathologic analyses and interpretation and contributed to manuscript drafting; Sheikh MR was responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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Abstract

BACKGROUND

There are several case reports of acute cholecystitis as the initial presentation of lymphoma of the gallbladder; all reports describe non-Hodgkin lymphoma or its subtypes on histopathology of the gallbladder tissue itself. Interestingly, there is no description in the literature of Hodgkin lymphoma causing hilar lymphadenopathy, inevitably presenting as ruptured cholecystitis with imaging mimicking gallbladder adenocarcinoma.

CASE SUMMARY

A 48-year-old man with a past medical history of diabetes mellitus presented with progressive abdominal pain, jaundice, night sweats, weakness, and unintended weight loss for one month. Work-up revealed a mass in the region of the porta hepatis causing obstructions of the cystic and common hepatic ducts, gallbladder rupture, as well as retroperitoneal lymphadenopathy. The clinical picture and imaging findings were suspicious for locally advanced gallbladder adenocarcinoma causing ruptured cholecystitis and cholangitis, with metastases to retroperitoneal lymph nodes. Minimally invasive techniques, including endoscopic duct brushings and percutaneous lymph node biopsy, were inadequate for tissue diagnosis. Therefore, this case required exploratory laparo-tomy, open cholecystectomy, and periaortic lymph node dissection for histopathological assessment and definitive diagnosis. Hodgkin lymphoma was present in the lymph nodes while the gallbladder specimen had no evidence of malignancy.

CONCLUSION

This clinical scenario highlights the importance of histopathological assessment in diagnosing gallbladder malignancy in a patient with gallbladder perforation and

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a grossly positive positron emission tomography/computed tomography scan. For both gallbladder adenocarcinoma and Hodgkin lymphoma, medical and surgical therapies must be tailored to the specific disease entity in order to achieve optimal long-term survival rates.

Key Words: Hodgkin lymphoma; Gallbladder perforation; Acute cholecystitis; Gallbladder adenocarcinoma; Case report

Core Tip: Here we present a case of Hodgkin lymphoma masquerading as gallbladder adenocarcinoma. In our patient, Hodgkin lymphadenopathy in the region of the porta hepatitis led to obstructions of the cystic and common hepatic ducts, causing acute cholecystitis and subsequent gallbladder perforation with associated cholangitis. Our case highlights the importance of histopathological assessment in diagnosing gallbladder malignancy when a patient presents with gallbladder perforation and a grossly positive positron emission tomography/computed tomography scan. For either gallbladder adenocarcinoma or Hodgkin lymphoma, chemotherapy tailored to the disease (and appropriate surgical intervention) are essential to achieve the best chance of cure and long-term survival.

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INTRODUCTION

Primary lymphoma of the gallbladder is rare but likely fits on the spectrum of lymphomas occurring in the gastrointestinal tract[1]. There are several case reports of acute cholecystitis as the initial presentation of lymphoma of the gallbladder, all of which describe non-Hodgkin lymphoma or its subtypes on histopathology of the gallbladder specimen[2-7]. Interestingly, there is no description in the literature of Hodgkin lymphoma causing hilar lymphadenopathy, inevitably presenting as ruptured cholecystitis and mimicking metastatic gallbladder adenocarcinoma on imaging. Here we present a case of Hodgkin lymphadenopathy in the region of the porta hepatitis which led to obstructions of the cystic and common hepatic ducts, causing an acute cholecystitis, gallbladder perforation, and cholangitis.

CASE PRESENTATION

Chief complaints

A 48-year-old man presented to the Emergency Department with acute nausea and vomiting for one day but did also endorse vague symptoms of nausea for the preceding two weeks. He also described having subjective fevers at home with rare right upper quadrant pain and without evidence of jaundice.

History of present illness

Patient described progressive right upper quadrant pain, jaundice, night sweats, weakness, and unintended weight loss for one month. His symptoms had worsened on the week prior to arrival, at which time he began to experience decreased oral intake with nausea. His acute onset of non-bloody, nonbilious vomiting on day prior to arrival is what led him to seek care. He initially presented to an urgent care center where computed tomography (CT) scan was done and showed acute cholecystitis. He was then sent to the emergency room.

History of past illness

The patient had a past medical history of diabetes mellitus and hypertension. His only home medication was a prostate medication of unknown name. He also had a remote history of laparoscopic appendectomy.

Personal and family history

Family history was noncontributory. Patient denied any alcohol, tobacco or illicit drug use.

Physical examination

His vital signs on arrival were temperature 36.4 ℃, heart rate 110 beats per minute, respiratory rate 16 breaths per minute, blood pressure of 125/82 mmHg. Physical exam was notable for right upper quadrant tenderness without peritoneal signs. His skin was jaundiced.

Laboratory examinations

Laboratory findings were significant for leukocytosis (white blood cell count 18.3 K/mm^3) and hyperbilirubinemia (total bilirubin 14.5 mg/dL). The remainder of the complete blood count and blood chemistries, as well as liver function panel were normal. Tumor markers included CEA level of 1.2 μg/L and CA19-9 level of 21 U/L. Electrocardiogram and chest X-ray were also normal.

Imaging examinations

An abdominal ultrasound demonstrated a distended gallbladder with a thickened, edematous wall, gallstones, and an apparent defect in the wall, as well as intrahepatic and extrahepatic ductal dilation. A magnetic resonance cholangiopancreatography identified a T2 hypointense right hepatic lobe lesion that involved the right hepatic artery and narrowing of the common bile duct (CBD). CT again demonstrated a contained perforation of the gallbladder, moderate intrahepatic ductal dilation, possible mass within the porta hepatis, and long narrowing of the CBD (Figure 1). Additional findings consisted of multiple large retroperitoneal and pelvic lymph nodes measuring up to 2.6 cm, located in proximity to the aortic bifurcation. Given the possibility of malignancy, a chest CT was performed to evaluate for metastatic disease, which demonstrated abnormally enlarged right hilar lymph nodes.

FINAL DIAGNOSIS

Pathologic examination of the para-aortic lymph nodes provided a definitive diagnosis of mixed-cellularity classic Hodgkin lymphoma (Figure 2). The gallbladder demonstrated chronic cholecystitis without evidence of dysplasia, adenocarcinoma, or lymphoma.

TREATMENT

The patient received intravenous antibiotics for presumed cholangitis and underwent endoscopic retrograde cholangiopancreatography for sphincterotomy and stent placement in the common hepatic duct. Bile duct brushings were negative for malignant cells. The patient then underwent percutaneous cholecystostomy tube placement. A specimen of the bilious drainage was cytologically negative for malignancy, but fluid culture grew extended spectrum beta-lactamase *Escherichia coli*. The patient was transitioned to the appropriate oral antibiotics and was discharged with the cholecystostomy tube in place.

The differential diagnosis included locally advanced (and metastatic) gallbladder adenocarcinoma, hilar cholangiocarcinoma, lymphoma, or severe cholecystitis and cholangitis causing intra-abdominal lymphadenopathy. One month after his initial presentation, the patient underwent positron emission tomography with 2-deoxy-2-(fluorine-18) fluoro-D-glucose integrated with CT (^{18}F-FDG PET-CT) and ultrasound-guided biopsy of the largest iliac lymph node. The ^{18}F-FDG PET-CT demonstrated a soft tissue density associated with intense hypermetabolic activity in the region of the gallbladder fossa at the junction of the cystic duct and proximal CBD. It also demonstrated hypermetabolic activity in the gallbladder wall and in several lymph nodes in the para-aortic region extending to the iliac vessels (Figure 3). The lymph

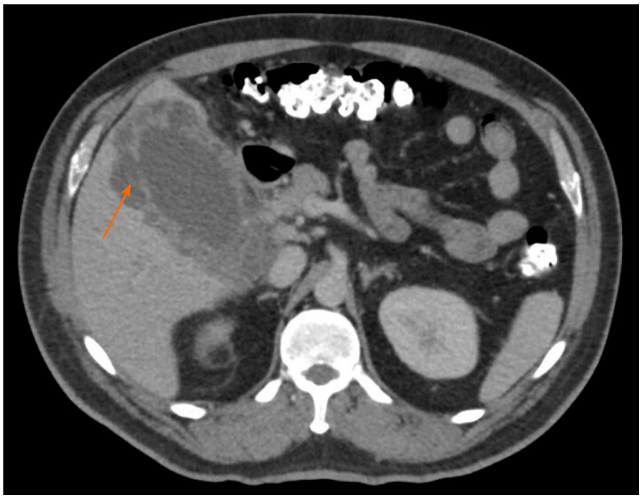

Figure 1 Abdominal computed tomography demonstrating discontinuity of the gallbladder wall consistent with perforation (orange arrow), as well as a soft tissue density in the area of the porta hepatis.

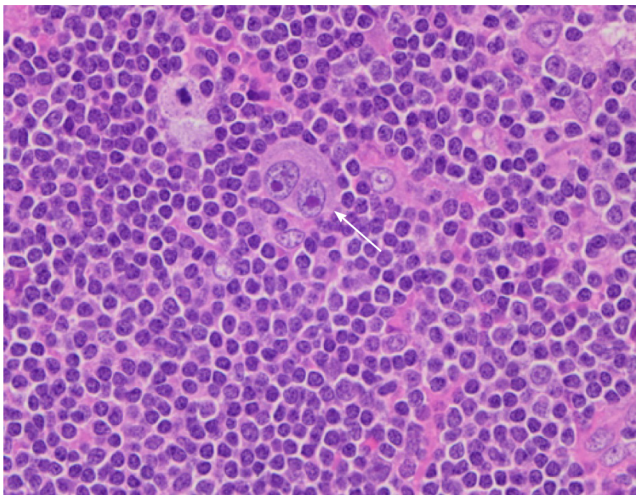

Figure 2 Micrograph of a para-aortic lymph node showing classic Hodgkin lymphoma. A typical binucleated Reed-Sternberg cell (arrow) is surrounded by small lymphocytes, macrophages and occasional plasma cells.

node biopsy showed the presence of lymphoid tissue but was otherwise inadequate for diagnosis.

The patient subsequently underwent surgical intervention for both diagnostic and therapeutic purposes. A para-aortic lymphadenectomy was performed first in order to obtain a diagnosis. If this was positive for gallbladder adenocarcinoma or cholangiocarcinoma, any further operative intervention would be aborted in favor of chemotherapy for metastatic disease. However, intra-operative pathology showed no evidence of adenocarcinoma, but rather cellular atypia suggesting lymphoma. An open cholecystectomy, without liver resection or portal lymphadenectomy was then performed.

OUTCOME AND FOLLOW-UP

The patient recovered well post-operatively and was discharged on post-operative day eight. Upon follow up to the surgery clinic, he was pleased with his care and thankful that a diagnosis had been made. He is scheduled to receive adriamycin, bleomycin, vinblastine, and dacarbazine chemotherapy as treatment for Hodgkin lymphoma.

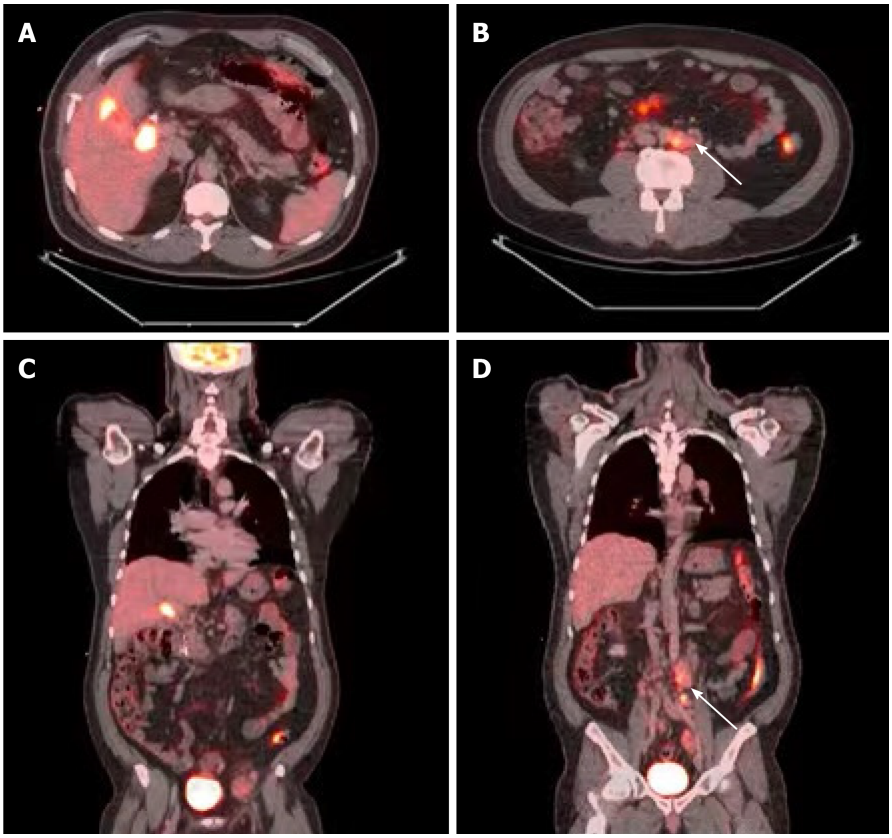

Figure 3 Positron emission tomography with 2-deoxy-2-(fluorine-18) fluoro-D-glucose integrated with computed tomography demonstrating the following findings. A and C: Axial and coronal views, respectively, displaying intense metabolic activity associated with the gallbladder, and a soft tissue density at the level of the proximal common bile duct and cystic duct; B and D: Axial and coronal views, respectively, displaying several enlarged and hypermetabolic peri-aortic lymph nodes proximal to the aortic bifurcation (white arrows).

DISCUSSION

Primary lymphoma of the gallbladder is rare but likely fits on the spectrum of lymphomas occurring in the gastrointestinal tract[5,7]. There are several case reports of acute cholecystitis as the initial presentation of lymphoma of the gallbladder and all describe non-Hodgkin's lymphoma or its subtypes on histopathology[2-5]. On the contrary, our case report describes Hodgkin's lymphoma of the portal lymph nodes, and benign pathology of the gallbladder itself, presenting as ruptured cholecystitis and mimicking gallbladder adenocarcinoma on imaging. Other authors have written about clinical situations where there is a mass in the region of the gallbladder or biliary ducts causing acute acalculous cholecystitis. In these settings, the distinction between lymphoma and gallbladder adenocarcinoma relies on histopathological assessment[2].

Given our patient's initial presentation with an inflamed, thickened and perforated gallbladder, along with ^{18}F-FDG PET avidity in a mass-like structure within the region of the gallbladder fossa and CBD, our differential diagnosis was highly concerning for primary gallbladder malignancy. Still, confirmation by tissue diagnosis was essential. Regarding surgical planning: With the mass-like structure involving the gallbladder, CBD, and right hepatic artery—surgical intervention would necessitate a right hepatic lobectomy. However, with distant lymphadenopathy concerning for metastatic disease, aggressive hepatobiliary resection(s) such as right hepatic lobectomy would be contraindicated. Conversely, if the mass-like structure was not a primary gallbladder or bile duct malignancy, the ruptured cholecystitis required surgical intervention, albeit less aggressive than liver resection. Unfortunately, minimally invasive techniques, including endoscopic duct brushings and percutaneous lymph node biopsy, were inadequate for pre-operative tissue diagnosis. Hence, exploratory laparotomy and para-aortic lymphadenectomy were required for histopathological assessment and definitive diagnosis. Once intra-operative pathology returned as likely Hodgkin lymphoma, open cholecystectomy was performed.

Classic Hodgkin lymphoma typically presents as an asymptomatic supradiaphragmatic lymphadenopathy. Constitutional "B" symptoms such as high fevers, night sweats and unintended weight loss occur in 33% of cases. In retrospect, our patient had constitutional "B" symptoms for at least one month leading up to his presentation to the hospital. Interestingly, peripheral and abdominal lymphadenopathy are prominent in the mixed-cellularity type, which was the subtype diagnosed in this case report. The pathologic hallmark of classical Hodgkin lymphoma is large multinucleated Reed-Sternberg cells with a characteristic reactive cellular background [8]. Hodgkin lymphoma is unique in that malignant cells (Reed-Sternberg cells) only constitute a small portion of the cell population within each tumor (Figure 2). As such, fine-needle aspiration and core-needle biopsies are often inadequate to make a definitive diagnosis[9]. In our case as well, several biopsies were non-diagnostic prior to our operative intervention and excisional lymph node biopsy.

To our knowledge, there are no cases documented of Hodgkin lymphoma presenting with gallbladder and biliary obstruction, leading to gallbladder perforation and cholangitis, respectively. Moreover, this unique case revealed benign pathology of the gallbladder. This further supports a pathophysiology that is distinct from the current literature review of acute cholecystitis due to primary lymphoma of the gallbladder.

CONCLUSION

This case highlights the importance of histopathological assessment in diagnosing gallbladder malignancy in a patient with gallbladder perforation and a grossly positive PET-CT scan. For either gallbladder adenocarcinoma or Hodgkin lymphoma, chemotherapy tailored to the disease (and appropriate surgical intervention) are essential to achieve the best chance of cure and long-term survival[4]. Therefore, in patients like ours, lymphoma must be ruled out definitively by pathology, which in this case required exploratory laparotomy and excisional lymph node biopsy.

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CASE REPORT

Whole circumferential endoscopic submucosal dissection of superficial adenocarcinoma in long-segment Barrett's esophagus: A case report

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Author contributions: Abe K and Goda K wrote the manuscript; Kanamori A, Suzuki T, Yamamiya A, Arisaka T, Sugaya T, Majima Y, Tominaga K, Iijima M, and Irisawa A contributed to the manuscript discussion and reviewed the manuscript; Hirooka S and Yamagishi H established pathological diagnosis.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report.

Conflict-of-interest statement: The

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Abstract

BACKGROUND

Esophageal adenocarcinoma (EAC) derived from long-segment Barrett's esophagus (LSBE) is extremely rare in Asia. LSBE-related EAC is often difficult to diagnose in the horizontal extent. If the tumor has spread throughout the LSBE, whole circumferential endoscopic submucosal dissection (ESD) should be performed, which is difficult to complete safely. Additionally, whole circumferential ESD can bring refractory postoperative stenosis. We hereby report a case of EAC involving the whole circumference of the LSBE, achieving complete endoscopic removal without complications.

CASE SUMMARY

An 85-year-old man with the chief complaint of dysphagia underwent esophagogastroduodenoscopy. We suspected a flat-type cancerous lesion that extended the whole circumference of the LSBE (C 3.5, M 4.0) using narrow-band imaging magnification endoscopy (NBI-M). We achieved circumferential en bloc resection of the lesion safely with special ESD techniques. Histology of the ESD specimens demonstrated that the superficial EAC extended the whole circumference of the LSBE, and papillary or well-differentiated tubular adenocarcinoma was confined

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in the lamina propria mucosa showing a vertical negative margin. To prevent post-ESD stenosis, we performed endoscopic local injection of steroids, followed by oral administration of steroids. There was no evidence of esophageal refractory stenosis or tumor recurrence 30 mo after ESD. In summary, we experienced a rare case of LSBE-related EAC. The horizontal tumor extent was accurately diagnosed by NBI-M. Additionally, we achieve whole circumferential ESD safely without postoperative refractory stenosis.

CONCLUSION
NBI-M, ESD, and steroid therapy enabled the curative resection of superficial full circumferential LSBE-related EAC without refractory postoperative stenosis.

Key Words: Endoscopic submucosal dissection; Long-segment Barrett's esophagus; Superficial esophageal adenocarcinoma; Steroid; Magnification endoscopy; Case report

Core Tip: Esophageal adenocarcinoma (EAC) arising from long-segment Barrett's esophagus is rare and tends to be diffuse. Preoperative diagnosis of the horizontal tumor extent and postoperative stenosis after endoscopic submucosal dissection (ESD) could be problematic in this case. We accurately diagnosed the horizontal extent of the EAC lesion by narrow-band imaging magnification endoscopy and achieved complete en bloc R0 resection *via* whole circumferential ESD. We also succeeded in preventing refractory stenosis after whole circumferential ESD by prophylactic steroid therapy combing local injection and oral administration.

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INTRODUCTION

The incidence of Barrett's esophagus-related adenocarcinoma has increased rapidly in western countries[1-3], and has also been gradually increasing in Asia[4]. In the west, the carcinoma has been reported to develop from long-segment Barrett's esophagus (LSBE) in more than half of cases[5], while in Asia, LSBE is extremely rare[6]. LSBE-related adenocarcinomas tend to be diffuse[7] and flat[8], and diagnosing the horizontal extent of the tumor can be more difficult than in short-segment Barrett's esophagus-related adenocarcinoma, which tends to have solitary or localized carcinogenesis[7]. Postoperative refractory stenosis can occur even if endoscopic submucosal dissection (ESD) can be performed for superficial esophageal adenocarcinoma (EAC) involving the whole circumference of the LSBE[9,10].

We hereby report a rare case of superficial EAC with suspected involvement of the whole circumference of the LSBE *via* narrow-band imaging magnification endoscopy (NBI-M). We achieved en bloc R0 resection with special ESD techniques. Additionally, we could prevent refractory postoperative stenosis by prophylactic steroid combination therapy.

CASE PRESENTATION

Chief complaints

An 85-year-old man complained of hoarseness and dysphagia. He was referred to our hospital for further medical work-up and treatment.

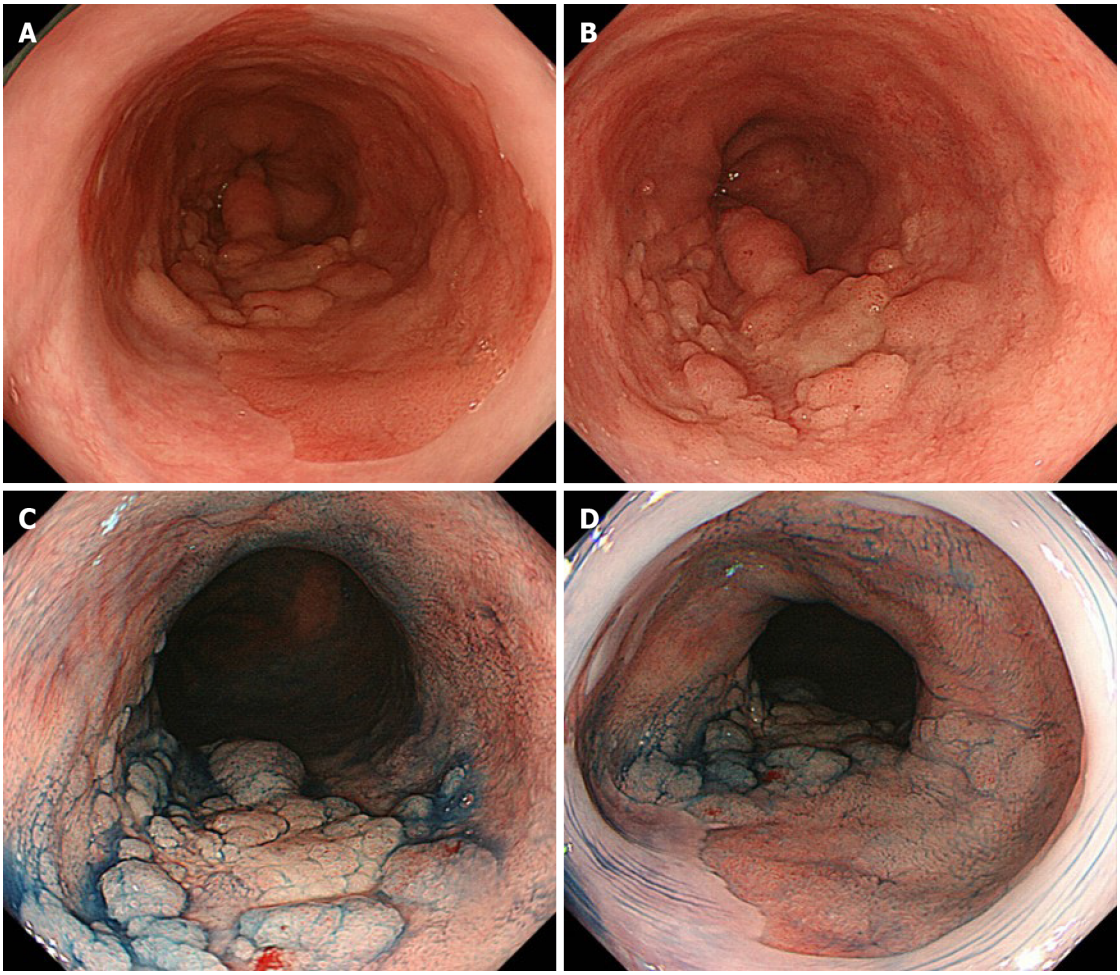

Figure 1 Images of esophagogastroduodenoscopy. A and B: Conventional white-light endoscopy shows a nodular aggregated protruded lesion in the long-segment Barrett's esophagus (C 3.5 M 4); C and D: Chromoendoscopy with indigo carmine shows the protruded lesion with irregularly sized granules. No obvious lesion was found in the mucosal surface of Barrett's esophagus other than the nodular aggregated protruded lesion.

History of present illness

The patient underwent esophagogastroduodenoscopy; A nodular aggregated protruded lesion was found in the lower esophagus. Histological analysis of the biopsy samples obtained from the protruded lesion showed adenocarcinoma.

History of past illness

The patient had a history of left glottic cancer and prostatic cancer, which were treated with radiation therapy and hormonal therapy, respectively.

Personal and family history

He had a smoking history of 40 cigarettes per day for 40 years. There was no remarkable family medical history.

Physical examination

The patient presented in a normal nutritional state and the physical examination was unremarkable.

Laboratory examinations

Laboratory studies, including total blood count, analysis of markers of kidney and liver failure, and analysis of tumor makers did not reveal any abnormalities.

Imaging examinations

Conventional white-light endoscopy (CWE) showed a protruded lesion in the LSBE (C 3.5 M 4; Figure 1A and B). CWE and indigo carmine chromoendoscopy could not visualize a definitive lesion other than the protruded lesion (Figure 1), whereas NBI-M visualized extensive irregular mucosal/vascular patterns in the flat areas surrounding

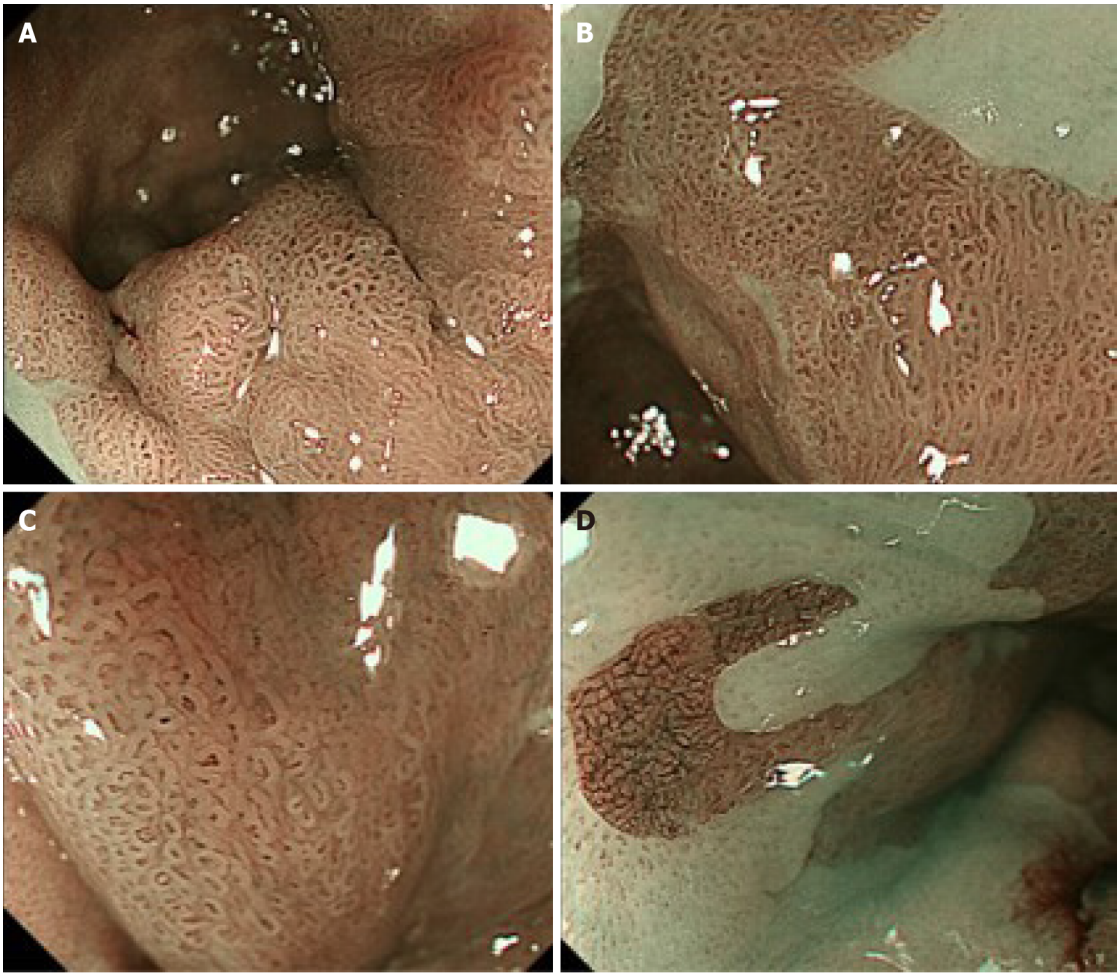

Figure 2 Images of narrow-band imaging magnification endoscopy. A: Narrow-band imaging magnification endoscopy (NBI-M) shows a visible mucosal pattern with villous structures in protruded or elevated portions, as well as in the surrounding flat portions in the long-segment Barrett's esophagus (LSBE); B: The villous patterns were rated as irregular because they showed variety in size and existed in a high density; C: In most of surrounding areas of the LSBE, mucosal patterns showed an irregular villous pattern [similar to the image (C)], and vascular patterns were rated as irregular because they showed a variety of forms and calibers under NBI-M observation with high magnification; D: In several flat areas, NBI-M demonstrated an invisible mucosal pattern with an irregular vascular pattern forming a network-like structure with a variety in caliber.

the nodular aggregated protruded lesion (Figure 2). The NBI-M findings were suggestive of a flat-type neoplastic lesion extending the whole circumference of the LSBE. The flat-type neoplastic lesion was suspected to longitudinally extend up to the esophagogastric junction. Adenocarcinoma and neoplastic glands were observed in the biopsy specimens obtained from the protruded and flat lesions, respectively. We predicted a diagnosis of superficial tumors spreading extensively along the whole circumference of the LSBE. The protruded lesion did not show poor distensibility or an expanding appearance but was semi-pedunculated. These findings suggested that the protruded tumor was confined to the mucosal layer. Contrast-enhanced computed tomography showed no metastatic lesions in the thorax and abdomen.

FINAL DIAGNOSIS

Histological analysis of the ESD specimen demonstrated that the superficial EAC extended the whole circumference of the LSBE (Figure 3). The protruding and flat extending tumors showed papillary and well-differentiated tubular adenocarcinoma, respectively (Figure 3). We achieved en bloc R0 resection with horizontal and vertical margins that were negative for cancer cells. Tumor invasion was confined to the superficial muscularis mucosa without lymphatic or vascular involvement.

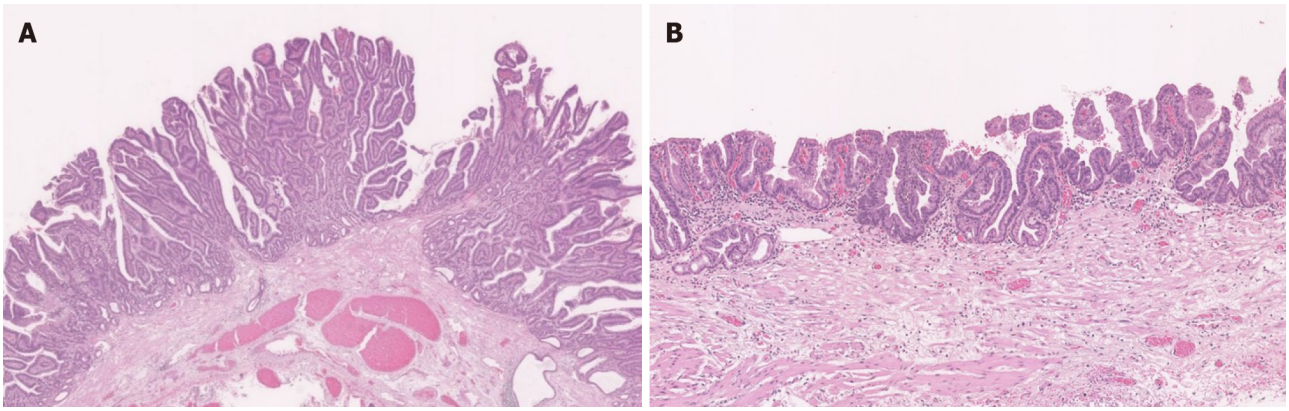

Figure 3 Pathological findings. A: Papillary adenocarcinoma with cancerous crypts exhibiting papillary proliferation accompanied by structural atypia was observed in the protruded and elevated positions (magnification: 1.5 ×); B: Well-differentiated tubular adenocarcinoma with short papillary glands accompanied by structural atypia and nuclear enlargement was extensively observed in the extensive flat portions (magnification: 2.0 ×).

TREATMENT

We achieved whole circumferential ESD with en bloc removal of the whole LSBE safely. We injected 0.4% sodium hyaluronate (MucoUp; Boston Scientific, Marlborough, MA, United States) into the submucosal layer during the ESD. We used special ESD techniques, including the submucosal tunneling method and a thread-traction method[11,12]. We created three submucosal tunnels from the oral side and dissected the submucosal tissue between the tunnels (Figure 4). The ESD specimen was 98 mm × 54 mm in diameter (Figure 5).

We injected a steroid solution containing 80 mg triamcinolone into the remaining submucosal layer immediately after ESD as prophylactic therapy for postoperative stenosis. Additionally, oral prednisolone was administered at an initial dose of 20 mg/d [0.5 mg/body weight (kg)] beginning on the second day post-ESD, which was gradually tapered every 2 wk, and completed 12 wk later.

OUTCOME AND FOLLOW-UP

Although the patient had mild narrowing of the esophageal lumen and did not complain of severe dysphagia, esophagogastroduodenoscopy showed mild stenosis in the lower esophagus. We performed prophylactic endoscopic balloon dilatation with a 12-15 mm balloon diameter (CRE balloon; Boston Scientific, Boston, United States) at 3 mo, 5 mo, and 6 mo post-ESD. The patient has a regular diet and no tumor recurrence 30 mo after ESD.

DISCUSSION

LSBE is a rare disease in Asia, including in Japan, and carcinogenesis from LSBE is even rarer. In EAC derived from LSBE, the histological distribution of dysplasia and EAC tends to be multiple and diffuse[7]. This often makes diagnosing the horizontal extent of the dysplasia and superficial EAC difficult. Unlike in western countries, ESD is commonly used in Japan to treat superficial EAC in the Barrett's esophagus. When the tumor has spread the whole circumference of the LSBE, as in the present case, the ESD procedure can be extremely challenging because of the high likelihood of perforation, severe hemorrhage, and refractory stenosis after whole circumferential ESD.

Using NBI-M, we were able to accurately diagnose the horizontal extent of this superficial EAC involving the whole circumference of LSBE and achieved complete en bloc R0 resection. In this case, an extensive flat-type tumor lesion surrounded the protruded tumor lesion. Diagnosing the horizontal extent of the flat-type tumor can sometimes be difficult by CWE or indigo carmine chromoendoscopy. Previous studies have shown that NBI-M is useful in the diagnosis of the flat-type superficial EAC lesions[13-15]. However, little is known about utility of NBI-M for LSBE-related

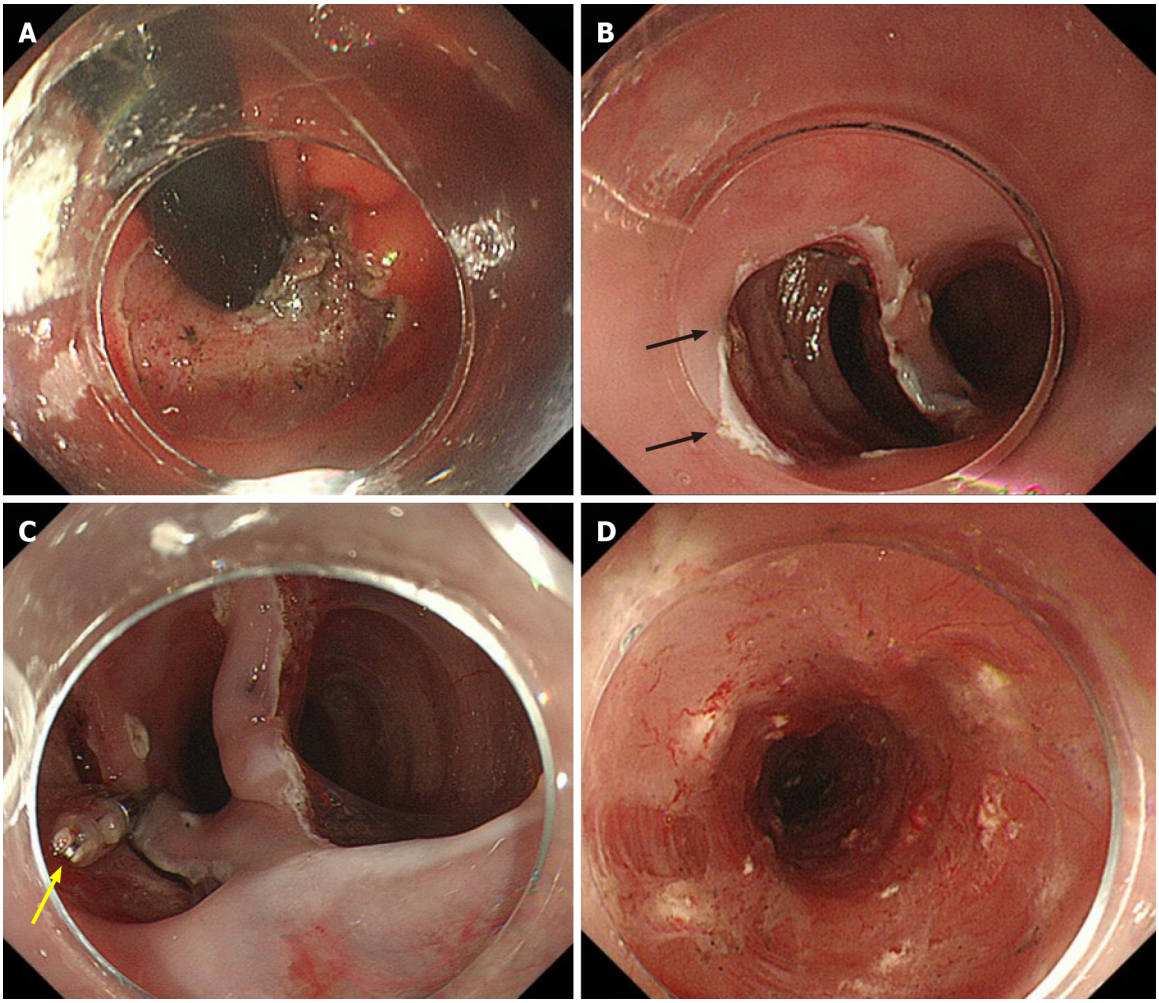

Figure 4 Images of intraoperative endoscopy. A: Barrett's esophagus-related neoplasia appears to spread up to the gastric cardia. Endoscopic submucosal dissection (ESD) was started in this cardiac area; B: After resecting and dissecting the cardiac lesion, three submucosal tunnels were created from the oral side (black arrow is the first tunnel); C: A clip with a thread was attached to the mucosal edge of each of the three tunnels, and the dissected tissue of the tunnels was pulled toward the oral side (yellow arrow); D: Whole circumferential ESD had been completed. Steroid solution was injected into the remaining submucosa (white spots) immediately after ESD to prevent postoperative stenosis.

superficial adenocarcinoma that tends to be diffuse and flat. The horizontal tumor extent of the LSBE-related superficial EAC was accurately diagnosed using NBI-M in the present case. Additionally, we utilized the following two ESD techniques and successfully completed a highly difficult procedure of whole circumferential ESD. The first ESD technique is a tunneling method[16,17], and the other is a thread-traction method[11]. The tunneling method creates tunnels in the submucosal layer of a lesion, which allow for the submucosal layer to be dissected easily and safely. In this case, after creating three tunnels, the mucosa at the entrance of a tunnel was pulled towards the oral side with a thread and clip. Combining the thread-traction method with the tunneling method enable the safe completion of ESD with good traction whilst maintaining a clear the view of the operative field. Refractory postoperative stenosis commonly occurs in patients who undergo extensive endoscopic resection of ≥ 75% of the circumference, and these patients often require repeated endoscopic balloon dilation[18].

Recently, studies have shown that steroid injection therapy and oral steroid administration prevented post-operative stenosis after extensive esophageal ESD (≥ 75% circumference)[19,20]. As alternative techniques for preventing post-ESD stenosis, other than steroid injection, polyglycolic acid (PGA) sheets and oral epithelial cell sheets may have the potential to prevent esophageal stricture after ESD[21-23]. However, these methods have not been widely used as a prophylactic measure for preventing stenosis because the PGA has a prolonged time for endoscopic delivery and fixation, and providing oral mucosal epithelial cell sheets in every hospital would be technically and financially difficult. We considered that this case had a considerably high risk for refractory postoperative stenosis because whole circumferential ESD was

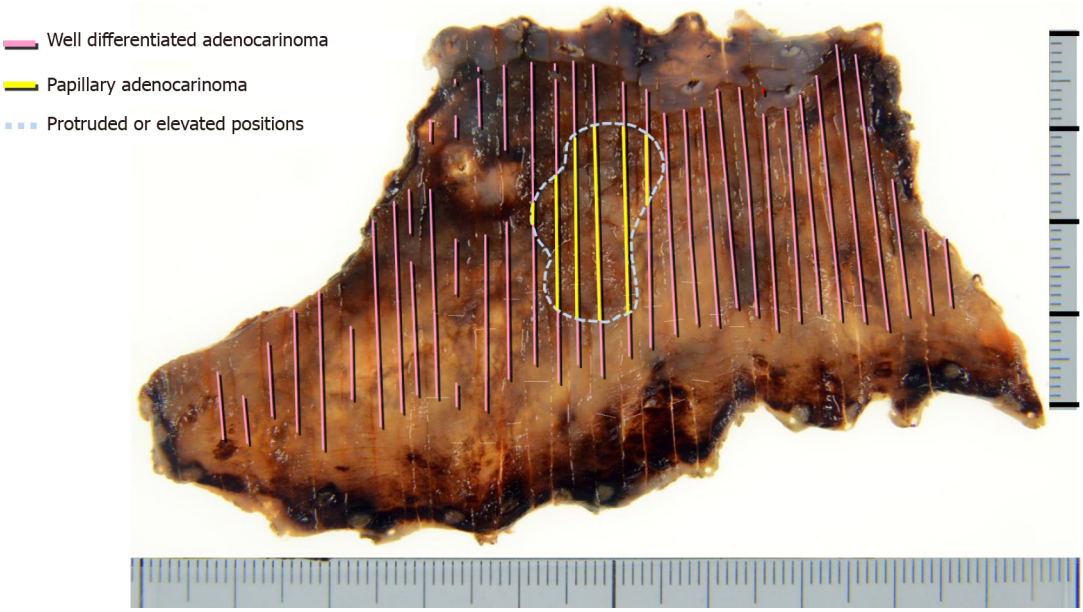

Figure 5 An endoscopic submucosal dissection en-bloc resected specimen and histological tumor distribution. The superficial carcinoma consisted of papillary and well-differentiated tubular adenocarcinoma in the protruded and elevated positions and extensive flat portions, respectively. The adenocarcinoma lesion extended the whole circumference of the long-segment Barrett's esophagus and was confined to the superficial muscularis mucosae.

performed. Consequently, we conducted combination therapy with local steroid injection and oral steroid administration, which enabled us to prevent refractory stenosis.

CONCLUSION

This case suggested that minimally invasive and radical treatment could be achieved for superficial EAC involving the whole circumference of the LSBE using ESD. NBI-M and steroid combination therapy enabled us to diagnose horizontal tumor extension accurately and prevent refractory postoperative stenosis, respectively.

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