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World Journal of Gastrointestinal Oncology (*World J Gastrointest Oncol*, *WJGO*, online ISSN 1948-5204, DOI: 10.4251) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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REVIEW

Metastatic tumors to the pancreas: The role of surgery

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Abstract

Pancreatic metastases from other primary malignancies are a rare entity. By far, the most common primary cancer site resulting in an isolated pancreatic metastasis is the kidney, followed by colorectal cancer, melanoma, breast cancer, lung carcinoma and sarcoma. Only few data on the surgical outcome of pancreatic resections performed for metastases from other primary tumor have been published, and there are no guidelines to address the surgical treatment for these patients. In this study, we performed a review of the published literature, focusing on the early and long-term results of surgery for the most frequent primary tumors metastasizing to the pancreas. Results for the Literature's analysis show that in last years an increasing number of surgical resections have been performed in selected patients with limited pancreatic disease. Pancreatic resection for metastatic disease can be performed with acceptable mortality and morbidity rates. The usefulness of pancreatic resection is mainly linked to the biology of the primary tumor metastasizing to the pancreas. The benefit of metastasectomy in terms of patient survival has been observed for metastases from renal cell cancer, while for other primary tumors, such as lung and breast cancers, the role of surgery is mainly palliative.

Key words: Pancreas; Pancreatic neoplasms/secondary; Pancreatectomy; Renal cell cancer; Breast cancer; Melanoma; Sarcoma; Lung carcinoma

Core tip: Pancreatic metastases represent a rare but increasing entity among pancreatic tumors. We have reviewed the literature's reports of the more common metastatic tumors to the pancreas, evaluating early and long-term results of surgery. Pancreatic resection may appear a safe and feasible option also in metastatic tumors, but long term survival is achieved substantially only in renal cell cancer. In other metastatic tumors, pancreatectomy may offer a good palliation in selected patients, but it is to remark that surgery is only one option in the multimodality treatment of metastatic disease to the pancreas.

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INTRODUCTION

Pancreatic metastases from other primary cancers are rare[1]. Approximately 2% of pancreatic cancers are metastatic from other primary site[2,3]. In different autopsy series, a wide range of malignant tumors have been found to metastasize to the pancreas and the most frequent primary locations of tumor were the kidney, breast, colon, skin and lung[4-6]. It may be difficult to differentiate a pancreatic metastasis from a primary pancreatic tumor, being the clinical presentation and the radiological characteristics similar for both primary and secondary neoplasms[7,8]. Pancreatic metastases are asymptomatic in more than 50% of cases: they are often detected during follow-up

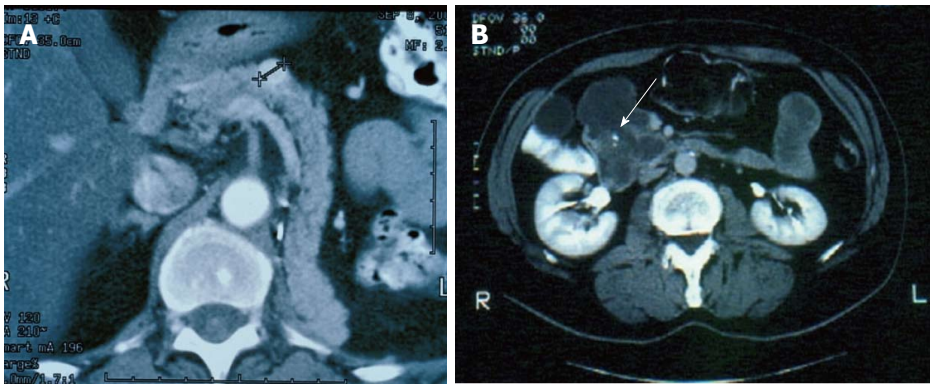

Figure 1 Computed tomography scan of the abdomen. A: Computed tomography (CT) scan of the abdomen showing a contrast-enhanced pancreatic metastasis from a renal cell carcinoma; B: CT scan of the abdomen showing an hypodense metastatic lesion of the pancreatic head from a colon carcinoma.

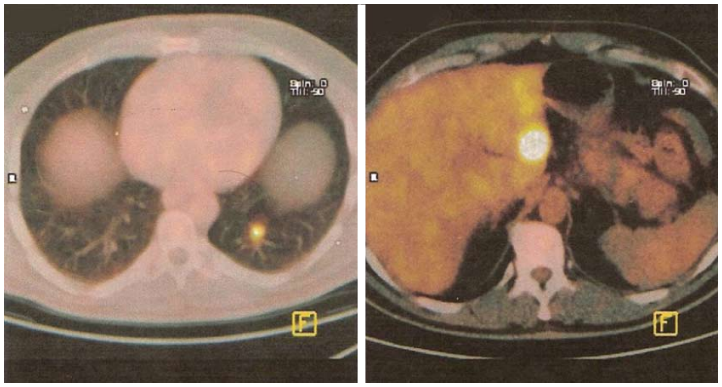

Figure 2 Positron emission tomography/computed tomography imaging showing a pathologic uptake of the tracer in the region of the pancreatic neck and in the left lung from a melanoma.

investigations after surgery for a primary lesion or as an incidental finding on imaging studies performed for an unrelated condition[9,10]. At CT scan, pancreatic metastases may appear as hypervascular lesions, like in renal cell cancer (RCC) metastases (Figure 1A) or, as in the case of colon and melanoma metastases, as hypodense masses (Figure 1B). Positron emission tomography may be helpful in order to exclude other metachronous lesions than the pancreatic one or other primary synchronous tumors (Figure 2).

Pancreatic metastases occur in two different clinicopathological settings, either as one manifestation in widespread disease or as an isolated mass of the pancreas. However, only few patients present with a single potentially resectable pancreatic lesion[11] and the most common presentation is that of a widespread metastatic disease[12]. The number of pancreatic resections for metastatic lesions in high volume centers has gradually increased, probably because of the greater knowledge of these clinical entities and the greater availability of radiological studies in asymptomatic patients[13]. In recent years, different studies showed an improved survival in patients undergoing lung or liver resection for metastatic lesions from colorectal cancer[14,15]. Pancreatic resections were for many years associated with high rates of morbidity and mortality, but recent data have clearly shown that pancreatic surgery is safe and feasible in high-volume clinical centers: the lower morbidity and mortality rates make pancreatic resection an acceptable indication also in case of metastatic lesions[16-18].

In this study, we have reviewed the literature's reports of the more common metastatic tumors to the pancreas, evaluating early and long-term results of surgery.

RESEARCH

The published Literature was systematically searched using PubMed and free text search engines up to October 2013. Search terms included: pancreatic neoplasms/secondary, pancreatectomy, renal cell cancer, breast cancer, melanoma, colorectal cancer, sarcoma, lung cell cancer. The "related articles" function was used to broaden the search and all abstracts, studies, and citations retrieved were reviewed. Only articles published in the English language, with abstracts, and human studies only were selected. Case reports were included for the less common neoplasms. In the case of sequential publications, the report with the most comprehensive information regarding the study population was selected. Studies were excluded from the analysis if: (1) the outcome and parameters of interest were not clearly reported, and (2) it was impossible to extract the data from the published results. Two investigators (LM and GP) reviewed the titles and abstracts and assessed the full text of the articles obtained to establish eligibility. The following data were extracted from each study: first Author, year of publication, number of patients, perioperative morbidity and mortality, and long-term outcome. For statistical analysis, overall

averages are presented as weighted means (range) unless otherwise stated.

The preliminary literature search showed 1536 studies matching the initial search criteria. After screening, 108 studies evaluating metastases to the pancreas were selected. There were 41 case series (more than two patients) and 67 single case reports, for a total of 418 patients with secondary tumor of the pancreas: metastases were mainly from RCC (n = 293), followed by melanoma (n = 38), colorectal cancer (n = 37), breast cancer (n = 19), sarcoma (n = 18), and lung cancer (n = 13).

The results of the Literature's review are showed for each tumor considered.

RCC

By far, the most common primary cancer site resulting in an isolated pancreatic metastasis is the kidney. RCC accounts for approximately 2% of all adult malignancies. Among kidney-limited diseases, RCC has a high overall survival rate (up to 95%)[19]. However 20% to 30% of patients have metastases at presentation, and the 5-year survival rate is less than 10% once metastases spread[20]. In autopsy series in primary RCC, pancreatic metastases were noted in 1.3% to 1.9%[21]. Hirota *et al*[22] revealed that a characteristic of the patients in this group was the long disease-free interval from the time of the nephrectomy to the diagnosis of metastatic disease. This long disease free interval indicates a biological pattern of slow growth, favouring local surgical resection. Pancreatic metastases are often the only metastatic lesions and they seems related to a good prognosis[17,23]. Pancreatic metastases are only rarely symptomatic; therefore a long follow-up (> 10 years) is indicated in patients with RCC[10]. At CT scans metastases from RCC appear as hypervascular lesions, and a differential diagnosis must be done with primary endocrine tumors[24]. OctreoScan® scintigraphy is not always able to differentiate neuroendocrine lesions from pancreatic metastases from RCC. A recent study on metastatic RCC showed the presence of positive scintigraphy, and thus the presence of somatostatin receptors, in 9 of 11 cases[25]. A percutaneous fine-needle biopsy to confirm the clinical suspicion is seldom necessary. Pancreatic metastases from RCC can occur a long time after the diagnosis of the primary RCC. The presence of synchronous pancreatic lesions is less frequent (15%-27% of cases)[22,26,27] and it may be an expression of a widespread disease, thus limiting the benefit of a pancreatic metastasectomy. In a recent review by Masetti *et al*[28], univariate analysis showed that a disease-free survival time less than 2 years in metachronous metastases was associated with a worse survival. The detection of multiple pancreatic metastases occurs more often in RCC than in other primary malignancies and this must be taken into account in the planning of the surgical treatment of these patients[23]. In a review of the literature we found 29 studies reporting on pancreatic resection for metastatic RCC (Table 1, [3,9,10,12,16,23,24,28-49]). Only reports with detailed clinical and follow-up informations on 2 or more patients were selected, while single case-reports were excluded. Informations on 293 patients have been published. Among these, the median interval between nephrectomy and pancreatic recurrence was 104 mo (range 0-348 mo). Perioperative mortality occurred in only 4 patients with a mortality rate of 1.5%. Morbidity was difficult to assess because this information wasn't always reported and because in many reports it wasn't possible to differentiate morbidity rate after resection for RCC from other primary tumors. Among the available data, the overall morbidity rate was 13.3%. Median follow-up was 36.8 mo (range 3-130 mo). Eighty patients died and among them 56 patients died of recurrent disease (in some reports this information was not available). Tanis *et al*[34], in a recent review of 421 patients undergoing resection of pancreatic RCC metastases, reported an actuarial 5 years survival rate, calculated on 321 patients for which data were available, of 72.6% and the survival of these patients was compared to that of 73 non-surgically treated patients: 2 and 5 years overall survival rates were 80% and 72% in the operated group and 41% and 14% in the non-operated group. Bassi *et al*[17] reported in a single-centre series a great 5-year survival benefit after surgical resection compared with conservative treatment of unresectable disease (53% *vs* 26%). Pancreatic metastases from RCC are reported to have a better prognosis when compared to other primary tumors, therefore an aggressive treatment, *i.e.*, surgical resection, should be considered in these patients. Reddy *et al*[9] demonstrated that the median survival for pancreatic metastases from RCC was 4.8 years *vs* 0.9 years for metastases from melanoma. Konstantinidis *et al*[12] reported a 5-year actuarial survival of 61%, and they demonstrated that RCC patients had a better median survival (8.7 years) compared to other pathologies. Chemotherapy, immunotherapy, and radiotherapy have generally proved to be ineffective for primary RCC or metastatic disease. Despite promising results with immunotherapy using IL-2, a complete response occurred in less than 15% and was rarely durable[50,51]. In more recent years several angiogenetic agents (bevacizumab, sunitinib, sorafenib) have showed promising results[52]. Therefore a multidisciplinary approach has to be recommended in the treatment of pancreatic metastates from RCC and further studies are needed to establish the way to combine surgery with medical treatment in the different periods of the disease.

Colorectal cancer

In the English Literature only few studies on pancreatic resection for metastatic colorectal cancers have been published so far[53], representing only single case reports, rarely more than two patients[54]. In recent years, several studies demonstrated encouraging results on surgical resections for metastatic colorectal cancer to the liver and lung; on the other hand, only few data are available for pancreatectomies in metastatic colorectal cancer[55]. In a review of the literature, we selected 24 studies regarding surgical treatment of pancreatic metastases from colorectal cancer (Table 2[9,24,26,29,37,54-72]). Informations on

Table 1 Pancreatic resections for metastates from renal cell carcinoma

Ref.	No. of patients	Treatment	Mortality-morbidity	Follow-up; (mo) median (range)	Dead
Niess *et al*[29]	16	DP (10); PPPD (3); PD (2); TP	0-NA	39 (4-76)	6 (37.5%)
Yazbek *et al*[30]	11	NA	5/11/2001	78 (12-108)	4 (36.3%)
Alzahrani *et al*[31]	12 (7 resected)	DP (3); TP (2); CP; PD	1/7/2000	19 (1-96)	5 (41.6%)
D'Ambra *et al*[32]	8 (7 resected)	NA	0–3/7	43 (12.9-74.5)	NA
You *et al*[33]	7	NA	0-NA	34 (7-69)	1 (14.3%)
Konstantinidis *et al*[12]	20	NA	0-NA	36.8 (0.5-143)	NA
Masetti *et al*[28]	6	TP (5); PD	1/6/2000	3	0
Tanis *et al*[34]	10	NA	0-NA	NA	3 (30%)
Zerbi *et al*[10]	36 (23 resected)	DP (11); enucleation (5); PD (4); TP (2); CP	0-14/23	31 (12-98)	9 (25%)
Reddy *et al*[9]	21	NA	0-NA	57.6 (4.2-219.6)	19 (90.5%)
Schauer *et al*[35]	10	TP (5); PD (3); PPPD; DP	2/10/2001	56 (56-60)	NA
Karimi *et al*[36]	3	DP (3)	NA	96 (60-156)	0
Eidt *et al*[37]	7	PPPD (4); TP (2); DP	0-NA	36 (12-156)	2 (28.6%)
Sellner *et al*[23]	3	NA	0–NA	48 (36-60)	0
Crippa *et al*[24]	5	DP (3); PPPD; PD	0-NA	41 (21-95)	1 (20.0%)
Wente *et al*[38]	15	DP (7); PD (3); TP (3); PP (2)	4/15/2000	10 (1-28)	1 (6.7%)
Jarufe *et al*[39]	7	NA	1-NA	24	NA
Moussa *et al*[40]	10 (7 resected)	PD (6); TP	1–NA	61	6 (60.0%)
Law *et al*[41]	14	NA	0–NA	130 (32-315)	3 (21.4%)
Sperti *et al*[16]	2	TP; CP + enucleation	0–NA	18 (14-21)	1 (50.0%)
Zacharoulis *et al*[42]	3 (2 resected)	NA	2/3/2000	26 (7-88)	0
Yachida *et al*[43]	5	NA	0–NA	12 (2-160)	0
Faure *et al*[44]	8	PD (5); TP (3)	1/8/2000	38 (13-83)	2 (25.0%)
Sohn *et al*[45]	10	PPPD (5); DP (2); PD (2); TP	0-3	8 (3-117)	2 (20.0%)
Ghavamian *et al*[46]	11	DP (8); TP (3)	0-NA	50 (5-120)	3 (27.3%)
Kassabian *et al*[47]	5	CP; PPPD; TP; PD; DP	0-NA	48	1 (20.0%)
Thompson *et al*[48]	21 (15 resected)	DP (9); PP (4); PD (2)	0-NA	NA	NA
Butturini *et al*[49]	5	NA	NA	19 (7-27)	1 (20.0%)
Z'graggen *et al*[3]	2	TP (2)	0-NA	20 (20-40)	2 (100%)
Total	293 (270 resected)	DP (59); TP (32); PD (31); PPPD (16); CP (3); PP (6); enucleation (6)	4 (1.5%)-36 (13.3%)	36.8	72/227 (31.7%)

NA: Not available; PD: Pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectony; DP: Distal pancreatectomy; CP: Central pancreatectomy; TP: Total pancreatectomy; PP: Partial pancreatectomy.

37 patients were available, 24 with a primary neoplasm of the colon and 11 with a primary rectal cancer. Among these patients, 28 presented with a single pancreatic metastasis and in 9 cases an associated surgical procedure was required for metastatic disease in other sites. There was no perioperative mortality. After pancreatic resection, a recurrence of disease occurred in 19 patients, with a median survival time of 21 mo (range 5-105 mo). Sixteen patients are alive with a median survival time of 12 mo (range 1.5-43 mo), while 5 patients are alive with recurrent disease (6 to 43 mo). It is interesting to note that all patients experienced a relief of symptoms (abdominal pain and obstructive jaundice) after surgical resection of metastases and they remained asymptomatic until recurrence of the disease. It is impossible to establish whether the same results can be achieved in these patients with a more conservative treatment, such as chemotherapy, because of the lack of information regarding the outcome of patients undergoing pancreatic resection and patients undergoing only chemotherapy. Considering the data available in the literature, it seems reasonable to consider surgery for pancreatic metastases from colorectal cancer a palliative treatment. However, it has to be remark that a multidisciplinary approach has to be recommended in the treatment of pancreatic metastates from colorectal cancer, and an aggressive surgical approach may be considered in selected cases, in particular in symptomatic patients with isolated pancreatic metastasis.

Melanoma

Metastases from malignant melanoma can be located in the gastrointestinal tract (50%-60% of cases of malignant melanoma in autopsy series), although the clinical diagnosis occur in only 1.5% to 4.4% of patients[73]. A few cases of long-term survival after radical surgical resection of melanoma metastases in the gastrointestinal tract have been reported[74,75], but the role of surgery in the treatment of pancreatic metastases from melanoma is unknown, due to the lack of data regarding these clinical entities[9,76]. When compared to other primary tumors metastasizing to the pancreas, melanoma seems related to a poor prognosis[28]. In a literature review, we collected a total of 23 reports (19 single-patient reports, 1 with two patients, 3 with more than 2 patients) on surgical treatment of pancreatic metastases from melanoma (Table 3[24,37,58,74,77-95]). Among these patients, 12 had a primary skin melanoma, 6 had an ocular melanoma, 1 had a melanoma of the nasal cavity and in 19 cases the primary

Table 2 Pancreatic resections for metastatic colorectal cancer

Ref.	Year	No	Site of primary	Interval (mo)	Treatment	Survival (mo)	
						Dead	Alive
Roland *et al*[56]	1989	1	Colon	NR	DP		27, AWD
Nakeeb *et al*[57]	1995	1	Colon	34	PD		43, AWD
Harrison *et al*[58]	1997	2	Colon	15	PD	41	
			Colon	15	PD	21	
Inagaki *et al*[59]	1998	1	Rectum	132	DP		8
Yoshimi *et al*[60]	1999	1	Colon	51	PD	24	
Le Borgne *et al*[26]	2000	1	Colon	60	PD	12	
Tutton *et al*[61]	2001	1	Colon	23	DP		12
Torres-Villalobos *et al*[62]	2004	1	Cecum	8	DP		6
Crippa *et al*[24]	2006	1	Colon	7	PPPD	13	
Matsubara *et al*[55]	2007	1	Rectum	28	PD	24	
Eidt *et al*[37]	2007	1	Colon	12	PPPD	105	
Shimoda *et al*[63]	2007	1	Rectum	44	PD	8	
Bachmann *et al*[64]	2007	2	Rectum	24	DP		1.5
			Rectum	30	DP		6
Sperti *et al*[54]	2008	9	Colon (7) Rectum (2)	10-80	PD (2) PPPD (3) DP (4)	525	30, AWD
Reddy *et al*[9]	2008	2	NR	NR	NR		42
Grève *et al*[65]	2008	1	Rectum	54	DP	NR	NR
Gravalos *et al*[66]	2008	1	Cecum	17	DP		12
Machado *et al*[67]	2010	1	Colon	105	DP	9	
Lasithiotakis *et al*[68]	2010	1	Colon	24	PD	27	
Lee *et al*[69]	2010	1	Rectum	24	DP		12
Stoltz *et al*[70]	2011	1	Colon	24	DP		6, AWD
Georgakarakos *et al*[71]	2011	1	Colon	12	PD		6
Tanemura *et al*[72]	2012	2	Rectum	72	MSPP		16
			Rectum	84	DP		6
Niess *et al*[29]	2013	2	Colon	0	PPPD	68	21, AWD
			Colon	14	DP		
Total		37	Colon (24) Rectum (11) NR (2)	24 (median)	PD (11) DP (17) PPPD (6) MSPP (1)	21 (median)	12 (median)

NR: Not reported; DP: Distal pancreatectomy; PD: Pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectomy; MSPP: Middle-segment-preserving pancreatectomy; SMV: Superior mesenteric vein; AWD: Alive with disease.

site of melanoma was unknown. No perioperative mortality was reported. Twenty patients died of recurrent disease: the median survival time of these patients was 10 mo (range 3-25 mo). Thirteen patients are alive at 6 to 108 mo (median 16 mo); 2 patients were alive, with recurrence, at 8 and 12 mo respectively. Although malignant melanoma is associated with a poor prognosis and the role of surgery seems limited to palliation, some cases of a prolonged survival after surgical removal of melanoma metastases have been reported[74] and, when possible, surgical resection seems to be the most effective therapeutic option available today[96,97]. However, there are no sufficient data in the literature to compare patients treated with only conservative management (chemotherapy) with surgical resected patients. Therefore surgical resection for pancreatic metastases from melanoma should be considered a palliative treatment, to be taken in account in pancreatic isolated lesions as a part of the multimodality treatment of this clinical entity.

Breast carcinoma

Pancreatic metastases from breast cancer are rare, with a reported rate of 13% in an autopsy series[98]. Metastatic breast cancer is usually a widespread disease, with isolated pancreatic lesions being an occasional event. In a literature review, we selected 16 studies regarding patients undergoing surgery for pancreatic metastases from breast cancer (Table 4[9,24,26,40,57,99-110]). Breast cancer that metastasize to the pancreas may have a long latency period between the primary tumor diagnosis and the metastasis occurrence (median 39.5 mo, range 0-216). Solitary pancreatic metastasis was present in 17 patients, and 1 underwent also a subtotal gastrectomy for extrapancreatic involvement. There was no perioperative mortality. Five patients died of recurrent disease: the survival time was available in only three of these patients and the median was 26 mo (range 7-36 mo). Fourteen patients are alive at 5 to 80 mo (median 19), although 5 patients had a short follow-up (up to 12 mo) and in one patients follow-up time is not reported; 3 patients were alive, with recurrence, at 11 to 48 mo. All patients experienced a relief of symptoms (abdominal pain and obstructive jaundice) after surgical resection of metastases and they remained asymptomatic until recurrence of the disease. Masetti *et al*[28]

Table 3 Pancreatic resections for metastatic melanoma

Ref.	Year	No	Interval (Yr)	Primary site	Surgery	Follow-up (mo)	Outcome
Dasgupta *et al*[77]	1964	1	2	Skin	DP + duodenal resection	10	DOD
Johansson *et al*[78]	1970	1	12	Ocular	PD	11	ANED
Lasser *et al*[79]	1990	1	8	Skin	PD	10	ANED
Bianca *et al*[80]	1991	1	NA	NA	PD	12	AWD
Brodish *et al*[81]	1993	1	34	Skin	DP	8	AWD
Harrison *et al*[58]	1997	1	NR	NA	PD	108	ANED
Medina-Franco *et al*[82]	1999	1	NA	NA	PPPD	6	DOD
Wood *et al*[74]	2001	8	NA	NA	PD	37.5%[1]	DOD
Hiotis *et al*[83]	2002	1	NR	NR	PD	NR	DOD
Camp *et al*[84]	2002	1	6	Ocular	DP	20	ANED
Nikfarjam *et al*[85]	2003	2	12, 13	Ocular	PPPD, TP	6, 7	ANED
Carboni *et al*[86]	2004	1	9	Skin	PD	4	DOD
Crippa *et al*[24]	2006	1	2.8	Skin	PPPD	14	DOD
Belágyi *et al*[87]	2006	1	6	Skin	Enucleation	4	DOD
Edit *et al*[37]	2007	4	3, 4, 4, 14	NA	PPPD (4)	12, 25 30, 76	DOD ANED
Vagefi *et al*[88]	2009	1	28	Ocular	DP	NR	NR
Sperti *et al*[89]	2009	1	3	NA	DP	24	DOD
He *et al*[90]	2010	1	5	Ocular	DP	25	ANED
Lanitis *et al*[91]	2010	1	5	Skin	PD	96	ANED
Moszkowicz *et al*[92]	2011	1	15	Skin	PD	NA	NA
Portale *et al*[93]	2011	1	7	Skin	DP	NA	ANED
Goyal *et al*[94]	2012	5	3, 22, ?, 5, ?	Skin (3), NA (2)	PPPD (4),DP(1)	15, 3, 11.4, 4.5, 25	DOD
Sugimoto *et al*[95]	2013	1	1	Nasal	DP	10	DOD
Total		38	6 (median)	Skin = 12; Ocular = 6; Nasal = 1; NA = 18; NR = 1	PD (16), DP (9), PPPD (11), TP (1), Enucleation (1)	11, 7 (median)	

[1]5 years survival rate. NR: Not reported; NA: Not available; DP: Distal pancreatectomy; PD: Pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectomy; MSPP: Middle-segment-preserving pancreatectomy; SMV: Superior mesenteric vein; DOD: Dead of disease; ANED: Alive not evidence of disease; AWD: Alive with disease.

analysing the prognostic factors in metastatic tumors to the pancreas, found at univariate survival analysis a 2-years probability of survival of 57.1% in pancreas metastases from breast cancer and a 5-years probability of survival of 34.3%. Even in the case of pancreatic metastases from breast cancer it is impossible to establish the course of the disease without surgical resection and to assess the real benefit in survival after metastasectomy. However, in selected patients with limited pancreatic disease, surgical resection could have a palliative role in association with chemotherapy, hormonal therapy and radiation therapy in the multimodality treatment of metastatic breast carcinoma.

Lung cancer

Lung cancer metastasize to many site, but most frequently to bone, liver and adrenal glands[111,112]. Isolated pancreatic metastases from lung cancer are extremely rare[76] and they are usually metachronous lesions, identified at follow-up investigation. The few reports available in the literature show that small cell lung cancer (SCLC) represents the most typical histological subtype metastasizing to the pancreas[113].

The usefulness of surgical resection for pancreatic metastasis from lung cancer is difficult to assess because of the rarity of this type of lesion. Additionally, most cases of pancreatic metastasis from lung cancer are unresectable at the time of diagnosis because the disease is already widespread. Z'graggen *et al*[3] and Moussa *et al*[40] reported four patients each with secondary metastasis from lung cancer (including small cell lung cancer): there were no resectable cases mainly due to local invasion and metastases to other organs. Hiotis *et al*[83] reported three cases of pancreatic resections for metastatic lung cancer, with a poor long-term survival after surgery. In a recent review of the literature, Reddy *et al*[9] reported pancreatic resections from lung cancer as having the worst outcome when compared to other primary tumors type metastatic to the pancreas. In a literature review, we selected 12 studies reporting surgical resection for pancreatic involvement from lung cancer (Table 5[24,26,57,68,82,83,102,114-118]). Among these patients, in 10 cases the primary lung cancer was a NSCLC, 1 case was a SCLC and in the last patient the primary lung cancer is not specified. One patient died after surgical resection. Five patients died of recurrent disease, with a median survival time of 7 mo (range 3-14 mo). Six patients are alive with a median survival time of 19 mo (range 6-24 mo). In all cases, preoperative symptoms (obstructive jaundice and abdominal pain) disappeared after surgery. Pancreatic metastases from lung cancer have a poor prognosis and treatment options for metastatic lung cancer lesions to the pancreas are mainly

Table 4 Pancreatic resections for metastatic breast cancer

Ref.	Yr	No	Interval (mo)	Treatment	Survival (mo)	
					Dead	Alive
Bednar *et al*[99]	2013	1	216	PD		48 mo, AWD
Razzetta *et al*[100]	2011	1	0	PD		11 mo, AWD
Bonapasta *et al*[101]	2010	1	23	PD	36	
Mourra *et al*[102]	2010	1	9	DP		20 mo
Sweeney *et al*[103]	2009	1	60	DP		NA
Reddy *et al*[9]	2008	1	NR	NR	NR	13 mo
Jiménez-Heffernan *et al*[104]	2006	1	0	PD		10 mo
Tohnosu *et al*[105]	2006	1	52	DP		5 mo
Crippa *et al*[24]	2004	3	60/36/84	PPPD (3)	26	21AWD/37
Moussa *et al*[40]	2004	1	45	TP	7	
Minni *et al*[106]	2004	1	26	enucleation		80
Ogino *et al*[107]	2003	1	72	PD	Dead (-)	
Le Borgne *et al*[26]	2000	1	0	PD		12
Nomizu *et al*[108]	1999	1	80	PD		18
Mehta *et al*[109]	1997	1	36	PD		27
Nakeeb *et al*[57]	1995	1	19	PD		12
Azzarelli *et al*[110]	1982	1	43	PD		72
Total		19	39.5 mo (median)	PD (10) DP (3) PPPD (3) Enucleation (1) TP (1)	26 (median)	19 (median)

NR: Not reported; DP: Distal pancreatectomy; NA: Not available; PD: Pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectomy; TP: Total pancreatectomy; AWD: Alive with disease.

palliative.

Sarcoma

Metastatic sarcoma has generally a poor survival, and radical surgical represent the only therapeutical chance for these patients. Isolated pancreatic involvement by sarcomas is rarely encountered: in a recent experience Yoon *et al*[119] reported only 2 cases (4%) of sarcomas among 53 patients with pancreatic metastases collected at their Institution. So, the outcomes for patients with metastatic sarcoma who did or did not pancreatic resection are unknown[53]. In their review, Reddy *et al*[53] collected only 10 patients with isolated pancreatic metastasis with a median survival of 40 mo and 5-year survival of 14%. Even if pancreatic metastases from sarcoma seem related with a modest survival, the few data available does not allow to draw any definitive conclusion. Recently, Robert *et al*[120] reported a case of leiomyosarcoma metastatic to the pancreas and collected 17 of the such cases published in the Literature. Clinical details were available in only 8 reports, and 7 patients underwent pancreatic resection: 5 patients were alive (one with disease) and 2 died, with a median survival time of 23 mo. As for other cancers, resection of pancreatic metastases from sarcoma is substantially justified in individual basis.

In recent years, an increased number of surgical resections for pancreatic metastases has been performed in high-volume centers. It seems reasonable that resection is indicated for an isolated and resectable metastasis in a patient fit to tolerate pancreatectomy, evaluating each single case on an individual basis and with a multidisciplinary approach.

The type of surgical procedure is another controversial aspect in pancreatic metastases. Standardized pancreatic resection adapted to the location of the tumor, in terms of partial pancreaticoduodencectomy, distal pancreatectomy, and total pancreatectomy, is generally recommended for the management of isolated pancreatic metastases. Bassi *et al*[17] observed a high rate of pancreatic recurrences after atypical resections and recommended standard radical resection. Considering the high frequency of multiple metastases, a recurrence after surgical resection could be related to multifocality of the tumor rather than to an atypical surgical procedure[18]. Since pancreatic metastases is often multifocal, partial pancreatectomies require thorough exploration of the pancreatic remnant by palpation and ultrasound. Intraoperative ultrasound is a very useful device: it guides the surgeon in choosing the most appropriate surgical procedure by defining the presence of multiple pancreatic lesions and the proximity of the metastasis to the Wirsung duct[18]. Surgical strategy should be tailored on each single case, in order to achieve an R0 resection and ensuring the absence of further disease in the pancreatic parenchyma. Surgical resection may be considered also in selected cases of extrapancreatic disease, if technically feasible[16]. The effectiveness of resection for pancreatic metastases is mainly dependent on the tumor biology of the primary cancer.

The benefit of metastasectomy in terms of patient survival has been observed for metastases from RCC, while for other primary tumors the role of surgery is mainly palliative. Patients with pancreatic metastases

Table 5 Pancreatic resections for metastatic lung cancer

Ref.	No	Interval (mo)	Type of primary	Treatment	Survival (mo)	
					Dead	Alive
Igai *et al*[114]	1	60	NSCLC	PD		6
Lasithiotakis *et al*[68]	1	6	NSCLC	PD	/	/
Mourra *et al*[102]	2	0, 10	NSCLC	DP (2)	10	20
Wilson *et al*[115]	1	NA	NSCLC	PD		22
Mori *et al*[116]	1	22	NSCLC	PPPD		24
Pericleous *et al*[117]	1	0	NSCLC	PPPD		18
Crippa *et al*[24]	1	5	NSCLC	PPPD	14	
García Vidal *et al*[118]	1	0	NSCLC	PD		NA
Hiotis *et al*[83]	1	NA	NA	DP	DOD	
Le Borgne *et al*[26]	1	0	SCLC	PD	4	
Medina-Franco *et al*[82]	1	17	NSCLC	PD		12
Nakeeb *et al*[57]	1	8	NSCLC	PD	3	
Total	13	6 (median)	NSCLC = 10 SCLC = 1	PD (7) DP (3) PPPD (3)	7 (median)	19 (median)

NSCLC: Non-small cell lung cancer; SCLC: Small cell lung cancer; NA: Not available; DP: Distal pancreatectomy; PD: Pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectomy; DOD: Dead of disease.

from RCC represent a favourable subgroup and surgical resection is recommended for these patients, whenever possible. However, a multidisciplinary approach has to be recommended and further studies are needed to establish the way to combine surgery with medical treatment in the different periods of the disease.

Considering the data available in the literature, it seems reasonable to consider surgery for pancreatic metastases from colorectal cancer a palliative treatment. However, an aggressive surgical approach may be considered in selected cases, in particular in symptomatic patients with isolated pancreatic metastasis.

Resection of melanoma metastatic to the pancreas appears to be only a palliative procedure. However, surgical resection may be considered in limited pancreatic disease with palliative intent. Even in the case of pancreatic metastases from breast cancer it is impossible to establish the course of the disease without surgical resection and to assess the real benefit in survival of the metastasectomy. However, in selected patients with a limited pancreatic disease, surgery may play a role in conjunction with chemotherapy, hormonal therapy and radiation therapy in the multimodality treatment of metastatic breast carcinoma. Solitary pancreatic metastases from lung cancer have a poor prognosis and treatment options for metastatic lung cancer lesions to the pancreas are mainly palliative. Finally, resection of pancreatic metastases from sarcoma is substantially justified in individual basis.

CONCLUSION

Pancreatic metastases, although uncommon, are an increasing clinical entity. Surgical resection is often advocated when the lesion is single and for patients fit to perform a pancreatectomy. The usefulness of pancreatic resection is mainly linked to the biology of the primary tumor metastasizing to the pancreas. The benefit of metastasectomy in terms of patient survival has been observed for metastases from RCC, while for other tumors the role of surgery is mainly palliative. In fact, from our data and from a review of the literature, pancreatic surgery for metastases from colorectal cancer and melanoma may be considered for palliation, even if in selected cases surgical resection can be advocated in the multimodality treatment of metastatic colorectal cancer. Even in the case of pancreatic metastases from breast cancer, an aggressive surgical approach appears useful for good palliation in selected patients with a limited pancreatic disease. Patients with solitary metastases from lung cancer have a poor outcome and do not benefit from surgical resection. Finally, resection of pancreatic metastases from sarcoma is substantially justified only in very selected patients.

Patients with pancreatic metastases should be evaluated with a multidisciplinary approach, being surgery part of the multimodality treatment of these clinical entities. Further studies are needed to establish the way to combine surgery with medical treatments in the different metastatic diseases to the pancreas.

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Multimodality management of resectable gastric cancer: A review

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Abstract

Adenocarcinoma of the stomach carries a poor prognosis and is the second most common cause of cancer death worldwide. It is recommended that surgical resection with a D1 or a modified D2 gastrectomy (with at least 15 lymph nodes removed for examination), be performed in the United States, though D2 lymphadenectomies should be performed at experienced centers. A D2 lymphadenectomy is the recommended procedure in Asia. Although surgical resection is considered the definitive treatment, rates of recurrences are high, necessitating the need for neoadjuvant or adjuvant therapy. This review article aims to outline and summarize some of the pivotal trials that have defined optimal treatment options for non-metastatic non-cardia gastric cancer. Some of the most notable trials include the INT-0116 trial, which established a benefit in concurrent chemoradiation and adjuvant chemotherapy. This was again confirmed in the ARTIST trial, especially in patients with nodal involvement. Later, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial provided evidence for the use of perioperative chemotherapy. Targeted agents such as ramucirumab and trastuzumab are also being investigated for use in locally advanced gastric cancers after demonstrating a benefit in the metastatic setting. Given the poor response rate of this difficult disease to various treatment modalities, numerous studies are currently ongoing in an attempt to define a more effective therapy, some of which are briefly introduced in this review as well.

Key words: Neoadjuvant chemotherapy; Adjuvant chemotherapy; Adjuvant chemoradiation; Gastric cancer; Gastric adenocarcinoma

Core tip: Gastric adenocarcinoma is a difficult disease to treat. Surgical resection is the definitive therapy but recurrences are frequent. The use of a multidisciplinary approach to treatment decision-making is imperative. Surgical resection should be an R0 resection (with clear macroscopic and microscopic margins) and at least a D1 lymphadenectomy with a minimum of 15 lymph nodes sampled in the United States and a D2 lymphadenectomy elsewhere. Perioperative chemotherapy is a reasonable option based on the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial. In patients who are evaluated after resection, adjuvant chemoradiation adds important survival benefit. Other options include adjuvant S-1 in Asian patients, capecitabine/oxaliplatin, and capecitabine/cisplatin.

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INTRODUCTION

Adenocarcinoma of the stomach is one of the most common malignancies in the world, ranking fifth after

lung, breast, colorectal, and prostate. According to the World Health Organization, 952000 new cases were diagnosed in 2012 alone, with more than 70% of all cases occurring in developing countries[1]. In the United States, an analysis using the Surveillance Epidemiology and End Results database of the National Cancer Institute found an increase in overall incidence of adenocarcinoma of the esophagus and the gastric cardia from 13.4 per million in 1973 to 51.4 per million in 2009[2]. It is also the second most common cause of cancer death as of 2010. There is a significant disparity in the incidence and survival rates between the Asian and Western countries. For example, the overall 5-year survival worldwide was about 20% according to a report in 2008 but more than 70% in Japan for resectable disease. Such a dramatic difference maybe due to the implementation of screening programs in Japan where there is a higher incidence of gastriccancer resulting in detection of disease at earlier stages. In contrast, patients in the United States are usually diagnosed later in stage as routine screening for gastric cancer is not recommended owing to cost ineffectiveness[3]. The survival benefit may also be related to a more frequent use of second-line chemotherapy in Asian countries, most commonly irinotecans and taxanes, compared to the West[4, 5].

While gastric adenocarcinoma obviously includes tumors arising from the stomach, the classification of tumors of the gastroesophageal junction (GEJ) has been a topic of debate. The most widely used classification was proposed by Rüdiger Siewert *et al*[6] in 2000: type I tumors are tumors in the distal esophagus and may extend to the GEJ from above, type Ⅱ tumors are adenocarcinomas of the cardia, arising at the GEJ, and type Ⅲ tumors are cancers that originated from below the cardia and extend to the GEJ and distal esophagus from below. It is also noted that the biologies of these distinct types of GEJ tumors are very different. Type I cancers are mostly associated with intestinal metaplasia and history of gastroesophageal reflux disease. On the other hand, types Ⅱ and Ⅲ cancers resemble proximal gastric cancer and have lymphatic spread preferentially to the celiac axis[6,7]. The American Joint Committee on Cancer (AJCC) updated the staging of stomach adenocarcinoma in the 7th edition to include cancers of the GEJ arising more than 5 cm distally of the GEJ or within 5 cm of the GEJ but without extension to the esophagus or GEJ[8]. This distinction is important because many of the clinical trials included cancers of the GEJ in addition to cancers of the stomach. More importantly, cancers of the GEJ as described above behave similarly compared to gastric cancer and are treated as such.

Currently, surgical resection is the only curative mode of treatment for non-metastatic gastric adenocarcinoma. However, median survival with surgery alone, historically, was poor. Patients who had undergone resection are prone to suffer from locoregional or distant recurrences of their disease. As a result, neoadjuvant and adjuvant therapies aimed at the eradication of micrometastases were studied in an attempt to reduce recurrence and prolong survival. This review article aims to outline some of the pivotal data that led to current clinical practices in resectable gastric cancer. It also briefly introduces ongoing trials in a global effort to improve overall survival for this difficult disease. Data presented in this review article were retrieved using a PubMed search with the key words "adjuvant," "neoadjuvant," "perioperative therapy," and "resectable gastric cancer."

CURATIVE RESECTION

Though this review aims to summarize available data in medical treatment of resectable gastric cancer, it is important to discuss surgical management given its central role in overall management. Controversies surround the surgical management of gastric cancer. In 1999, Bozzetti *et al*[9] found no difference in survival between total and subtotal gastrectomies but that subtotal gastrectomy was associated with improved nutritional status and quality of life. With the advancement of laparoscopic techniques, laparoscopic gastrectomy was found to have similar outcomes but with fewer complications compared to open gastrectomy in meta-analyses and case-control studies[10-13]. Furthermore, a resection margin of 1 mm was found to be sufficient as long as the resection margins were free of tumor[12].

The depth of lymphadenectomy has been a topic of debate as well. A D1 dissection involves a gastrectomy and the removal of the greater and lesser omental lymph nodes. A D2 dissection involves the above plus the removal of all lymph nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum and splenic artery. The D1 dissection was traditionally favored in the West, specifically in the United States, whereas D2 resection was preferred in the East[14] and Europe. This discrepancy was based on early randomized trials that failed to show a survival benefit with D2 lymphadenectomy[15,16]. Subsequent studies showed that D2 resection indeed offered a survival benefit, prompting a change in practice. Recently, Shrikhande *et al*[17] established the non-inferiority of perioperative gastrectomy with D2 lymphadenectomy for locally advanced resectable gastric adenocarcinoma when combined with neaoadjuvant chemotherapy. More importantly, half of those patients who achieved a pathologic response were found to have lymph node involvements, arguing for the necessity of D2 gastrectomy[17]. A randomized trial comparing D1 and D2 dissections found that there was no difference in overall 5-year survival between the two practices. However, subgroup analyses suggest that D1 resection may be beneficial for those with pT1 disease while a trend towards improved survival was seen with D2 lymphadenectomy in patients with nodal involvement[18]. Based on some of these trials in addition to other clinical data, the National Comprehensive Cancer Network guidelines currently recommends a D1 or a modified D2 gastrectomy with at least 15 lymph nodes removed for examination in

the United States, though noting that D2 lymphadenectomies should be performed at experienced centers[19].

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant treatment has the appeal of allowing for a more complete surgical resection while assessing for response to chemotherapy and risk for recurrence. However, robust data to support use of neoadjuvant therapy are limited at this time. Schuhmacher *et al*[20] reported data from the European Organisation for Research and Treatment of Cancer 40954 trial comparing neoadjuvant cisplatin, folinic acid, and infusional fluorouracil with surgery alone. A total of 144 patients with locally advanced adenocarcinoma of the stomach and GEJ were recruited and randomized. Those assigned to chemotherapy received 48-d cycles of neoadjuvant biweekly cisplatin, weekly L-folinic acid and fluorouracil for 2 cycles. The study was closed prematurely due to poor accrural. Only 62.5% of patients assigned to the chemotherapy arm completed 2 cycles of treatment.

Median follow-up was about 4 years. Preoperative chemotherapy reduced tumor size and nodal involvement compared to surgery alone. Given the low accrural, this study was ultimately underpowered at 25%. Progression-free survival had a hazard ratio of 0.76 but was not statistically significant (95%CI: 0.49 to 1.16, $P = 0.2$). The 2-year survival rates were 72.7% in the chemotherapy arm and 69.9% in the surgery only arm. The hazard ratio for overall survival was 0.84 in favor of chemotherapy, though it was not a statistically significant finding (95%CI: 0.52 to 1.35, $P = 0.466$). The authors noted that while this was a negative study with a small sample size, the rate of R0 resection was higher in the group that received neoadjuvant chemotherapy at 81.9%, compared to 66.7% in the group that did not ($P = 0.036$)[20]. Whether this difference would have translated into a benefit in progression-free survival or overall survival remains unanswered.

Additional albeit limited trial data emerged recently in attempts to further characterize the use and benefits of neoadjuvant chemotherapy. A small randomized, double-blinded controlled trial from Tehran found similar survival rates after a follow-up period of about 10 mo when comparing use of preoperative docetaxel, cisplatin, and 5-fluorouracil (DCF) followed by surgery with surgery alone[21]. In a recent phase Ⅱ study, the use of neoadjuvant paclitaxel and cisplatin was found to provide a pathologic response of 34.6% and a 3-year overall survival of 41.5% (95%CI: 27.4% to 55.0%)[22]. A small non-randomized study from China compared the use of epirubicin, oxaliplatin, and capecitabine (EOX) with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX). An improved pathologic response was found with use of EOX. This study, however, enrolled 87 patients in the FOLFOX arm and only 26 patients in the EOX arm[23].

Given the paucity and variability of information, systemic reviews were conducted to attempt to clarify the role of neoadjuvant chemotherapy. A meta-analysis was performed investigating the effectiveness of 5-fluorouracil-based chemotherapy in the neoadjuvant setting. Seven randomized controlled trials were included for analysis with a total of 1249 patients. The results showed that neoadjuvant chemotherapy improved overall survival with an odds ratio of 1.40 (95%CI: 1.11 to 1.76, $P = 0.0005$). The 3-year progression-free survival was also higher in the chemotherapy group at 37.7% compared to 27.3% in the control group, odds ratio of which was 1.62 (95%CI: 1.21 to 2.15, $P = 0.001$). There was no difference in perioperative mortality or complication rates between the two groups. Combination chemotherapy was superior to monotherapy. Additionally, intravenous administration of chemotherapy was found to have a greater impact than oral administration. Finally, it demonstrated a preference in Western countries for neoadjuvant treatment compared to Asian countries[24].

On the other hand, Liao *et al*[25] did not find an improvement in overall survival or R0 resection with use of neoadjuvant therapy. A meta-analysis of 6 randomized, controlled trials with 781 patients was conducted. The odds ratio was 1.16 for overall survival with use of neoadjuvant chemotherapy (95%CI: 0.85 to 1.58, $P = 0.36$) and 1.24 for R0 resection (95%CI: 0.78 to 1.96, $P = 0.36$)[25], neither of which were statistically significant. Currently, available data further illustrates the controversy in defining the optimal neoadjuvant treatment.

PERIOPERATIVE CHEMOTHERAPY

The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial in 2006 established the role of perioperative chemotherapy for resectable gastroesophageal cancer as the standard of care. A total of 503 treatment-naïve patients with adenocarcinoma of the stomach or lower third of the esophagus were randomized to receive perioperative epirubicin, cisplatin, and infused fluorouracil (ECF) or surgery alone. The trial was initially designed to recruit gastric adenocarcinomas but was extended to include tumors of the GEJ due to its increased incidence. Patients had stage Ⅱ and Ⅲ disease or locally advanced but inoperable disease.

Two hundred and fifty patients were randomized to receive 3 cycles of preoperative epirubicin (50 mg/m^2 on day 1), cisplatin (60 mg/m^2 on day 1), and fluorouracil (200 mg/m^2 daily) for 21 d, followed by surgical resection and 3 additional cycles of ECF. A total of 215 patients, 86% of those randomized to the perioperative chemotherapy arm, completed chemotherapy; 41.6% of these patients completed all 6 cycles of chemotherapy. Median follow-up was about 4 years. Preoperative chemotherapy significantly reduced tumor size at time of resection with a median maximum diameter of 3 cm (compared to 5 cm in those without chemotherapy, $P < 0.001$). There was also more T1 and T2 tumors as well as N0 and N1 disease in the group exposed to chemotherapy. Five-year survival rates were 36.3% in the perioperative chemotherapy arm and 23% in the surgery arm with an overall sur-

vival hazard ratio of 0.75 (95%CI: 0.60 to 0.93, $P = 0.009$). Progression-free survival was also improved with chemotherapy with a hazard ratio of 0.66 (95%CI: 0.53 to 0.81, $P < 0.0019$). Local recurrence was noted in 14.4% of patients in the perioperative chemotherapy group and in 20.6% in the surgery group. Distant metastases were also less frequent in those who received chemotherapy (24.4% *vs* 36.8%)[26]. The benefits of this regimen was confirmed in 2013 when Mirza *et al*[27] found an improvement in survival when patients completed both the pre- and postoperative cycles.

In 2007, the results for the FNLCC ACCORD07-FFCD 9703 trial were presented at the annual American Society of Clinical Oncology meeting and later published in 2011. A total of 224 patients with adenocarcinoma of the stomach or GEJ were randomized to receive 2-3 cycles of fluorouracil at 800 mg/m^2 for days 1-5 and cisplatin 100 mg/m^2 on day 1, for a 28-d cycle followed by surgery and postoperative chemotherapy for an additional 3-4 cycles or surgery alone. The planned maximum cycles were set at 6. The trial was closed early as a result of accrural difficulties.

The median follow-up was 5.7 years. In the chemotherapy arm, 97% of patients received at least 1 cycle of preoperative chemotherapy, 87% received at least 2 cycles. Of these, 50% went on to receive post-operative chemotherapy. R0 resection rate was 84% in the chemotherapy group compared to 74% in the surgery group ($P = 0.04$). There was a trend towards less nodal involvement at time of surgery in the chemotherapy group (67% *vs* 80%, $P = 0.054$) but the sizes of tumors at resection were similar in both groups. Five-year survival was 38% (95%CI: 29% to 47%) in the chemotherapy group and 24% (95%CI: 17% to 33%) in the surgery group. Five-year disease-free survival was also significantly improved with chemotherapy at a rate of 34% (95%CI: 26% to 44%) compared to 19% (95%CI: 13% to 28%). Furthermore, the chemotherapy arm also offered improved overall survival with a hazard ratio of 0.69 (95%CI: 0.50 to 0.95, $P = 0.02$) and disease-free survival with a hazard ratio of 0.65 (95%CI: 0.48 to 0.89, $P = 0.003$).

It is important to note, however, that this study was originally designed to include patients with cancer of the esophagus and was only extended to include cancer of the stomach in 1998. Consequently, 64% of accrued patients had disease of the GEJ while only 25% had gastric carcinoma. In a multivariate analysis, it was noted that preoperative chemotherapy and tumor site at the GEJ were significant prognostic factors for overall survival, $P = 0.01$ and $P < 0.01$, respectively. The other pathologies were not noted to have a statistically significant benefit when analyzed separately because of small sample sizes[28,29].

In a small non-randomized study, the use of perioperative FOLFOX was compared with adjuvant FOLFOX. A total of 73 patients with resectable T3 and T4 gastric adenocarcinoma were recruited between December 2001 and September 2005, 33 of which were assigned to the perioperative arm while 37 patients were assigned to the adjuvant arm. Those receiving perioperative chemotherapy received 3-wk cycles of FOLFOX for 2-4 cycles, followed by surgery and further chemotherapy for a total of 6 cycles. Those allocated to the adjuvant arm received the same FOLFOX regimen for a total of 6 cycles. The median follow-up duration was 53 mo. The 4-year overall survival was 78% (95%CI: 64% to 92%) in the perioperative chemotherapy group compared to 51% (95%CI: 35% to 67%, $P = 0.031$) in the adjuvant group. The 4-year disease-free survival was 78% (95%CI: 64% to 92%) and 48% (95%CI: 32% to 64%, $P = 0.022$), respectively[30]. While this was a very small, non-randomized study, it provided evidence for further investigational efforts to evaluate the role of FOLFOX in a perioperative setting.

Finally, the use of perioperative chemotherapy, with or without radiation, was confirmed as advantageous compared to surgery alone in a Cochrane database meta-analysis of randomized controlled trials. The hazard ratio with use of chemotherapy was 0.81 (95%CI: 0.73 to 0.89), which corresponded to a 5-year relative survival increase of 19% and an absolute increase of 9%[31].

ADJUVANT CHEMORADIATION

In 2001, Macdonald *et al*[32] published clinical results from the INT-0116 (Intergroup 0116) study evaluating effects of adjuvant chemoradiation using concurrent fluorouracil and leucovorin followed by 2 cycles of fluorouracil and leucovorin after completion of radiation as compared to surgery alone. The regimen used is now commonly known as the Macdonald regimen. This study also changed the standard of care for gastric adenocarcinoma. It recruited 603 patients between 1991 and 1998 with stages IB to IV(M0) gastric or gastroesophageal adenocarcinoma. Gastric primaries comprised of about 80% of total recruited patients. Sixty-four percent of those randomized to chemoradiation completed treatment. Median follow-up was 5 years with median survival of 36 mo in the chemoradiation group and 27 mo in the control group. Three-year survival rates were 50% in the chemoradiation arm and 41% in the surgery arm, with a hazard ratio of 1.35 (95%CI: 1.09 to 1.66, $P = 0.005$) in the surgery arm. The median progression-free survival was 30 mo with adjuvant treatment compared to 19 mo without, which translated to three-year rate of progression-free survival of 48% and 31%, respectively. One of the criticisms of this trial was that more than half of the patients had less than D1 resections. It was possible that the adjuvant treatment acted to compensate for the suboptimal surgery. The effect of adjuvant radiotherapy in setting of D2 resections remains unclear from this data set[32].

After median follow-up of 10.3 years, an update to the INT-0116 trial was presented in 2012. The hazard ratio for progression-free survival was 1.51 (95%CI: 1.25 to 1.83, $P < 0.001$) and 1.32 (95%CI: 1.10 to 1.60, $P = 0.0046$) for overall survival without the addition of

chemoradiation. Median progression-free survival was 27 mo for adjuvant therapy compared to 19 mo without ($P < 0.001$). Median overall survival was 35 mo with additional treatment compared to 27 mo without ($P = 0.0046$). There was no notable long term adverse effect found. This update confirmed earlier findings that additional adjuvant chemoradiation offered significant benefit in gastric cancer[33].

With the approval of capecitabine in 1998 for breast cancer and subsequently colorectal cancer, a new oral option became available. Using this new oral fluorouracil prodrug, the ARTIST (Adjuvant Chemoradiation Therapy in Stomach Cancer) trial expanded on the idea of adjuvant chemoradiation. It compared adjuvant capecitabine and cisplatin with capecitabine, cisplatin and concurrent capecitabine chemoradiation. From 2004 to 2008, 458 patients with adenocarcinoma of the stomach who had undergone an R0 gastrectomy with at least D2 lymph node dissection were randomized. Those assigned to the chemotherapy arm received 6 cycles of capecitabine (1000 mg/m^2 twice daily on days 1-14) and cisplatin (60 mg/m^2 on day 1) every 3 wk. Those assigned to the chemoradiation received 2 cycles of the same doses of capecitabine and cisplatin, followed by concurrent capecitabine (825 mg/m^2 twice daily) and radiation, followed by 2 additional cycles of capecitabine and cisplatin in 3-wk cycles.

Median duration of follow-up was 53.2 mo. Treatments were completed by 75.4% of those randomized to the chemotherapy arm and 81.7% of those assigned to the chemoradiation arm. Three-year disease-free survival rates were 78.2% in the concurrent chemoradiation group and 74.2% in the chemotherapy alone group ($P = 0.0862$). While this was not statistically significant, a subgroup analysis found a statistically significant improvement in 3-year disease-free survival in patients with nodal involvement using chemoradiation (77.5% *vs* 72.3%, $P = 0.0365$), which corresponded to a hazard ratio of 0.6865 (95%CI: 0.4735 to 0.9952, $P = 0.0471$). Overall survival data had not matured at time of publication. It should be noted that while disease-free survival was improved with the addition of radiation, the rate of locoregional recurrence and distant metastases were not different between the two study groups[34].

CALGB 80101, a US Intergroup study, compared the INT-0116 protocol regimen (bolus FU and leucovorin with FU plus concurrent RT) versus postoperative ECF before and after FU plus concurrent RT in 546 patients with completely resected gastric or GEJ tumors that extended beyond the muscularis propria or were node positive[35]. The fraction of enrolled patients with GEJ versus gastric primary tumors was not reported. In a preliminary report presented at the 2011 meeting of the American Society of Clinical Oncology, patients receiving ECF had lower rates of diarrhea, mucositis, and grade 4 or worse neutropenia. Overall survival, the primary endpoint, was not significantly better with ECF (at three years, 52% *vs* 50% for ECF and FU/LV, respectively). The trial was not adequately powered to assess non-inferiority. The location of the primary tumor GEJ *vs* proximal versus distal stomach did not have any effect on treatment outcome.

A meta-analysis also confirmed the utility of adjuvant chemoradiation in resectable gastric adenocarcinoma after an R0 resection[36].

ADJUVANT CHEMOTHERAPY

As perioperative and adjuvant chemoradiation became widely accepted, the benefit of adjuvant chemotherapy was also investigated. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) trial sought to answer this question. S-1 is an oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine combination of tegafur, gimeracil, and oteracil. Once ingested, tegafur is converted *in vivo* to fluorouracil. This was a phase Ⅲ, randomized study that recruited 1059 patients with stage Ⅱ or Ⅲ adenocarcinoma of the stomach from 2001 to 2004. All patients underwent a D2 gastrectomy with an R0 resection. Those patients assigned to adjuvant therapy received S-1 in 80, 100, or 120 mg daily doses, estimated based on body surface area, for 4 wk with 2 wk of rest for 1 year.

The study initially found, after a median follow up of 3 years, that the 3-year overall survival was 80.1% in the S-1 group compared to 70.1% in the surgery alone group. The hazard ratio was 0.68 (95%CI: 0.52 to 0.87, $P = 0.003$). The investigators performed an updated analysis of the results after 5 years of follow-up in 2011, which found a hazard ratio of 0.669 (95%CI: 0.54 to 0.828). Overall survival was 71.7% (95%CI: 67.8% to 75.7%) and 61.1% (95%CI: 56.8% to 65.3%) in the chemotherapy and observation groups, respectively. The 5-year relapse-free survival was 65.4% (95%CI: 61.2% to 69.5%) in the treatment arm compared to 53.1% (95%CI: 48.7% to 57.4%) in the surgery alone arm; hazard ratio was 0.653 (95%CI: 0.537 to 0.793). This reduction in hazard ratio was seen across all disease stages in subgroup analyses[37].

S-1, or tegafur, is not approved for use in the United States by the FDA. Based on pharmacokinetics studies, it has been documented that the drug is metabolized differently between Asians and Caucasians. The difference lies in the presence of CYP2A6, which occurs at a higher frequency in Eastern Asians. This enzyme is associated with reduced activity and subsequently reduced conversion of the prodrug *in vivo* to fluorouracil. Chuah *et al*[38] found that given the same dosing, the exposure to fluorouracil was similar in both ethnic groups. This was suggested by the investigators to be a result of increased renal clearance in Caucasians. Despite the same degree of exposure to the active metabolite, Caucasians were noted to have more grades 3 and 4 gastrointestinal toxicities compared to Asians (21% *vs* 0%)[38]. As a result of this difference, there is concern that tegafur use in the United States population may require dose reductions and efficacy of lower doses for resectable gastric cancer has not been addressed.

The First-Line Advanced Gastric Cancer Study evaluated an international cohort of patients with unresectable,

locally advanced or metastatic gastric and gastroesophageal adenocarcinoma using a protocol that compared S-1 and cisplatin with fluorouracil and cisplatin. It did not find significant differences in efficacy or toxicity profiles between the various ethnic groups[39]. This phase Ⅲ, randomized trial suggests that tegafur can be effective in Caucasians with advanced gastric cancer; however, further studies for resectable gastric carcinoma are warranted.

In 2012, a Korean group published results of the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) trial, which compared adjuvant capecitabine and oxaliplatin after D2 gastrectomy with R0 resection with surgery alone in stage Ⅱ and Ⅲ gastric adenocarcinomas. A total of 1035 patients were recruited between 2006 and 2009 in centers in South Korea, China, and Taiwan. Patients were randomized to either adjuvant chemotherapy or observation alone. Those assigned to chemotherapy received capecitabine (1000 mg/m^2 twice daily on days 1-14) and oxaliplatin (130 mg/m^2 on day 1) of a 3-wk cycle for a total of 8 cycles.

Median duration of follow-up was about 34 mo in both arms and 67% of those receiving chemotherapy completed 8 cycles of treatment. The 3-year disease-free survival was 74% (95%CI: 69% to 79%) and 59% (95%CI: 53% to 64%) in the chemotherapy and surgery alone groups, respectively, with a hazard ratio for chemotherapy of 0.56 (95%CI: 0.44 to 0.72, $P < 0.0001$). The 3-year overall survival was 83% (95%CI: 79% to 87%) in the treatment group compared to 78% (95%CI: 74% to 83%) in the observation group. The hazard ratio for overall survival was 0.72 (95%CI: 0.52 to 1.00, $P = 0.0493$). Estimation of median overall survival was not available at time of publication. In the subgroup analyses, survival benefit was seen in all disease stages and N1 and N2 diseases. There was no significant benefit for those with N0 disease[40].

A small randomized, double-blinded study was conducted to evaluate use of adjuvant FOLFOX4 *vs* fluorouracil/leucovorin in resectable gastric adenocarcinoma. A total of 80 patients were recruited from 2005 to 2009 after D2 gastrectomy with an R0 resection. Median duration of follow-up was about 36 mo. The 3-year overall survival was 36 mo in the FOLFOX4 group compared to 28 mo in the control group ($P < 0.05$). Similarly, the 3-year recurrence-free survival was 30 mo with the addition of oxaliplatin compared to 16 mo without ($P < 0.05$)[41].

Most recently, a phase Ⅲ study conducted by Kang *et al*[42] found an advantage using adjuvant cisplatin, mitomycin-C, and doxifluridine (iceMFP). Known as AMC 0101 trial, 521 patients were randomly assigned to receive mitomycin-C and doxifluridine (Mf, control) or the study arm, which included use of intraperitoneal cisplatin. The hazard ratio for recurrence in the iceMFP group was 0.70 (95%CI: 0.54 to 0.90, $P = 0.006$) with a 30% risk reduction for recurrence. The recurrence-free survival at 3 years was 60% (95%CI: 54% to 67%) in the study group compared to 50% (95%CI: 43% to 57%) in the control group. Median recurrence-free survival was not yet reached in the iceMFP arm but was 34.5 mo (95%CI: 24.2 to 63.8) in the Mf arm. Three-year overall survival rates were 71% (95%CI: 65% to 77%) and 60% (95%CI: 53% to 66%) for iceMFP and Mf, respectively[42]. Doxifluridine is another oral prodrug of 5-fluorouracil. Though doxifluridine is not FDA-approved for use in the United States, it is approved for use in Asia, calling into question the efficacy of cisplatin, mitomycin, and 5-fluorouracil (or its equivalent) in the United States.

ONGOING TRIALS AND FUTURE DIRECTIONS

Given the tenacious natural history of gastric cancer, many trials are currently ongoing to define more optimal treatments. Early phase I and Ⅱ data found promise in some new regimens, such as perioperative docetaxel, cisplatin, and capecitabine (DCX) and DCF[43,44], neoadjuvant S-1 and cisplatin or paclitaxel and cisplatin[45], and neoadjuvant docetaxel with S-1[46].

Of note, one highly anticipated trial, known as the Chemoradiotherapy after Induction Chemotherapy in Cancer of the Stomach trial, is a phase Ⅲ, randomized, multicenter trial designed to compare overall survival in patients with resectable gastric cancer when treated with 3 cycles of preoperative epirubicin, cisplatin, and capecitabine (ECC) followed by surgery and either an additional 3 cycles of ECC or concurrent chemoradiation with cisplatin, capecitabine, and 45 Gy. Accrual started in 2007 with results last updated in 2011, having enrolled 350 patients at that time[47].

In the United Kingdom, the MAGICB/ST03 study is exploring epirubicin, cisplatin and capecitabine (ECX) with or without bevacizumab followed by surgery, and adjuvant ECX with and without maintenance bevacizumab.

Neoadjuvant therapy is under study in a European trial comparing preoperative FU and cisplatin *vs* surgery alone and a joint Swiss/Italian trial of preoperative docetaxel, cisplatin and FU compared to surgery alone. Similarly, a Japanese study is evaluating preoperative cisplatin plus S-1 (an oral fluoropyrimidine) followed by surgery and postoperative S-1 *vs* surgery and postoperative S-1 alone (KYUH-UHA-GC04-03).

The Korean ARTIST Ⅱ trial is comparing adjuvant chemotherapy (S-1 *vs* S-1/oxaliplatin) with or without radiotherapy for completely resected gastric adenocarcinoma.

A randomized trial, the TOPGEAR trial, is underway in Europe and Canada to directly compare preoperative chemotherapy alone (ECF) *vs* chemoradiotherapy (two cycles of ECF followed by concurrent fluoropyrimidine-based chemoradiotherapy) in patients with resectable adenocarcinoma of the stomach and GEJ; both groups will receive three further cycles of ECF postoperatively

Uses of targeted agents are also being actively investigated. Recently, the REGARD trial, which was a random-

Table 1 Notable trial data for neoadjuvant and adjuvant therapies for gastric (or gastroesophageal) adenocarcinoma

Trial	No. of patients	Median survival (mo)	Overall survival	Progression-free survival
Neoadjuvant chemotherapy				
EORTC 40954[20]			(2 yr)	
5FU, cisplatin, folinic acid	72	64.62	72.70%	NR
Surgery alone	72	52.53	69.90%	NR
Perioperative chemotherapy				
MAGIC Trial[26]			(5 yr)	
ECF	250	NR	36.30%	NR
Surgery alone	253	NR	23%	NR
Fnlcc accord07/ffcd 9703[29]			(5 yr)	(5 yr)
5FU, cisplatin	113	NR	38%	34%
Surgery alone	111	NR	24%	19%
Adjuvant chemoradiation				
INT-0116 trial[32]			(3 yr)	(3 yr)
5FU, CRT	281	36	50%	48%
Surgery alone	275	27	41%	31%
Artist trial[34]				(3 yr)
Capecitabine, cisplatin, CRT	230	NR	NR	78.20%
Capecitabine, cisplatin	228	NR	NR	74.20%
Adjuvant chemotherapy				
ACTS-GC Trial[37]			(3, 5 yr)	(5 yr)
S-1	529	NR	80.1%, 71.7%	65.40%
Surgery alone	530	NR	70.1%, 61.1%	53.10%
Classic trial[40]			(3 yr)	(3 yr)
Capecitabine, oxaliplatin	520	NR	83%	74%
Surgery alone	515	NR	78%	59%

NR: Not reported; 5FU: 5-fluorouracil; ECF: Epirubicin/cisplatin/5-fluorouracil; CRT: Chemoradiation therapy.

ized, double-blinded, placebo-controlled, international study, established ramucirumab as an active biologic agent in advanced gastric cancer. Ramucirumab is a fully human IgG monoclonal antibody. It functions as a VEGFR-2 antagonist by preventing ligand binding and subsequent receptor-mediated pathway activation in endothelial cells, thus causing a decrease in tumor growth. Eligible patients had unresectable locally advanced recurrent or metastatic gastric or GEJ adenocarcinoma that progressed after first-line therapy. The majority population in both arms (approximately 75%) were patients with gastric adenocarcinoma. Median overall survival was 5.2 mo with ramucirumab and 3.8 mo with placebo. Hazard ratio was 0.776 (95%CI: 0.603 to 0.998, $P = 0.047$). Estimated overall survival and progression free survival were also improved[48]. This pivotal study established the role of ramucirumab as a single agent in advanced or metastatic gastric cancer. Further studies are sure to follow.

In the United Kingdom, the MAGICB/ST03 study is exploring epirubicin, cisplatin and capecitabine (ECX) with or without bevacizumab followed by surgery, and adjuvant ECX with and without maintenance bevacizumab.

The ToGA trial established use of trastuzumab in HER2-positive metastatic gastric cancer[49]. Similar promise was found with the use of trastuzumab in combination with chemotherapy[50-53] and additional clinical trials are currently underway. For instance, the TOXAG study is a phase Ⅱ clinical trial looking at the safety profile of adjuvant oxaliplatin, capecitabine, and trastuzumab with radiation. It is currently recruiting patients.

With respect to surgical interventions, new modes of treatment are being reviewed. A randomized trial known as CCOG 1102 has been planned to study the efficacy of extensive intraoperative peritoneal lavage compared to traditional surgery in resectable advanced gastric cancer with a primary end point of disease-free survival. A total of 300 patients are planned for accrual[54]. And finally, in regards to the controversy surrounding the extent of lymphadenectomy, a prospective randomized trial has been planned to compare D1 and D2 lymphadenectomy with a primary endpoint of 5-year overall survival.

CONCLUSION

Adenocarcinoma of the stomach, unfortunately, carries a poor prognosis and has a high mortality rate despite current available therapies. Most clinicians now treat GEJ and proximal gastric (*i.e.*, cardia) cancers as esophageal cancers, using preoperative chemoradiotherapy. However, it is important to note that tumors arising from within 5 cm of the GEJ without extension into the esophagus are classified in the same category as gastric cancer according to the updated AJCC Staging Manual and should be treated as such. This review outlines evidence-based approaches in the management of this difficult disease.

For patients with non-cardia gastric cancer, randomized trials and meta-analyses provide support for a number of approaches including adjuvant chemoradiotherapy, as shown in the INT-0116 trial, perioperative chemotherapy (preoperative plus postoperative), as was used in the MAGIC trial. Few studies have compared these approaches; however, the optimal way to integrate

combined modality therapy has not been definitively established. Decisions are often made based on institutional and/or patient preference. A major problem, at least in the United States, is that some patients with gastric cancer undergo surgery prior to consultation by medical or radiation oncologists.

Currently, a multidisciplinary approach and definitive surgical resection are recommended for locally advanced, early stage cancer. The gastrectomy should be performed laparoscopically if possible. It should be with negative margins and accompanied by a D1 lymphadenectomy with at least 15 lymph nodes sampled. A D2 lymphadenectomy should be performed in well-experienced centers.

For patients who have already undergone potentially curative gastric resection, we suggest adjuvant chemoradiotherapy rather than surgery alone for patients with N1 disease (which would include T1N1 stage IB), and for patients with T3N0 (stage ⅡA) disease and above, based upon the results of US Intergroup trial INT-0116[22]. For the subgroup of patients with T2N0 disease, either observation or adjuvant treatment is acceptable, and the decision can be based upon individualized patient (such as age, performance status, and motivation for treatment) and disease risk factor (*e.g.*, histologic grade or the presence of lymphovascular or perineural invasion) considerations.

An acceptable alternative approach for patients who are seen prior to resection is perioperative chemotherapy alone (ECF). It is reasonable to select patients utilizing the eligibility criteria for the MAGIC trial (patients of any age with a performance status of 0 or 1), a histologically proven adenocarcinoma of the stomach that was considered to invade through the submucosa (stage T2 or higher), with no evidence of distant metastases or locally advanced inoperable disease, as evaluated by CT, ultrasonography or laparoscopy[17].

East Asian patients with resected node-positive disease or T3N0 (stage ⅡA) disease and above, may take one year of postoperative S-1 chemotherapy. It is difficult to know whether the benefit of adjuvant therapy with S-1, as demonstrated in the Japanese ACTS-GC trial[26], can be extrapolated to other populations, given the markedly better outcomes seen in both the treated and the surgery alone control groups, stage for stage, when compared to outcomes in other non-Japanese populations. Until further information becomes available, we suggest that this approach be limited to East Asian patients. Other alternative chemotherapy regimens for adjuvant therapy include capecitabine plus oxaliplatin, as was used in the CLASSIC trial[29], or capecitabine plus cisplatin, as was used in the ARTIST trial[24]. Table 1 summarizes the available data from pivotal trials.

As technology moves increasingly toward molecular targeted therapy, biologic agents such as trastuzumab and ramucirumab hold great promise in the treatment of this disease as well. Their roles have not yet been defined in locally advanced gastric cancer but they are important new advances in the era of personalized medicine.

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MINIREVIEWS

Neoadjuvant therapy for esophageal cancer

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Abstract

Esophageal cancer is increasing in incidence more than any other visceral malignancy in North America. Adenocarcinoma has become the most common cell type. Surgery remains the primary treatment modality for locoregional disease. Overall survival with surgery alone has been dismal, with metastatic disease the primary mode of treatment failure after an R0 surgical resection. Cure rates with chemotherapy or radiation therapy alone have been disappointing as well. For these reasons, over the last decade multi-modality treatment has gained increasing acceptance as the standard of care. This review examines the present data and role of neoadjuvant treatment using chemotherapy and radiation therapy followed by surgery for the treatment of esophageal cancer.

Key words: Neoadjuvant therapy; Esophageal cancer; Esophagectomy; Chemotherapy

Core tip: This review evaluates the current literature on the use of neoadjuvant chemotherapy with or without radiation therapy for the treatment of locally advanced esophageal cancer. Major randomized controlled trials and co-operative group studies have been evaluated. Response rates, survival, complete response and outcomes have been thoroughly reviewed.

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INTRODUCTION

Nearly 500000 patients are diagnosed with esophageal cancer worldwide yearly, and its incidence has nearly doubled in North America over the last 2 decades[1]. Adenocarcinoma is now the most common cell type in the western hemisphere followed by squamous cell cancer[2]. For locoregional disease, surgery has been the mainstay of therapy with 5-year survival rates ranging from 10%-40% and distant metastasis being the most common mode of treatment failure[3]. Radiation therapy alone has been evaluated for local control and, in one large series 3-year survival was only 6%[4]. Chemotherapy for locally advanced esophageal cancer has a response rate of 45% to 75% in numerous studies but relapse rates are high and long-term survival rates are very low.

Use of chemotherapy with or without radiation therapy before surgery has several theoretical benefits. It may improve baseline dysphagia, the most common symptom on presentation. It can help downstage the tumor, which may increase resection rates, and can treat micro-metastatic disease that is not detected on imaging studies. It has the potential to indicate the biologic behavior of the tumor by its response to treatment that may help guide further therapy.

The role of multi-modality treatment as a way to achieve higher long-term survival rates has been debated for many years. The roles of chemotherapy and radiation therapy to improve surgical results remain controversial; randomized trials have shown mixed results. This review will examine the data and survival rates for using pre-

operative chemotherapy and radiation therapy, alone or in combination, in the management of localized esophageal cancer.

NEOADJUVANT CHEMOTHERAPY

In a study by Boonstra *et al*[5], 169 patients with squamous cell cancer were randomized to 2-4 cycles of cisplatin and etoposide followed by surgery or surgery alone. Median overall survival in the two groups was 16 and 12 mo respectively. The 5-year survival in the chemotherapy group was 26% *vs* 17% in the surgery alone group ($P = 0.03$, hazard ratio 0.71; 95%CI: 0.51-0.98). Contrary to this study result, a large North American Intergroup 113 trial failed to show a survival benefit for three cycles of preoperative cisplatin/5-FU followed by surgery and two additional cycles of cisplatin/5-FU compared to surgery alone[3]. Both squamous and adenocarcinoma patients were included. With a study size of 440 patients, overall survival in each group was 20% and there was no benefit of chemotherapy seen in resection rates, local failure, or distant metastasis.

In a much larger study by the Medical Research Council Oesophageal Cancer Working group[6], 802 patients were randomized to two cycles of cisplatin/5-FU followed by surgery *vs* surgery alone. Median and 2-year survivals were improved in the chemotherapy group (16.8 mo *vs* 13.3 mo-difference 107 d; 95%CI: 30-196, and 43% *vs* 34%-difference 9%; 95%CI: 3-14, respectively). The curative resection rate was improved marginally from 55% to 60%. The MAGIC trial, performed in the United Kingdom[7], further reinforced the findings seen in the Medical Research Council study. A total of 503 patients with distal esophageal, GE junction and gastric adenocarcinoma were randomized to three cycles of pre and postoperative cisplatin/5-FU/epirubicin or surgery alone. Overall survival in the chemotherapy group was significantly better (36% *vs* 23%, $P = 0.009$), but fewer than one third of the patients in this study had distal esophageal adenocarcinoma. In a French study[8] of 224 patients randomized to 2-3 cycles of preoperative cisplatin/5-FU followed by surgery *vs* surgery alone, there was a significantly improved R0 resection rate (84% *vs* 73%, $P = 0.04$), 5-year disease free survival (34% *vs* 21%, $P = 0.003$), and 5-year overall survival (38% *vs* 24%, $P = 0.02$) following chemotherapy.

The data published in these studies are quite heterogeneous. Some studies have both squamous and adenocarcinoma patients while some have only adenocarcinoma patients. The chemotherapy drugs and regimens vary between studies as well. In a meta-analysis of 12 randomized trials in which pre-operative chemotherapy was used, the 5-year overall survival benefit was only 4%[9]. The benefit was somewhat smaller for squamous cell cancer compared to adenocarcinoma (4% *vs* 7%). Thus, the available data do not suggest that the use of neoadjuvant chemotherapy significantly improves survival.

NEOADJUVANT RADIATION THERAPY

In a trial of 96 patients by Kelsen *et al*[10], patients were assigned to preoperative radiotherapy or chemotherapy. The morbidity and mortality of surgery following preoperative treatment was no different compared to historical controls of surgery alone but there was no survival benefit of preoperative treatment. Another randomized trial of 176 patients comparing preoperative radiation (20 Gy in 10 treatments) followed by surgery *vs* surgery alone[11] showed no benefit of radiotherapy with overall 5-year survival of 13%. In a Scandinavian trial of 186 patients, Nygaard *et al*[12] showed an improved 3-year survival in patients receiving preoperative radiotherapy compared to patients undergoing surgery alone or chemotherapy and surgery.

A meta-analysis has not shown a statistically significant survival benefit for preoperative radiation[13]. At a median follow-up of 9 years, the survival benefit at 2 and 5 years was 3% and 4% respectively ($P = 0.062$). Thus neoadjuvant radiation therapy alone cannot be advocated for the management of esophageal cancer.

NEOADJUVANT CHEMORADIOTHERAPY (COMBINED THERAPY, TRIMODALITY THERAPY)

Neither preoperative radiation therapy nor chemotherapy alone in the neoadjuvant setting have been proven beneficial based on the trials[5,7-9] performed. This may be related to the low complete pathologic response rates, mostly between 2.5%-4%. The improvement in R0 resection and overall survival has been limited as well. Most patients who undergo surgical resection die from distant metastatic disease in spite of an R0 resection. Considering these results and for the reasons listed earlier in this review for using neoadjuvant therapy, combination therapy with all three modalities has been utilized to try to improve overall outcomes. We will first review the studies looking at trimodality therapy vs surgery alone.

Trimodality therapy vs surgery alone

Bosset *et al*[14] randomized 282 patients to preoperative cisplatin and concurrent radiation or surgery alone. Although the curative resection rate was higher with combined therapy (81% *vs* 69%), disease-free survival was improved (HR 0.6, 95%CI: -0.4-0.9, $P = 0.003$), and risk of local recurrence decreased (HR 0.6, 95%CI: -0.4-0.9, $P = 0.01$), there was no difference in overall survival. This may at least in part be due to higher than expected treatment related mortality in the chemo-radiation arm (12% *vs* 4%). This study only included patients with squamous cell cancers, and radiation was given using a split-dose technique.

Burmeister *et al*[15] in an Australian study randomized 256 patients to one cycle of cisplatin/5-FU and radiation

followed by surgery or to surgery alone. R0 resection was achieved in 80% of the patients in the combined therapy group *vs* 59% in the surgery alone arm. However, the overall survival was no different between the two groups. Patients with adenocarcinoma had a decreased rate of complete pathologic response and were more likely to have disease progression during the follow-up period.

In a study from the University of Michigan[16], 100 patients were randomized to preoperative cisplatin/5-FU/vinblastine plus radiation or to surgery alone. There was a significant decrease in the rate of local recurrence with combined therapy (19% *vs* 42%, $P = 0.03$) and a trend towards improved survival at 3 years (30% *vs* 16%, $P = 0.15$). In an Irish study of 113 patients, Walsh *et al*[17] showed a significant improvement in overall survival at 3 years (32% *vs* 6%) with preoperative cisplatin/5-FU/radiation followed by surgery *vs* surgery alone. All patients in this study had adenocarcinoma but the extremely poor 3-year survival in the surgery alone arm (6%) could not be explained. In 2012, a multi-institutional phase Ⅲ study (CROSS trial)[18] evaluated the benefit of induction therapy using carboplatin/taxol/41Gy radiation *vs* surgery alone. Only a quarter of the patients had squamous histology. There was an anastomotic leak rate of 22%-30% in each arm. Median survival was 49 mo in the combined therapy arm compared to 24 mo in the surgery arm ($P = 0.003$). The overall 5-year survival was much improved in the combined therapy arm (47% *vs* 34%, $P = 0.03$). Patients with squamous histology derived a larger benefit. An updated analysis[19] of this group of patients showed a lower local recurrence rate (34% *vs* 14%, $P < 0.001$) and lower risk of peritoneal carcinomatosis (14% *vs* 4%, $P < 0.001$) following neoadjuvant chemoradiation and that squamous cell carcinoma was an independent prognostic variable in the surgery alone group.

Neoadjuvant chemoradiation vs neoadjuvant chemotherapy alone

Stahl *et al*[20] reported their data of 120 patients with T3 or higher and/or node positive patients who were randomized to preoperative cisplatin/5-FU/leucovorin followed by surgery *vs* cisplatin/5-FU/leucovorin followed by chemoradiotherapy with cisplatin/etoposide and then surgery. Trimodality patients had a higher rate of pathologic complete response (16% *vs* 2%, $P = 0.03$) and node-negative status (64% *vs* 37%, $P = 0.01$). The overall 3-year survival was not statistically significantly different in the two groups with a median overall survival of 32.8 *vs* 21.1 mo ($P = 0.14$).

In a recent meta-analysis[9] of 10 randomized trials of trimodality therapy *vs* surgery alone and 8 trials of preoperative chemotherapy *vs* surgery alone, trimodality therapy was associated with a 13% benefit in survival at 2 years, both in squamous and adenocarcinoma. Preoperative chemotherapy alone translated to a 7% benefit in survival at 3 years, more in adenocarcinoma than in squamous cell cancer. Thus, these data suggest a synergistic benefit using neoadjuvant chemotherapy plus radiotherapy in the management of esophageal cancer.

CONCLUSION

The three mainstays of treatment for esophageal cancer-surgery, chemotherapy, and radiation therapy result in poor overall survival and high relapse rates when used alone. Preoperative combination therapy offers several theoretical advantages but for stage 1 and 2 esophageal cancers, there is, as of now, no convincing evidence that neoadjuvant chemoradiation is of any benefit. Neoadjuvant chemoradiotherapy achieves the highest complete pathologic response rates, R0 resection rates, and improves 3-5 years survival rates in patients with locally advanced esophageal cancer. The addition of neoadjuvant radiotherapy to preoperative chemotherapy may facilitate a better complete surgical resection *via* its effect on the periphery of the tumor. Squamous cell cancer and adenocarcinoma appear to have similar disease-free and overall survival rates following neoadjuvant chemoradiotherapy. Further randomized, prospective trials will be required to build on these early studies to try to improve the prognosis of patients with this terrible disease.

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MINIREVIEWS

Peritoneal metastases of colorectal origin treated by cytoreduction and HIPEC: An overview

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Abstract

Colorectal peritoneal carcinomatosis was considered a terminal condition with a merely palliative treatment that included only supportive care, palliative surgery and the best systemic chemotherapy. Since the birth of a new approach, cytoreductive surgery with peritonectomy procedures together with hyperthermic intraperitoneal chemotherapy and/or early postoperative intraperitoneal chemotherapy to treat peritoneal carcinomatosis, many research groups contributed with promising results using this procedure being up to date this strategy the only one that has shown curative benefits on colorectal peritoneal carcinomatosis achieving reported overall survival rates up to 64 mo and five-year survival rates up to 51%. The aim of this paper is to expose an updated overview of the therapeutic possibilities of these procedures in colorectal peritoneal metastases in the same way that our Unit of Oncologic Surgery has performed since 1997 with more than four hundred procedures.

Key words: Carcinomatosis peritoneal; Colon cancer; Intraperitoneal chemotherapy; Cytoreduction; Peritonectomy

Core tip: The carcinomatosis peritoneal from colon origin has turned from a terminal condition to a curative scenery. The cytoreduction and peritonectomy procedures with hyperthermic intraperitoneal chemotherapy have achieved 50% in 5 years overall survival, with a low morbidity that is not higher than other major surgical procedures.

Arjona-Sánchez A, Medina-Fernández FJ, Muñoz-Casares FC, Casado-Adam A, Sánchez-Hidalgo JM, Rufián-Peña S. Peritoneal metastases of colorectal origin treated by cytoreduction and HIPEC: An overview. *World J Gastrointest Oncol* 2014; 6(10): 407-412 Available from: URL: http://www.wjgnet.com/1948-5204/full/v6/i10/407.htm DOI: http://dx.doi.org/10.4251/wjgo.v6.i10.407

INTRODUCTION

Colorectal cancer (CRC) is considered the third most common cancer. One of the major aspects related to treatment failure is the appearance of peritoneal metastases (PM), which are thought to be present in about 40% of patients with CRC at some time during the natural history of this disease[1]. The occurrence of PM may be a result of the growth of the primary tumor allowing the exfoliation of malignant cells intraperitoneally when the serosa is exceeded or be the consequence of a surgical manipulation when lymphatics or blood vessels are transected.

In the past, colorectal peritoneal carcinomatosis was considered a terminal condition with a merely palliative treatment that included only supportive care, palliative surgery and the best systemic chemotherapy, achieving

survival rates not exceeding seven months according to the multicenter study EVOCAPE[2] with 5-FU and Leucovorin, reaching up to 23.4 mo survival with modern chemotherapy like Oxaliplatine and Irinotecan[3]. Fortunately, in the 80's decade, a renewed interest in malignant diseases with peritoneal extension and the introduction of the concept of initial loco-regional disease resulted in the birth of a new approach. Thus, Elias *et al*[4] described and popularized several procedures, including cytoreductive surgery (CRS) (with peritonectomy procedures) together with hyperthermic intraperitoneal chemotherapy (HIPEC) and early postoperative intraperitoneal chemotherapy (EPIC), to treat peritoneal carcinomatosis[5]. Many research groups contributed with promising results using complete cytoreduction of macroscopic disease combined with HIPEC in order to treat microscopic disease. Although preliminary data were viewed with great scepticism, to date, this strategy is the only one that has shown curative benefits on colorectal peritoneal carcinomatosis achieving reported overall survival rates up to 46 mo[6] and five-year survival rates up to 51%[3].

The aim of this paper is to expose an updated overview of the therapeutic possibilities of these procedures in colorectal PM.

PATIENT SELECTION

The importance of a good general health status must be emphasized. The candidates for these procedures should be younger than 70 years with physiological age of less than 65 years, but it is a relative condition. Severe cardiorespiratory disease, renal failure, untreated malignant neoplasm or World Health Organization (WHO) index > 2 are considered major contraindications to CRS + HIPEC[7]. Furthermore, all patients included to CRS with curative intention shouldn't present tumour progression while on chemotherapy. The key to a successful outcome is an appropriate selection of patients in order to achieve complete cytoreduction, since this is an essential prognostic factor[8]. To this respect, it has been demonstrated that patients with incomplete cytoreduction and residual tumor ⩾ 2.5 mm don't achieve more than 6 mo survival[9,10].

In that sense, preoperative evaluation should include complete colonoscopy and CT scan of the chest and abdomen, focused the attention on radiologic manifestations of PM such as: ascites, peritoneal nodules or masses, peritoneal thickening and enhancement or mesenteric effacement. In those cases in which any extra-peritoneal or extra-abdominal disease is suspected, positron emission tomography (PET) may be useful to evaluate the extension of the disease.

From a preoperative point of view, some authors have related certain preoperative clinical and radiological variables with the possibility of achieving complete cytoreduction. Among them, it is worth to remark, the absence of extra-abdominal disease, not more than 3 small-size and resectable liver metastases, no high volume of disease in the gastrohepatic ligament, no evidence of multiple enteric, ureteric or biliary obstruction, as well as no evidence of gross involvement of mesentery or several segments of intestine which cause intestinal obstruction[11].

The extension of the peritoneal disease represents one of the major prognosis factors for survival and, thus, could represent another criteria for patient selection. To quantify it, several index have been proposed, but presently, the most widely used is the Peritoneal Cancer Index (PCI) described by Sugarbaker. In relation to this index, some authors have considered that a PCI higher than 10 lead to a worse prognosis and a score greater than 20 as a possible contraindication to CRS and HIPEC, as the 5-year survival rate in patients with PCI > 19 is 7%[10]. To evaluate more accurately PCI, diagnostic laparoscopy may be useful as reported by Valle *et al*[12] who performed staging laparoscopy in 97 patients, achieving good correlation between the PCI subsequently assessed at the time of laparotomy. However, this is a challenging evaluation procedure, especially in those patients previously operated on, due to the risk of iatrogenic injury during the exploration.

In addition to the PCI, recently, a new preoperative severity index of peritoneal carcinomatosis called "Peritoneal Surface Disease Severity Score" (PSDSS) has been described. This score, which includes the PCI and other variables such as clinical symptomatology and histopathology of the primary tumor, consists on four grades, showing that the stages III and IV have a negative impact on survival (Table 1)[13].

The presence of multiple liver metastases represents a relative contraindication as several studies have shown that there is no negative impact on survival rates when liver metastases are inferior to 3, chemo-sensitive, and can be fully resected at the time of surgery[14]. In this study, 3 year-overall and disease-free survivals were 41.5% and 26% respectively. In the same line, other authors have observed similar findings in similar scenarios, especially when PCI is low[15]. On the contrary, the presence of extra-abdominal metastases and massive retroperitoneal lymphatic involvement, mainly in cases of non-responsive to systemic chemotherapy, should be considered absolute contraindications. Nevertheless, some authors have proposed that extrahepatic disease might not be a contraindication to attempt an R-0 resection if the number of sites of metastases is less than five[16].

CYTOREDUCTIVE SURGERY WITH PERITONECTOMY AND PERIOPERATIVE INTRAPERITONEAL CHEMOTHERAPY PROCEDURES

Maximum CRS aims to remove all macroscopic disease using extensive visceral resections and peritonectomy procedures as described by Sugarbaker[5]. When tumour fully invades the visceral surface of different organs,

Table 1 Peritoneal Surface Disease Severity Score

Symptomatology	PCI	Histology
No symptoms (0)	< 10 (1)	Well differentiated or moderately differentiated + N0 (1)
Moderate symptoms (1)	10-20 (3)	Moderately differentiated + N1 or N2 (3)
Severe symptoms (6)	> 20 (7)	Poorly differentiated or ring seal (9)

(): Score. Moderate symptoms is defined as weight loss of < 10%, moderate abdominal pain, ascites asymptomatic. Severe symptomatology is defined as weight loss of > 10%, pain that continues, intestinal obstruction, symptomatic ascites. PCI: Peritoneal Cancer Index (0-39). Histology of the primary tumor. N regional lymph node metastasis. Grade Ⅰ: Summation result = (2-3); Grade Ⅱ: (4-7); Grade Ⅲ: 8-10; Grade Ⅳ: > 10.

resection may be necessary. One of the major technical limitations found by an oncological surgeon is the whole involvement of the small bowel as prevents to perform a complete tumour cytoreduction.

The realization of CRS along with HIPEC improves the outcomes in a single surgical act. However, to achieve this goal, an optimal debulking without macroscopic tumor residue (CC-0 resection) or with a tumor residue less than 2.5 mm (CC-1 resection) must be accomplished, since complete cytoreduction has been shown the most important prognostic factor for survival[17,18]. Other major prognostic factors associated with worse outcomes are: grades 2 and 3 *vs* grade 1 histopathologic grade, PCI > 20, lymph node-positive primary tumors and volume of preoperative PM[17-19].

Intuitively, minimally invasive approach for therapeutic purpose might appear not to be useful in this setting, nevertheless, in carefully selected patients, totally laparoscopic CRS and HIPEC has been performed successfully. In that way, Esquivel *et al*[20] have reported success rates up to 95% with acceptable morbidity in patients with a PCI < 10[21,22]. Although others authors have also remarked this possibility, these data are preliminary and must be taken cautiously.

Intraperitoneal administration of cytostatic drugs presents pharmacokinetic advantages because of the plasma-peritoneum barrier that allows the administration of loco-regional high doses of chemotherapy with minimal systemic effects. This characteristic may also lead to a positive effect on recurrence and survival rates[4]. Perioperative administration lead to an extensive intrabdominal diffusion without any of limitations related to postoperative adhesions. Furthermore, hyperthermia has shown greater cytotoxic capacity. Therefore, in *in vitro* tests at 42.5 °C, certain cytostatic drugs such as Oxaliplatin, Mitomycin C, Doxorubicin, Irinotecan or Cisplatin, have demonstrated to increase their cytotoxicity and penetration, and thus, their antitumor effects[23]. However, at present, the use of HIPEC is only indicated in cases achieving complete cytoreduction since the penetration of intraperitoneal chemotherapy is limited to several millimetres. On the other side, the administration of EPIC is related to a higher morbidity as Elias *et al*[24] showed in randomized trial as the use of this variety of chemotherapy has been introduced in different treatment protocols[25].

New chemotherapy drugs such as bevacizumab, an humanized monoclonal antibody that produces angiogenesis inhibition by inhibiting vascular endothelial growth factor A (VEGF-A), are being tested at the moment in animal models and might be useful as perioperative chemotherapeutic agent in the next future[26,27].

SURVIVAL OUTCOMES AND MORBIMORTALITY OF CYTOREDUCTIVE SURGERY AND HIPEC

The results contributed by many authors, although mainly in a retrospective way, demonstrate that degree of cytoreduction is the most determining factor for survival. All comparative trials report a median survival superior to 2 years for patients treated with complete CRS (CC-0) or with residual tumor less than 2.5 mm (CC-1), reaching some of them survival rates above 50% at 5 years[3,28]. Dutch randomized phase III trial conducted by Verwaal *et al*[9,29] first published in 2003 and latest updated in 2008, compared CRS and HIPEC (Mitomycin C) with intravenous chemotherapy and palliative surgery as sole treatment in patients suffering from colorectal peritoneal carcinomatosis. This trial showed significant differences in terms of overall survival (22.2 mo *vs* 12.6 mo), and a 5-year survival up to 45% in favour of the patients treated with CRS and HIPEC. These data forced to stop the trial for ethical issues. In addition, another similar study conducted by Elias *et al*[3] that compared latest systemic chemotherapy to CRS and HIPEC showed a significantly better outcomes in favour of the combined procedure, reaching a median survival of 63 mo and 51% at 5 years overall survival, being these, the best outcomes reported to date using CRS and HIPEC in colorectal PM.

To date, only one systematic review and meta-analysis has been published regarding CRS + HIPEC in colorectal PM. In that study, de Cuba *et al*[30] concluded that when liver metastases are presented in addition to isolated PM, there is a trend towards a lower overall survival after curative resection. Furthermore, these authors also support that CRS + HIPEC is superior to modern systemic chemotherapy in increasing overall survival.

Since 2003, numerous studies reporting the outcomes of CRS and HIPEC have been published. Table 2 summarizes the characteristics of most of them.

On the other hand, since CRS and HIPEC were described, these procedures have been criticized due to a high morbidity. This fact could be true at the beginning; however, currently the morbidity, when this surgery is performed in experienced units, is not superior to that which presents any major gastrointestinal surgery. In that sense, the combination of CRS and HIPEC is a complex procedure that exposes the patient to an acceptable mor-

Table 2 Survival outcomes of patients underwent cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Ref.	Type of study	Year	*n*	Overall survival (mo)	Five-year survival	Overall morbidity[1]	Perioperative mortality
Verwaal *et al*[9]	RCT	2003	39	22	NR	NR	NR
Glehen *et al*[31]	RMS	2004	377	32	40%	22.9%	4%
da Silva *et al*[17]	RS	2006	70	33	32%	NR	NR
Kianmanesh *et al*[15]	RS	2007	30	38	44%	39%	2.3%
Bijelic *et al*[32]	RS	2008	49	33	20%	NR	NR
Shen *et al*[33]	RS	2008	121	34	26%	42%	5.5%
Yan *et al*[34]	RS	2008	50	29	NR	NR	NR
Elias *et al*[3]	CRS	2009	48	63	51%	NR	NR
Chua *et al*[19]	RS	2009	54	33	NR	NR	NR
Franko *et al*[28]	CRS	2010	67	34.7	26%	NR	NR
Elias *et al*[10]	RMS	2010	523	32	30%	31%	3%
Quenet *et al*[35]	PS	2011	146	41	41.8%	47.2%	4.1%
Ung *et al*[6]	RS	2013	211	46.8	42%	NR	NR

[1]Morbidity data comes from different classifications and grades, so major morbidity might be lower in most cases. RCT: Randomized clinical trial; RMS: Retrospective multicenter study; RS: Retrospective Study; CRS: Comparative Retrospective Study; PS: Prospective Study; NR: Not reported.

bidity and mortality (Table 2). To this respect, main high-grade morbidity of these patients is related to surgery and presented in form of anastomotic leak, intraperitoneal sepsis or abscesses, and hematologic and renal toxicities related with HIPEC. Multivariate analyses including in different studies show the extension of disease, number of anastomosis, duration of intervention and incomplete cytoreductive surgery as independent risk factors for morbidity[10].

RECOMMENDATIONS FOR THE MANAGEMENT OF PATIENTS DIAGNOSED FOR COLORECTAL PERITONEAL CARCINOMATOSIS

All surgeons or oncologists diagnosing a colorectal peritoneal carcinomatosis, before, during or after surgery; especially in young patients with limited disease, should consider the evaluation of the case for a multidisciplinary team in a specialized unit in order to offer the realization of this therapeutic approach with curative intent. An exploratory laparotomy without a description of the extent of the disease should be a prohibited action. In this sense, when a peritoneal carcinomatosis is discovered intraoperatively, it is recommended that the surgeon describe in detail the extension and allocation of PM according to the PCI. This conduct will allow the correct evaluation of these patients in specialized units, avoiding inappropriate transfers, resource consumptions and discomfort to the patient. Likewise, a very detailed description of the PM extent will prevent an unnecessary laparotomy in those cases in which a complete cytoreduction is not possible[11].

In the same way, the realization of CRS without HIPEC should be avoided since this conduct limits the possibility of receiving a combined treatment with curative intent and better outcome. Resection of peritoneum without HIPEC allows free tumor cells to implant and grow all over the abdominal cavity, which impairs future treatment options and increase the risk of morbidity[11]. From this point of view, there are a group of patients that although undergoing complete resection without HIPEC, are at high-risk of developing colorectal peritoneal carcinomatosis. Thus, resected minimal synchronous macroscopic PM, synchronous ovarian metastases and perforated primary tumors could benefit of second-look surgery with CRS and HIPEC as it seems to be that up to 55% of asymptomatic patients may present PM at one year[36].

Finally, an emergency surgeon that incidentally is faced with a colorectal peritoneal carcinomatosis should avoid unnecessary surgical dissection and solve the urgent situation (obstruction and/or perforation and/or abdominal sepsis) using the minimum necessary surgical gesture.

CONCLUSION

At present, CRS and HIPEC procedures represent a therapy with curative intent in selected patients with colorectal peritoneal carcinomatosis. The finding of a peritoneal carcinomatosis requires surgeons and oncologists to not ignore this treatment option and to refer such patients to experienced units in the treatment of peritoneal surface malignancies, in order to limit morbidity and increase their survival.

It is clear that there are many unknowns pending to be solved in the next few years such as different modes, time, dose, temperature and drugs for HIPEC to decrease local recurrence after CC-0 resections. Furthermore, at this moment, several trials are evaluating the role of second-look surgery with CRS + HIPEC as well as the possibility of prophylactic HIPEC when primary colorectal cancer shows synchronous PM or is a high risk patient to develop carcinomatosis[36]. These novel strategies might be incorporated in the future therapeutic protocols of colorectal PM.

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RETROSPECTIVE STUDY

Plasma monocyte chemotactic protein-1 remains elevated after minimally invasive colorectal cancer resection

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Abstract

AIM: To investigate plasma Monocyte Chemotactic Protein-1 levels preoperatively in colorectal cancer (CRC) and benign patients and postoperatively after CRC resection.

METHODS: A plasma bank was screened for minimally invasive colorectal cancer resection (MICR) for CRC and benign disease (BEN) patients for whom preoperative, early postoperative, and 1 or more late postoperative samples (postoperative day 7-27) were available. Monocyte chemotactic protein-1 (MCP-1) levels (pg/mL) were determined *via* enzyme linked immuno-absorbent assay.

RESULTS: One hundred and two CRC and 86 BEN patients were studied. The CRC patient's median preoperative MCP-1 level (283.1, CI: 256.0, 294.3) was higher than the BEN group level (227.5, CI: 200.2, 245.2; P = 0.0004). *Vs* CRC preoperative levels, elevated MCP-1 plasma levels were found on postoperative day 1 (446.3, CI: 418.0, 520.1), postoperative day 3 (342.7, CI: 320.4, 377.4), postoperative day 7-13 (326.5, CI: 299.4, 354.1), postoperative day 14-20 (361.6, CI: 287.8, 407.9), and postoperative day 21-27 (318.1, CI: 287.2, 371.6; $P < 0.001$ for all).

CONCLUSION: Preoperative MCP-1 levels were higher in CRC patients (*vs* BEN). After MICR for CRC, MCP-1 levels were elevated for 1 mo and may promote angiogenesis, cancer recurrence and metastasis.

Key words: Colorectal cancer; Monocyte chemotactic protein-1; Minimally invasive colorectal resection angiogenesis

Core tip: In our past published studied we have shown that plasma levels of the pro-angiogenic proteins, vascular endothelial growth factor, angiopoietin-2, placental growth factor, and soluble vascular adhesion

molecule-1, are significantly elevated for 2-4 wk following minimally invasive colorectal resection for colorectal cancer (CRC). Additionally, we also showed that postoperative plasma from cancer patients stimulates *in vitro* endothelial cell proliferation, migration, and invasion, all of which are critical steps in angiogenesis. In this manuscript we are presenting data to show that plasma Monocyte chemotactic protein-1 (MCP-1), a pro-angiogenic protein, in CRC patients remain elevated for month after MICR. Furthermore, we are also showing that the median preoperative plasma level of MCP-1 is significantly higher in the CRC patients than in the BEN group.

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INTRODUCTION

Surgery remains the mainstay of treatment for colorectal cancer (CRC), however, a significant number of patients develop disease recurrence following a "curative resection", presumably from unrecognized tumor microfoci or from viable tumor cells that persist in the circulation[1]. There is growing evidence that tumor resection may indirectly stimulate the growth of residual cancer *via* surgery-related immunosuppression and elevated blood levels of proangiogenic proteins during the early postoperative period. Thus, the early postoperative period may be a dangerous time window for cancer patients who potentially harbor residual disease.

Plasma levels of the proangiogenic proteins, vascular endothelial growth factor (VEGF), angiopoietin-2 (Ang-2), placental growth factor (PlGF), and soluble vascular adhesion molecule-1 (sVCAM-1), have been noted to be significantly elevated for 2-4 wk following minimally invasive colorectal resection for CRC[2-5]. Additionally, prior studies have shown that postoperative plasma from cancer patients stimulates *in vitro* endothelial cell (EC) proliferation, migration, and invasion, all of which are critical steps in angiogenesis[6].

Monocyte chemotactic protein-1 (MCP-1), a member of the C-C chemokine family, is a protein that has several proangiogenic effects. Evidence shows that MCP-1 is produced by certain tumor cells as well as stromal cells such as fibroblasts, endothelial cells (EC's), and monocytes[7]. It is a known chemo attractant for monocytes, macrophages, eosinophils, and lymphocytes, and is also a ligand for CC chemokine receptor 2 (CCR2)[7,8]. MCP-1 is thought to mediate angiogenesis *via* recruitment of proangiogenic protein producing monocytes and macrophages and endothelial cells into wounds and tumors. The chemotaxis of EC'ss is inhibited by MCP-1 antibodies *in vitro* and *in vivo*[9]. MCP-1, by binding to CCR2 on the surface of EC's, has also been shown to promote EC migration, which is a critical early step in angiogenesis[9,10]. There also appears to be an intimate relationship between MCP-1 and VEGF. Interestingly, VEGF increases MCP-1 mRNA expression in EC *in vitro* cultures[11,12]. Also, there is evidence that MCP-1 modulates VEGF's effects; MCP-1 antibody diminishes VEGF mediated tubule formation in angiogenesis assays[12].

Angiogenesis is fundamental to both wound healing and tumor growth. MCP-1 is found abundantly during the initial inflammatory stage of wound healing[9], where it plays a role in recruiting monocytes and macrophages[11,12]. Weber *et al*[10] showed that the presence of a MCP-1 receptor antagonist or neutralizing MCP-1 antibody impaired the ability of ECs to migrate and close wounds, whereas the addition of MCP-1 facilitated repair. Thus, MCP-1 appears to induce EC migration during wound repair[10]. Additionally, endothelial MCP-1 secretion is increased in the setting of multiple wounds[10]. Finally, wound re-epithelialization is significantly delayed in MCP-1 knockout mice[13].

There is also experiment evidence suggesting that MCP-1 plays a role in tumor growth. Nakashima *et al*[14] demonstrated that transfection of MCP-1 into a murine CRC cell line promoted lung metastases by augmenting neovascularization. Further, Salcedo *et al*[9] showed that treatment of immunodeficient mice, in whom metastases had been established *via* inoculation with human breast carcinoma cells, with administration of a neutralizing antibody to MCP-1 resulted in significant longer survival and decreased growth of lung micrometastases[9]. MCP-1 has also been associated with multiple human cancers. A study of breast cancer patients revealed high levels of MCP-1 expression in primary breast cancers by enzyme linked immuno-absorbent assay (ELISA) and immunohistochemical analysis; this expression correlated significantly with macrophage accumulation in the tumors[15]. In another study, patients with primary and recurrent ovarian cancer were shown to have significantly higher MCP-1 serum levels compared to patients with benign ovarian pathology[16]. Furthermore, MCP-1 serum levels have been shown to correlate with histological grade in ovarian cancer patients[16].

The impact of CRC on plasma levels of MCP-1 is unknown. Further, the effect of minimally invasive colorectal resection (MICR) on postoperative (PostOp) plasma MCP-1 levels is unknown. MCP-1 may contribute to the overall proangiogenic state of plasma noted following surgery. The purpose of this study was twofold: (1) to assess plasma levels of MCP-1 before surgery in CRC and BEN disease patients; and (2) to determine levels after MICR for cancer.

MATERIALS AND METHODS

Study population

Consenting patients with CRC or benign colorectal

disease (BEN) that underwent elective MICR during the period of 2003-2011 were identified from a larger population of patients who had been enrolled in an IRB-approved multicenter prospective data and blood banking protocol. The broadly stated purpose of this effort is to study the physiologic, immunologic, and oncologic ramifications of major abdominal surgery. Enrolled patients underwent surgery alone and did not receive a novel drug or other therapy. The indications and type of surgery as well as the demographic, operative, and short term recovery data was prospectively collected for all patients. Recently transfused patients, immunosuppressed patients (medication-related, HIV+, *etc.*), and those who received radio- or chemotherapy within 6 wk of surgery were excluded. Patients undergoing urgent or emergent surgery were, likewise, excluded.

Blood sampling and processing

To be eligible for entry into this study plasma samples for the following time points needed to be available for CRC patients who underwent MICR: preoperative (PreOp), postoperative day (POD) 1, POD 3, and at least 1 later postoperative specimen from POD 7-28. Of note, blood samples after POD 7 were obtained at follow up office appointments but were not scheduled on a specific POD. Many patients refused late blood draws. Because the number of specimens on any given late postoperative day was small it was necessary to "bundle" the specimens from 7 d time blocks (POD 7-13, 14-20, 21-27) and consider these as single time points. PreOp blood samples were obtained prior to surgery and processed in an identical manner for comparison of MCP-1 levels in CRC patients and the BEN group. Samples were collected in heparin-containing tubes, were processed within 5-6 h of collection. After centrifugation, the plasma was frozen and stored at -80 ˚C until the assays were performed.

Plasma MCP-1 determination

Plasma levels of MCP-1 were determined in duplicate using a commercially available enzyme linked immunoabsorbent assay (R and D Systems, Minneapolis, MN) according to the manufacturer's instructions. MCP-1 concentrations (pg/mL) were calculated using a standard curve made in every assay and were reported as median and 95% confidence intervals for the PreOp *vs* PostOp MCP-1 comparisons, the preoperative CRC *vs* BEN group comparison, and for the Stage 1-3 CRC sub group comparisons.

Statistical analysis

Demographic and clinical data are expressed as the mean and SD for continuous variables. Preoperative MCP-1 values in the cancer and Benign populations were not normally distributed and, thus, the median values for each group were calculated and compared using the Mann and Whitney *U* test. In regards to the CRC Pre *vs* Postoperative MCP-1 comparisons, the results are reported as the median and 95%CIs and the Wilcoxon paired test was used to analyze the data. Significance was set at $P < 0.01$ (Bonferroni adjustment was applied). In regards to the sub group comparisons of preoperative MCP-1 values *vs* the stage 1-3 CRC subgroups, the results are reported as the median and 95%CIs and the Mann and Whitney *U* test was utilized for the analysis. Correlation between postoperative MCP-1 plasma levels *vs* incision size and length of surgery was evaluated by the Spearman's rank correlation coefficient (rs) and the correlation between complication rate and PostOp MCP-1 levels was calculated *via* logistic regression analysis. All data analysis was performed using SPSS version 15.0 (SPSS, Inc., Chicago, IL).

RESULTS

Overall, a total of 102 CRC patients (59 males, 43 females with a mean age of 67.1 ± 12.3 years) were included in the study. Seventy patients (69%) had colon cancers while 32 (31%) had rectal lesions. The final cancer stage breakdown is as follows: Stage Ⅰ, 30.5%; Stage Ⅱ, 30.5%; Stage Ⅲ, 37%; and Stage Ⅳ, 2%. The majority of patients (66%) underwent laparoscopic-assisted (LA) resections, whereas 34% had a hand-assisted or hybrid laparoscopic (HAL) procedure. The types of resection performed, as well as other operative data are provided in Table 1. The overall complication rate for the CRC patients was 21% and there were no anastomotic leaks, intra-abdominal abscesses, or perioperative deaths. The complications noted included the following: wound infections (2 patients); cardiac (2); pulmonary (3); ileus (6); urinary retention (5); SBO (3); and *C. difficile colitis* (1).

A group of 86 benign colorectal disease patients (BEN) who underwent MICR served as the control group for the preoperative MCP-1 levels comparison. The indications for MICR in the BEN group were diverticulitis ($n = 30$) and benign neoplasms ($n = 56$). The CRC group was significantly older than the BEN group (67.1 ± 12.3 *vs* 59.3 ± 13.4 years, $P < 0.0001$; Table 1) but with similar male to female ratios.

Preoperative MCP-1 plasma levels in CRC vs BEN group

The median PreOp MCP-1 plasma level in the CRC patients (283.1, CI: 256.0, 294.4) was modestly but significantly higher (24%) than the level noted in the BEN patient group (227.5, CI: 200.2, 245.2; $P = 0.0004$; Figure 1).

Preoperative MCP-1 plasma levels in the Stage 1-3 CRC subgroups

In regards to final cancer stage, the median PreOp values for the Stage 1 to 3 CRC groups were as follows: Stage Ⅰ, 296.5 (CI: 231.2, 343.7); Stage Ⅱ, 274.2 (CI: 217.3, 292.2); and Stage Ⅲ, 285.9 (CI: 251.1, 296.9). Although the results for each Stage group (1-3) were significantly higher than the BEN group's median value, there was no significant difference amongst the Stage 1, 2, and 3 groups [Note: There were too few Stage 4 patients ($n = 2$) in the CRC population to permit statistical analysis].

Table 1 Demographic and clinical characteristics of the study population

	Cancer (n = 102)
Age, yr (mean ± SD)	67.1 ± 12.3
Sex (n)	
Male	59
Female	43
Incision length, cm (mean ± SD)	7.1 ± 2.8
Operative time, min (mean ± SD)	266.5 ± 113
Length of stay, d (mean ± SD)	5.9 ± 2.3
Type of resection	
Right	39 (38%)
Transverse	4 (4%)
Left	8 (8%)
Sigmoid/Rectosigmoid	14/4 (18%)
LAR/AR	24/2 (25%)
APR	3 (3%)
Subtotal/total	2/2 (4%)
Surgical method	
Laparoscopic-assisted	67 (66%)
Hand-assisted/hybrid laparoscopic	35 (34%)

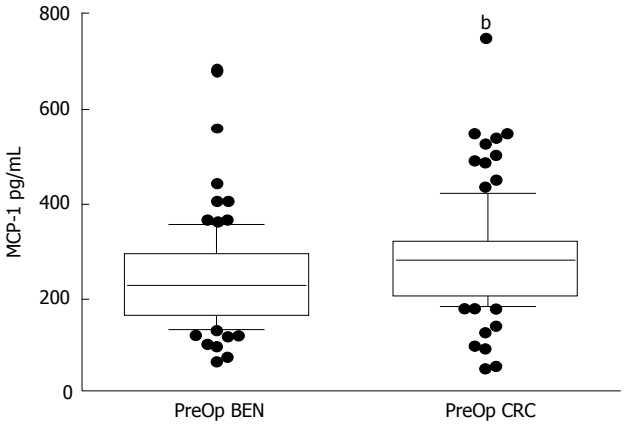

Figure 1 Enzyme linked immuno-absorbent assay determined preoperative plasma monocyte chemotactic protein-1 levels of patients in the benign and malignant group. Monocyte chemotactic protein-1 (MCP-1) levels are expressed as median and CI. [PreOp Benign (n = 86) *vs* PreOp Cancer (n = 102), ^{b}P = 0.0004]. PreOp: Preoperative; BEN: Benign disease; CRC: Colorectal cancer.

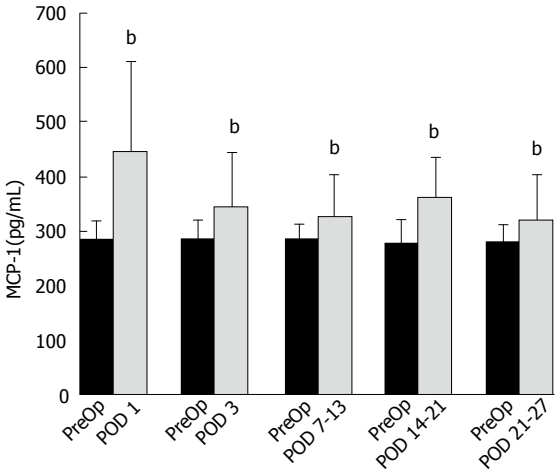

Figure 2 Enzyme linked immuno-absorbent assay determined preoperative and postoperative monocyte chemotactic protein-1 levels of colorectal cancer patients. Monocyte chemotactic protein-1 (MCP-1) levels are expressed as expressed as median and 75% quartile range [PreOp *vs* POD 1 (n = 102), PreOp *vs* POD 3 (n = 100), PreOp *vs* POD 7-13 (n = 61), PreOp *vs* POD 14 -20 (n = 27), PreOp *vs* POD 21-27 (n = 28), ^{b}P < 0.001]. PreOp: Preoperative; POD: Postoperative day.

Comparison of Pre vs postop MCP-1 plasma levels in CRC patients

The median PreOp MCP-1 level in CRC patients was 283.1 (CI: 256.1, 294.4) pg/mL (n = 102). When compared to PreOp levels, significantly elevated mean MCP-1 plasma levels (pg/mL) were observed on POD 1 (446.3, CI: 418.0, 520.1; n = 102, P < 0.001), POD 3 (342.7, CI: 320.4, 377.4; n = 100, P < 0.001), POD 7-13 (326.5, CI: 299.4, 354.1; P < 0.001), POD 14-20 (361.6, CI: 287.8, 407.9; n = 27; P < 0.001), and POD 21-27 (318.1, CI: 287.2, 371.6; n = 28; $P \leq$ 0.001). Because the "n" for the POD 3 and later time points was less than 102 and unique for each time point, the PreOp baseline level for each of these time points was somewhat different. This is reflected in Figure 2, which provides in bar graph form the mean PreOp baseline for each postoperative time point.

The percent increase over the PreOp baseline for each postoperative time point is as follows: POD 1 (73.5%); POD 3 (37.2%); POD 7-13 (24.6%); POD 14-20 (39.7%); and POD 21-27 (25%).The percentage of CRC patients that had plasma levels increased from the median PreOp baseline levels of each subgroup were: POD 1 (79%); POD 3 (81%); POD 7-13 (73.8%); POD 14-20 (89%); and POD 21-27 (89.3%).

Correlation of post-operative plasma MCP-1 levels vs incision length and length of surgery

There was a weak correlation between plasma MCP-1 levels on POD1 and the incision length (r_s =0.217, P = 0.006) as well as the length of surgery (r_s = 0.268, P = 0.007). There was no such correlation noted for the 4 other postoperative time points in regards to incision or operation length. Also, there was no correlation found between the presence of complication(s) and the degree of the postoperative plasma MCP-1 elevation at any of the postoperative time points.

DISCUSSION

The median preoperative plasma level of MCP-1 was significantly higher in the CRC patients than in the BEN disease group. This suggests that, in some patients, the tumor is generating MCP-1, either directly or indirectly. Unfortunately, this study did not include tumor analysis (microarray or RT-PCR) and thus, we can only speculate as to the origin of the additional MCP-1. Of note, no correlation was identified between PreOp levels and tumor stage.

In regards to the comparison of PreOp and Postop MCP-1 levels in the CRC patients, plasma levels were

significantly elevated for the first month after MICR. The greatest increase was observed during the first week after surgery. MCP-1, therefore, joins the list of proteins whose blood levels are altered after MICR. The vast majority of surgery-related blood protein alterations (CRP, IL-6, IL-2, FGF, HGF, angiostatin, endostatin, *etc*.) are short lived and resolve within the first 3 to 5 d after surgery. Of note, the percent change from base line in regards to MCP-1 is amongst the highest when compared to the previously mentioned proteins. Many of the short duration blood compositional changes are related to the acute phase inflammatory response to surgical trauma as well as to the anesthesia. Because blood levels were increased during the entire first month after surgery, MCP-1 joins the small list of proteins (VEGF, Ang-2, PlGF, and sVCAM) with long duration plasma elevations; interestingly, all of these proteins play a role in angiogenesis[2-5]. MCP-1 facilitates angiogenesis through several mechanisms, including its intimate relationship with VEGF[17,18].

Interestingly, VEGF increases MCP-1 mRNA expression in endothelial cell *in vitro* cultures[17,18]. Also, there is evidence that MCP-1 modulates VEGF's effects; MCP-1 antibody diminishes VEGF mediated tubule formation in angiogenesis assays[18]. Collectively; the above mentioned group of proteins play a role in the early stages of neovascularization and most modulate VEGF's effects. What is the source of the plasma MCP-1 increases after MICR?

The authors believe that the tumor produced MCP-1 is not responsible for the postoperative increases in plasma MCP-1 levels. Logically, the blood levels should decrease after resection if the source of the added MCP-1 was the tumor. The significant correlation observed between POD1 MCP-1 levels and incision length and length of surgery suggests that the MCP-1 levels on POD 1 could be attributed, in part, to the surgical stress and the initial inflammatory response which takes place early after surgery. Of note, no such correlation was found from POD 3 onward. It is the authors' opinion that the sustained plasma MCP-1 elevation is related to wound healing. MCP-1, in wounds, accelerates macrophage trafficking into inflammatory foci and also plays a role in angiogenesis. Angiogenesis is critical to wound healing which is a lengthy process that lasts, at least, 6 to 8 wk. There is evidence that VEGF levels in wounds are very high; it is assumed that some of the wound VEGF finds its way into the blood, raising plasma concentrations[19-21]. Although unproven, the authors believe it is likely that wound levels of the other proangiogenic proteins, including MCP-1, whose blood levels are persistently increased after surgery are also notably increased.

Interestingly, as mentioned earlier, it has been demonstrated *via* EC cultures that plasma from the second and third weeks after MICR stimulates EC proliferation (specifically, branch point formation which is the culture equivalent of microtubule formation), migration, and invasion when compared to culture results obtained with preoperative plasma. These EC functions are critical early steps in the process of neovascularization, critical to both wound healing and solid tumor growth beyond 2 mm[22]. Similar EC culture results were noted when plasma from open CRC resection patients was similarly assessed. What are the possible ramifications, if any, of the proangiogenic postoperative plasma?

In the proportion of patients that harbor residual micrometastases the proangiogenic postoperative plasma changes may promote tumor growth. Persistently elevated levels of MCP-1 after MICR for CRC may promote recurrence in patients who harbor tumor micro foci. The complex process of residual tumor growth and metastasis may be supported by other angiogenic proteins whose blood levels remained elevated after MICR for CRC such as VEGF, PLGF, sVCAM-1 ANG2 and MMP3. There are case reports of rapid tumor growth and the development of metastases in cancer patients who undergo major surgery[23,24]. Of note, there is also experimental evidence that laparotomy and bowel resection, in the murine setting, in general, are associated with increased rates of systemic tumor establishment and growth postoperatively[25-27]. Furthermore, human postoperative serum from POD 1 has been shown to stimulate *in vitro* growth of human colon cancer cells when compared to culture results obtained with preoperative plasma[28]. It is also well documented that surgery induces transient postoperative cell-mediated immune suppression. In addition, surgery also impairs lymphocyte and neutrophil chemotaxis, macrophage function, and delayed type hypersensitivity responses[29-31]. These changes might impact early postoperative tumor growth as well.

Thus, the first month after surgery may be a dangerous time for cancer patients. Standard adjuvant chemotherapy is most often started 4 to 8 wk after surgery because of fears that earlier administration may inhibit wound and anastomotic healing. Perhaps, the logical next step is to search for anti-cancer drugs that could be safely given during the first month following surgery to serve as a bridge between "curative" resection and the start of adjuvant chemotherapy. The ideal agent would effectively target tumor cells that remain after surgery without interfering with wound or anastomotic healing. The authors have done one human and numerous murine studies that have assessed the anti-cancer impact of perioperative administration of a number of immunomodulatory and anti-cancer agents[32-34].

One weakness of the present study is the limited number of blood samples obtained beyond the first postoperative week. The majority of these samples were obtained during office follow up visits, which were scheduled at the discretion of the patient. Additionally, many patients refused to have late samples drawn. Therefore, it was impossible to obtain blood samples on a set postoperative timeline. To permit statistical analysis, late samples were bundled into 7-d blocks and considered as single time points. Given the limited number of postoperative samples obtained after the first postoperative month, we were also not able to determine when MCP-1 levels re-

turn to baseline.

At baseline, plasma MCP-1 levels are significantly elevated in CRC patients. Also, for at least 1 mo after minimally invasive tumor resection, plasma MCP-1 levels are significantly elevated from the preoperative baseline. The early postoperative elevations (1st week) may be related to the acute inflammatory response associated with surgical trauma and anesthesia. Although unproven, it is believed that the elevations observed during weeks 2 through 4 are related to wound healing. MCP-1 joins the growing list of pro-angiogenic proteins whose blood levels are persistently elevated after colorectal resection (VEGF, PlGF, sVCAM, ANG-2, MMP-3, *etc.*). These surgery-related plasma compositional changes may stimulate the growth of residual micrometastases early after resection. Further investigations are needed to determine the clinical ramifications, if any, of these transient yet significant changes. The search for and administration of anti-cancer agents that do not inhibit wound healing may be indicated.

COMMENTS

Backgrounds

Blood levels of proangiogenic proteins are increased after minimally invasive colorectal cancer resection. Postoperative plasma enriched in proangiogenic proteins promotes angiogenesis *in vitro*. The angiogenic proteins in question [vascular endothelial growth factor (VEGF), angiopoetin-2 (Ang-2), placental growth factor (PlGF), soluble vascular adhesion molecule-1 (sVCAM-1) and Matrix metalloproteinase 3 (MMP-2)] have been noted to be significantly elevated for 2-4 wk following minimally invasive colorectal resection for CRC. Monocyte chemotactic protein-1 (MCP-1) has documented proangiogenic effects, however, little is known about plasma MCP-1 levels preoperatively in CRC and benign disease patients or in CRC patients after MICR.

Research frontiers

MCP-1, a member of the C-C chemokine family, is expressed by some cancers and has been shown to support tumor angiogenesis and development. MCP-1 is thought to mediate angiogenesis *via* recruitment of proangiogenic protein producing monocytes and macrophages and endothelial cells into wounds and tumors. The authors evaluated preoperative and post-MICR MCP-1 levels in CRC patients. The concern is that significantly elevated blood levels of MCP-1 perioperatively may enhance the plasma's proangiogenic properties during the first month after surgery which, in turn, may promote tumor angiogenesis in residual lesions.

Innovations and breakthroughs

Previous studies have established that significant elevations in plasma levels of VEGF, Ang-2, PlGF, sVCAM-1 and MMp-3 occur for 2-4 wk following MICR for CRC. Additionally, prior studies have shown that postoperative plasma from cancer patients stimulates *in vitro* endothelial cell (EC) proliferation, migration, and invasion, all of which are critical steps in angiogenesis and tumor development. This study found elevated levels of plasma MCP-1, a protein with proangiogenic effects, before and for 1 mo after surgery. Collectively, the sustained elevations in blood levels of the above mentioned group of proangiogenic proteins may support metastasis formation and the growth of residual tumors.

Applications

This study further supports the concept that surgery-related stress and post-surgery wound healing related plasma compositional changes may stimulate the growth of residual micrometastases early after resection. The search for and administration of anti-cancer agents during the perioperative period appears warranted; agents used in this time from must not inhibit wound healing.

Terminology

It has earlier been shown that both MICR and open colorectal resection are associated with sustained (2-4 wk after surgery) plasma protein changes that collectively enhance the angiogenic properties of plasma. These changes, thought to be related to wound healing, may support tumor angiogenesis early after surgery. This study shows that plasma levels of MCP-1, another proangiogenic protein, are elevated after MICR for a month. Thus, another proangiogenic protein is added to the list. Collectively, these prolonged blood elevations may support the growth of residual cancer and initiation of cancer by circulating tumor cells.

Peer review

This study is interesting and I would like to give my suggestions to impact the authors understanding of the tumor tissue in the elucidation of aberrant molecular aspect changes in the tumor microenvironment and surgical margins to impact the paper.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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