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Contents

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Contents

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BRIEF ARTICLE

Sixth and seventh tumor-node-metastasis staging system compared in gastric cancer patients

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Abstract

AIM: To investigate the clinical relevance and prognosis regarding survival according to the changes of the tumor-node-metastasis (TNM) in gastric cancer patients.

METHODS: We retrospectively studied 347 consecutive subjects who underwent surgery for gastric adenocarcinoma at the Division of General Surgery, Hospital of Busto Arsizio, Busto Arsizio, Italy between June 1998 and December 2009. Patients who underwent surgery without curative intent, patients with tumors of the gastric stump and patients with tumors involving the esophagus were excluded for survival analysis. Patients were staged according to the 6th and 7th edition TNM criteria; 5-year overall survival rates were investigated, and the event was defined as death from any cause.

RESULTS: After exclusion, our study population included 241 resected patients with curative intent for gastric adenocarcinoma. The 5-year overall survival (5-year OS) rate of all the patients was 52.8%. The diagnosed stage differed in 32% of 241 patients based on the TNM edition used for the diagnosis. The patients in stage Ⅱ according to the 6th edition who were reclassified as stage Ⅲ had significantly worse prognosis than patients classified as stage Ⅱ (5-year OS, 39% *vs* 71%). According to the 6th edition, 135 patients were classifed as T2, and 75% of these patients migrated to T3 and exhibited a significantly worse prognosis than those who remained T2, regardless of lymph node involvement (37% *vs* 71%). The new N1 patients exhibited a better prognosis than the previous N1 patients (67% *vs* 43%).

CONCLUSION: 7th TNM allows new T2 and N1 patients to be selected with better prognosis, which leads to different staging. New stratification is important in multimodal therapy.

Key words: Gastric cancer; Tumor-node-metastasis staging system; Survival analysis; Prognostic factor; Lymphadenectomy

Core tip: The 7th edition of the tumor-node-metastasis (TNM) staging system appears to exhibit improved accuracy in staging and prognostic stratification with more precise indication for adjuvant and neoadjuvant therapy in the multimodal treatment era. Our data show the importance of standardization of treatment and the type of surgical lymphadenectomy for comparing different experiences. Further studies are necessary to improve the TNM system, particularly regarding the parameter N and the division into substages.

Zurleni T, Gjoni E, Ballabio A, Casieri R, Ceriani P, Marzoli L, Zurleni F. Sixth and seventh tumor-node-metastasis staging system compared in gastric cancer patients. *World J Gastrointest Surg* 2013; 5(11): 287-293 Available from: URL: http://www.

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INTRODUCTION

In addition to age, comorbidities, lesion site, macro- and microscopic type of tumor, quality of surgery and residual tumors, the main factors that influence the long-term survival of patients with gastric cancer are (1) the depth of tumor penetration into the gastric wall (T parameter); (2) the amount of the metastatic regional lymph nodes involved (N parameter); and (3) the presence of distant metastases (M parameter).

The tumor-node-metastasis (TNM) classification of cancer was developed between 1943 and 1952 by Prof. Pierre Denoix at the Institute Gustave-Roussy. In 1987, the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) TNM classifications were unified. The following are the main objectives of the classifications: to aid the clinician in the planning of treatment, to provide an indication of prognosis, to assist in the evaluation of the results of treatment; to facilitate the exchange of information between treatment centers, to contribute to the continuing investigation of human cancer and to support cancer control activities[1,2]. Since January 1st 2010, the UICC/AJCC TNM 7th edition differs from the previous version regarding some aspects of the T parameter and is completely renewed regarding the N parameter (Table 1).

Particularly, the subserosa infiltration by the tumor, which was previously classified as T2b, is now classified as T3, and the perforation of serosa changed from T3 to T4a. Regarding the parameter N, the UICC/AJCC TNM 7th edition changes the lymph nodes "cut-off". Tumors classified as N1 in the 6th edition with more than 2 positive nodes are classified as N2 in the 7th edition, while N2 is classified as N3a, and N3 is classified as N3b. In the new stratification by stage, the number of substages is increased. According to the 7th edition, only patients with distant metastases are classified as the fourth stage. Another important change to the criteria concerns distant metastases. In the new edition of the TNM staging system, a positive peritoneal cytology is considered as M1.

Several studies, which were mostly performed in eastern countries, have demonstrated the superiority of the 7th edition TNM criteria and highlighted issues still in dispute for improvement.

The aim of the present study is to compare the sixth and the seventh edition of the TNM classification in patients who underwent surgery for gastric cancer in a single center to confirm the superiority of the new edition regarding its prognostic stratification and reliability. We considered the parameters T, N and the lymph node ratio (LNR) individually regardless of stage as additional prognostic parameters. We observed and followed how these changes in the allocation of pT and pN parameters according to the two editions of the classification affect determining the prognosis and the type of treatment for these patients.

Table 1 Tumor-node-metastasis staging system 6th and 7th edition

TNM staging system 6th edition				TNM staging system 7th edition			
Stage	T	N	M	Stage	T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
I A	T1	N0	M0	I A	T1	N0	M0
I B	T1	N1	M0	I B	T2	N0	M0
	T2a	N0	M0		T1	N1	M0
	T2b	N0	M0	II A	T3	N0	M0
II	T1	N2	M0		T2	N1	M0
	T2a	N1	M0		T1	N2	M0
	T2b	N1	M0	II B	T4a	N0	M0
	T3	N0	M0		T3	N1	M0
III A	T2a	N2	M0		T2	N2	M0
	T2b	N2	M0		T1	N3	M0
	T3	N1	M0	III A	T4a	N1	M0
	T4	N0	M0		T3	N2	M0
III B	T3	N2	M0		T2	N3	M0
IV	T4	N1	M0	III B	T4b	N0, N1	M0
	T4	N2	M0		T4a	N2	M0
	T4	N3	M0		T3	N3	M0
	T1	N3	M0	III C	T4a	N3	M0
	T2	N3	M0		T4b	N2, N3	M0
	T3	N3	M0	IV	AnyT	AnyN	M1
	Any T	Any N	M1				

MATERIALS AND METHODS

Patient cohort

We retrospectively studied 347 consecutive patients who underwent surgery for gastric adenocarcinoma at the Division of General Surgery, Hospital of Busto Arsizio (Varese), Italy from June 1998 through December 2009. For the survival analysis, we excluded the following patients: (1) patients with distant metastases; (2) patients who underwent surgery without curative intent; (3) patients with tumors of the gastric stump after gastric resection for benign disease; (4) patients with other tumors at the time of diagnosis; and (5) patients with a large involvement of the esophagus requiring total esophagectomy.

None of the patients considered for inclusion in the study underwent neoadjuvant chemotherapy or radiochemotherapy. Because of the heterogeneous and unsystematic indication for adjuvant chemotherapy, treatment protocols and number of cycles, details of the postoperative chemotherapy were not considered in this study.

Regarding the surgical method, en bloc resection of the primary tumor and lymphatic drainage area was routinely performed. D2 lymphadenectomy was performed in 87% of patients, while the remaining 13% underwent a D1 lymphadenectomy according to the Japanese Guidelines[3,4]. The principles of tumor resection and lymphadenectomy by experienced surgeons were similar among all the resected patients. No local excision was performed.

Follow-up

For all patients, a regular 6th month follow-up within 5

Table 2 Univariate survival analysis of clinicopathologic variables in 241 patients *n* (%)

Variable	*n* (%)	5-year overall survival rate (%)	*P* value
All	241	52.80	
Sex			0.740
Female	116 (48.1)	50.40	
Male	125 (51.9)	54.30	
Age (yr)			0.000
1 (≤ 50)	14 (5.8)	78.60	
2 (51-60)	18 (7.5)	32.00	
3 (61-70)	78 (32.3)	57.50	
4 (71-80)	87 (36.1)	57.30	
5 (> 80)	44 (18.3)	35.20	
Site			0.006
S	40 (16.6)	33.30	
M	50 (20.7)	70.80	
I	150 (62.2)	51.50	
Surgery			0.400
Total gastrectomy	191 (79.3)	53.10	
Subtotal gastrectomy	50 (20.7)	52.60	
Lauren			0.500
Intestinal	150 (62.2)	56.50	
Diffuse	58 (24.0)	48.50	
Mixed	15 (6.2)	33.90	
T stage (6th edition)			< 0.0001
T1	64 (26.6)	86.20	
T2	135 (56.0)	45.40	
T3	37 (15.3)	23.30	
T4	5 (2.1)	0.00	
T stage (7th edition)			< 0.0001
T1	64 (26.6)	86.20	
T2	33 (13.7)	71.00	
T3	102 (42.3)	37.30	
T4	42 (17.4)	20.50	
N stage (6th edition)			< 0.0001
N0	81 (33.6)	77.30	
N1	73 (30.3)	55.70	
N2	50 (20.7)	27.60	
N3	37 (15.4)	22.90	
N stage (7th edition)			< 0.0001
N0	81 (33.6)	77.30	
N1	39 (16.2)	67.50	
N2	35 (14.5)	43.00	
N3	86 (35.7)	25.90	
Stage (6th edition)			< 0.0001
I	87 (36.1)	76.40	
II	59 (24.5)	61.50	
III	55 (22.8)	24.40	
IV	40 (16.6)	21.20	
Stage (7th edition)			< 0.0001
I	70 (29)	85.60	
II	56 (23.3)	61.50	
III	115 (47.7)	27.00	
Lymph node ratio			< 0.0001
I (0)	81 (33.6)	77.30	
II (0.01-0.09)	41 (17.1)	65.40	
III (0.1-0.25)	50 (20.7)	44.50	
IV (> 0.25)	69 (28.6)	21.00	

S: Superior; M: Middle; I: Inferior.

years from surgery consisted of the following procedures: serum tumor biomarker and laboratory biochemical examinations, radiological and UltraSound imaging, endoscopic control (1/year) and physical examination. Annual follow-ups after 5 years were performed until the patients died. In this study, a period of 120 mo was considered as the end of the patient's observation. The median follow-up was 48 mo (range: 0-120 mo).

Statistical analysis

The depth of primary tumor invasion (T) and lymph node involvement (N) were classified according to the 6th and 7th UICC/AJCC edition TNM classification. All patients were restaged using the 6th and 7th editions of the UICC/AJCC TNM staging system. Survival curves were estimated using the Kaplan-Meier method[5]. The overall survival (OS) rates were investigated, and the event was defined as death for any cause. The Log rank test was used to identify the differences between the survival estimates of the different patient groups. Hazard ratio (HR) and 95%CI were also generated. A *P* value of less than 0.05 was considered significant. All tests were two-tailed. Statistical analysis and graphics were performed with MedCalc Software bvba, Mariakerke, Belgium.

RESULTS

From June 1998 until December 2009, a total of 347 patients in our department underwent surgery for gastric adenocarcinoma. After exclusion, the study population consisted of 241 resected patients, and 112 patients are currently alive.

The clinical and pathological characteristics are shown in Table 2. The median age was 71 years (range: 37-94 years), and 51.9% of the patients ($n = 125$) were male.

Total gastrectomy was performed in 191 (79%) patients, and subtotal gastrectomy was performed in 50 (21%) patients.

A D2 lymphadenectomy was performed in 208 (87%) patients. The median number of lymph nodes retrieved was 37 (range: 5-100); the value reached 40 (range: 13-100) in D2 lymphadenectomy and 16 (range: 5-45) in D1. The incidence of positive node patients was 67%. The 5-year overall survival of the 241 patients was 52.8%, and the ten-year overall survival was 34.7%. In the univariate analysis, age, site, T parameter, N parameter and Stage were significantly associated with overall survival.

We also studied the LNR as a prognostic factor among parameters of the univariate analysis. We considered 4 cutoff based on Marchet *et al*[6] (Table 2).

Survival analysis by stage

Stage migration occured in 33% of the patients: 19.5% of the I st stage were reclassified to II nd stage, and 33.9% of the II nd stage patients were reclassified as III rd stage. All the patients we considered as stage IV in the 6th ed. of the TNM staging system were reclassified as III rd stage using the 7th edition TNM staging system.

The patients classified as stage II according to the 6th edition and reclassified as stage III exhibited significantly worse prognosis than the patients who remained in stage II (5-year OS, 71% *vs* 39%; $P = 0.01$, HR = 2.3, 95%CI: 0.9-5.8) (Figure 1).

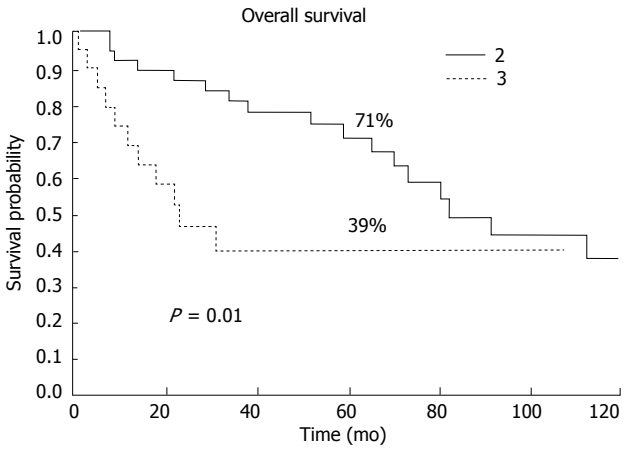

Figure 1 Ⅱ nd stage patients according to the 6th edition of the tumor-node-metastasis staging system reclassified as Ⅱ nd or Ⅲ rd stage according to the 7th edition of the tumor-node-metastasis staging system.

Important changes regarding the survival rates and stage reclassification were observed in our analysis. As shown in Table 3, the patients assigned stages using the sixth edition (orizzontally) exhibit a statistically significant difference in the prognosis when reclassified in a different stage according to the seventh edition criteria. However, a statistically significant difference in the prognosis was not observed when comparing the prognosis of patients assigned stages using the seventh edition criteria (vertically) with the stages assigned using the sixth edition (Table 3).

Regarding the substages in the 7th edition, the 5-year survival rates are comparable between substage Ⅰ B and Ⅱ A (5-year OS 59% *vs* 55%; $P = 0.8$). However, there is a significant difference regarding the survival probability at 5 years among substages Ⅲ A, Ⅲ B and Ⅲ C (5-year OS Ⅲ A: 47%, Ⅲ B: 20%, Ⅲ C: 24%; $P = 0.07$). The patients who belong to substage Ⅲ C exhibit similar survival to M+ patients.

Survival analysis by T category

We also analyzed the T category on T2b patients reclassified as T3 in the new edition of the TNM. In our population, 135 T2 patients were classified according to the 6th edition (56%), and 75% of these patients were reclassified as T3 using the most recent revision of the TNM system. The 5-year survival rates of the migrated patients and the patients who remained as T2 were 71% and 37%, respectively ($P = 0.008$, HR = 2.1, 95%CI: 1.3-3.5) (Figure 2A). The T2aN+ patients exhibited significantly better survival compared with the T2b patients with lymph node involvement (N+) according to the 6th edition (5-year OS 73% *vs* 37%; $P = 0.009$, HR = 2.5, 95%CI: 1.4-4.4) (Figure 2B).

Survival analysis by N category

Patients stratified according to the N-stage using the 6th and 7th editions of the TNM are now classified as N1 with the 7th edition and exhibit a 5-year OS probability of 67%. The N2 patients classified according to the 7th edition. TNM exhibit a 5-year OS of 43% ($P = 0.04$) (Figure 3).

Table 3 Stage migration from the sixth to seventh edition of the tumor-node-metastasis system

		7th edition TNM			
6th edition TNM	Stage (patients)	Ⅰ	Ⅱ	Ⅲ	*P*
	Ⅰ	70	17		0.004
	Ⅱ		39	20	0.040
	Ⅲ			55	
	Ⅳ			40	
	P		0.09	*P* (Ⅱ-Ⅲ) = 0.3 *P* (Ⅳ-Ⅲ) = 0.1	

TNM: Tumor-node-metastasis.

DISCUSSION

In this retrospective study, we focused on the major changes between the 6th and 7th edition of the TNM system regarding gastric cancer. The analysis of this migration reveals the most important prognostic factors and possible modifications introduced in multimodal treatment.

We observed an OS of 52.8%. That goes to 54% of survival in the D2 type of lymphadenectomy that represented 87% of the sample. In our study population, more than 50% of the patients were diagnosed with T2 lesions according to the 6th edition regarding the parameter of infiltration of the tumor in the gastric wall (T parameter). Other studies reported variable incidences of T2 (Sarela *et al*[7]: 30%; Marchet *et al*[8]: 32%; Nitti *et al*[9]: 51.4%; Park *et al*[10]: 30%; Lu *et al*[11]: 40%).

In our study, 102 out of 135 patients (75%) classified as T2 according to the 6th edition of the TNM system were reclassified as T3 based on the 7th edition of the TNM system. The shift exhibits a statistically significant prognostic difference in 5-year OS regardless of nodal involvement (Figure 2).

Our results concerning the prognostic differentiation between T2 and T3 are also confirmed by other studies[12,13]. Sarela *et al*[7] reported a statistically significant difference between patients classified as T2N1 and T3N1, (56% *vs* 44%; $P = 0.3$). Fotia *et al*[14] obtained different results (74% *vs* 67% for T2 to T1 to 5 years; $P = 0.2$).

Recently, Marchet *et al*[8] reported 5-year survival values of 67% for T2 and 52% for T3. When N+ patients were included in their analysis, 5-year survival rates of 66% and 47% were obtained for T2N+ and T3N+. In conclusion, the results of this study emphasize the prognostic value of T2/T3 categories and the importance of identifying subgroups of patients (T2b 6th edition) that may benefit from adjuvant chemotherapy. Based on our results, these patients would also be candidates for neoadjuvant treatment[15-17].

The renewal of the lymph node cut-off (N parameter) has allowed us to select patients with better prognosis

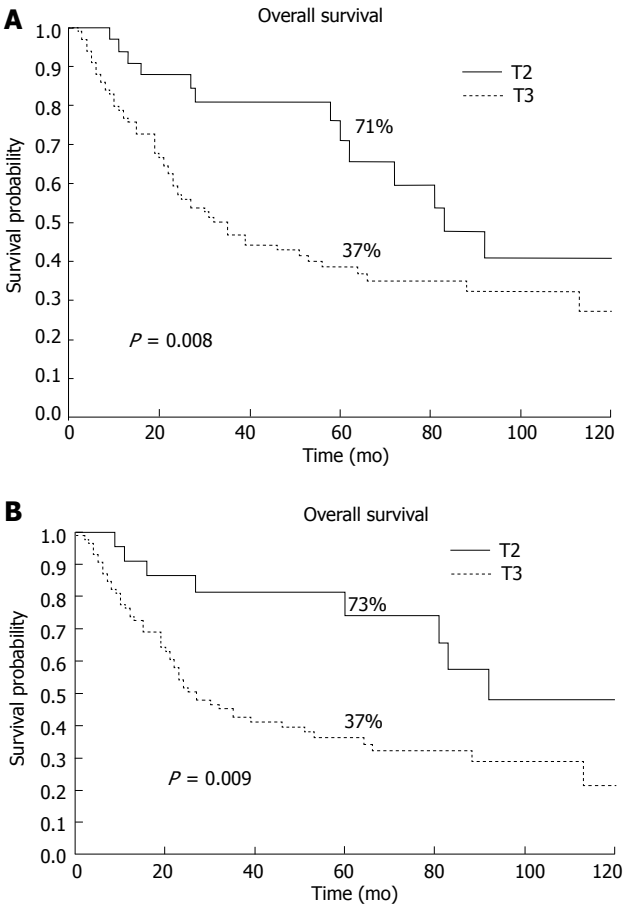

Figure 2 Overall survival. A: T2 patients according to the 6th edition of the tumor-node-metastasis (TNM) staging system reclassified as T2 or T3 with the 7th edition; B: T2N+ patients according to the 6th edition of the TNM staging system reclassified as T2 or T3 with the 7th edition.

(new N1). The involvement of 1-2 lymph nodes was associated with a better prognosis in our cases than patients with N2 (3-6 positive nodes). The 5-year OS rates were 67.5% for N1 and 43% for N2; ($P = 0.04$). Similar results were obtained from the study published by Ahn *et al*[13] (N1: 76.5% *vs* N2: 58%).

In our analysis, we did not investigate the difference between N3a and N3b because of the small sample size. However, according to other reports, a possible reclassification of the N3 category would be desirable because N3a and N3b exhibit significant differences in survival[13,18,19].

The analysis of the LNR (linf+/linftot) showed good prognostic stratification among the 4 curves ($P < 0.0001$). Some studies have described the usefulness of the LNR in Japan and South Korea[20,21].

As demonstrated by the work of Kong *et al*[22], the power of the differential staging of the LNR system was fortified with a higher number of examined lymph nodes and represents appropraite N-staging.

In a retrospective multicenter study of 1853 patients operated for gastric cancer, Marchet *et al*[6] showed that the LNR was an independent prognostic factor regardless of the type of lymphadenectomy.

Wang *et al*[23] showed that the "TNratioM System" may predict survival more accurately in patients who undergo

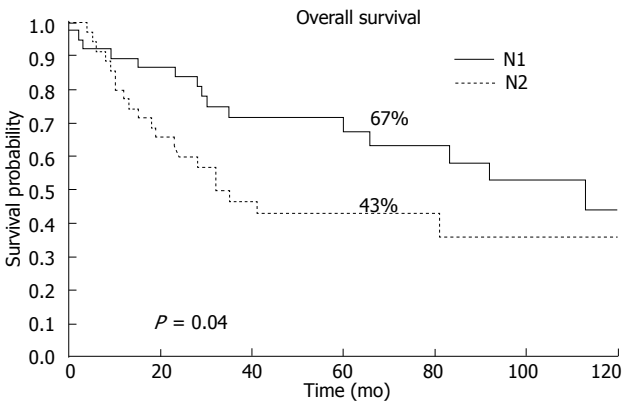

Figure 3 Comparison between N1 patients and N2 patients according to the 7th edition.of the tumor-node-metastasis staging system.

limited lymph node analysis.

The changes in the parameters N and T have generated stage migration, which confirms the superiority of the 7th edition. of the TNM system. The new TNM edition groups patients with similar prognoses and separates subjects with different prognoses better that the previous version of the TNM system (Table 3). Similar rates of survival are shown in the analysis by Marrelli *et al*[24]. Evaluating the substages in our population, we observed that the 5-year survival values were similar between I B and II A. Similar findings were reported in a large series of western patients with gastric cancer[18].

A significant difference regarding the 5-year survival was observed between the substages of stage III (III A, III B and III C). In a study by Wang *et al*[12] on 1503 patients, the tumor size (> 5 cm or < 5 cm) was a determining factor in the differentiation of the prognosis between I B and II A. According to Wang *et al*[12], three subgroups of the fourth stage exhibit different biologic behaviors of relapse or metastasis models and need further analysis.

In conclusion, the 7th edition of the TNM system seems to have improved accuracy in staging and prognostic stratification, the 7th edition provides more precise indication for adjuvant and neoadjuvant therapy in the multimodal treatment era, our data show the importance of standardization of treatment and the type of surgical lymphadenectomy to compare different experiences and further studies are necessary to improve the TNM system particularly regarding the parameter N and the division into substages.

COMMENTS

Background

The Union for International Cancer Control and the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging system is the most important classification of tumors. The main objectives of TNM cancer staging are to help the clinician plan the treatment, to give an indication of prognosis and to evaluate the results of treatment. In the new edition of the TNM (7th) staging system, there are important changes in the field of gastric cancer.

Research frontiers

The 7th edition of the TNM system appears to exhibit improved accuracy in staging and prognostic stratification. Different experiences need to be compared to

improve the reliability of the TNM classification system.

Innovations and breakthroughs

The TNM 7th edition differs from the previous version regarding gastric cancer on some aspects of the T and M parameters and is completely renewed regarding the N parameter. Several studies, which were predominantly performed in Eastern countries have demonstrated the superiority of the new edition criteria and the highlighted issues still require improvement.

Applications

The study results suggest that the 7th edition of the TNM system is superior to the previous version regarding prognostic stratification. However, further studies are necessary to improve the TNM system particularly regarding the N parameter and the division into substages.

Terminology

The TNM classification uses three parameters to divide the patients into different stages: depth of tumor penetration into the gastric wall (T parameter), the number of metastatic regional lymph nodes involved (N parameter) and the presence of distant metastases (M parameter).

Peer review

The retrospective study compares the 6th and 7th edition of the TNM classification in a single Italian institution to confirm the superiority of the new edition for prognostic accuracy. According to the experience, standardization of surgical therapy and a multidisciplinary approach are necessary to develop a multimodal tailored treatment.

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BRIEF ARTICLE

Comparative analysis of open and laparoscopic colectomy for malignancy in a developing country

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Abstract

AIM: To compare the short-term, including oncologic, outcomes of open *vs* laparoscopic colectomy for cancer in a developing country.

METHODS: The records of patients who underwent elective open and laparoscopic colectomies for cancer at the University Hospital of the West Indies between January 2005 and December 2010 were retrospectively reviewed. Demographic (age, gender, Charlson comorbidity index score), peri-operative, post-operative and oncologic data were collected for each patient. Specific oncologic variables included lymph node yield, pathologic stage, grade, proximal, distal and circumferential margin involvement. Fisher's exact, Mann-Whitney, and binary logistic regression tests were used for analysis. Significance level was set at $P < 0.05$.

RESULTS: There were 87 cases for open colectomy (OC) and 17 cases for laparoscopic colectomy (LC). Demographics did not significantly differ between OC and LC groups. Intra-operative blood loss and post-operative analgesic requirements did not significantly differ between groups. There was a trend towards longer operating times in OC group and shorter hospital stay in the LC group. Lymph node yield (14 *vs* 14, $P = 0.619$), proximal (10 cm *vs* 7 cm, $P = 0.353$) and distal (8 cm *vs* 8 cm, $P = 0.57$) resection margin distance and circumferential margin involvement (9 *vs* 0, $P = 0.348$) did not significantly differ between groups. Thirty-day morbidity was equivalent between groups (22 *vs* 6, $P = 0.774$). There were 6 deaths within 30 d of initial procedure, all in the OC group (6.9%).

CONCLUSION: Laparoscopic colectomy in a developing country is oncologically safe and represents a option for colonic malignancies in these regions. Such data encourage the continued laparoscopic development.

Key words: Laparoscopy; Colectomy; Cancer; Developing country; Colorectal; Oncology; Short-term; Outcomes

Core tip: The development of laparoscopic colectomy in developing countries has been slow despite strong evidence to support its benefit. The demonstration that laparoscopic procedures can be performed safely in these environments supports and encourages further incorporation of laparoscopy in these environments. Notwithstanding proven feasibility of laparoscopic colectomy for cancer in developing countries, there is the need to demonstrate equivalent oncologic outcomes to open surgery in order to establish safety. This study shows that laparoscopic colectomy for cancer in a developing country is not only feasible but is oncologically safe.

Leake PA, Pitzul K, Roberts PO, Plummer JM. Comparative analysis of open and laparoscopic colectomy for malignancy in a developing country. *World J Gastrointest Surg* 2013; 5(11): 294-299 Available from: URL: http://www.wjgnet.com/1948-9366/full/v5/i11/294.htm DOI: http://dx.doi.org/10.4240/wjgs.v5.i11.294

INTRODUCTION

Laparoscopic colectomy, first described in the early 1990s for diverticular disease, has become a viable option for the management of colorectal cancer. The first case of laparoscopic colonic resection for neoplasia was documented in 1991 following successful resection for a villous adenoma[1]. Subsequently, reports on the successful use of laparoscopic colectomy for cancer cases were increasingly published[2].

Early concerns related to the oncologic equivalence to open colectomy (inadequacy of resection, staging inaccuracies and the possibility of the pneumoperitoneum affecting tumour dissemination) have been dispelled by randomized controlled trials (RCTs)[3-6] and meta-analyses[7]. These have demonstrated similar long-term oncologic outcomes compared to open colectomy, while also demonstrating superior short-term outcomes expected of the laparoscopic approach.

The incorporation of laparoscopic techniques in developing countries has been challenging, due in particular to the high costs of equipment and lack of expertise[8]. Despite these ongoing challenges, the continued use of laparoscopy is still encouraged[8]. Many laparoscopic procedures, including appendicectomy[9], cholecystectomy[10,11] and hysterectomy[12], splenectomy[13], have successful been performed in developing countries. A recent study from our institution demonstrated that laparoscopic colectomy for neoplasms is safe and feasible. Studies from other developing countries such as Argentina[14], China[15,16], Mexico[17] and Turkey[18], have demonstrated the feasibility and safety of laparoscopic colectomy, but have neglected to demonstrate the equivalence to the open approach in these settings. Demonstrating oncologic outcomes similar to those achieved in a developed setting will further support the continued growth of laparoscopy for cancer in a developing country. There are currently limited data referencing the oncologic safety of laparoscopic colectomy in these settings. The present study provides further evidence regarding the oncologic safety of laparoscopic colectomy in a developing country. The primary aim of this study was to compare the short-term outcomes, particularly oncologic outcomes, of laparoscopic versus open colectomy for cancer.

MATERIALS AND METHODS

Ethics

This work has been carried out in accordance with the Second International Helskinki Declaration[19]. This study was ethically approved by the Faculty of Medical Sciences/University of the West Indies Ethics Committee (File number: ECP 04, 13/14).

Setting and operative approach

Surgical procedures were undertaken at a tertiary academic centre in a developing country. All surgeons were trained in Jamaica, while surgeons performing laparoscopic colectomy either had formal laparoscopic training or had undertaken mentorship programmes. The operative details have previously been published by Plummer *et al*[20]. Briefly, the laparoscopic equipment included a standard laparoscopic tower, reusable trocars and reusable bowel graspers. Vascular control was achieved using clips or Ligasure® (when available) as opposed to stapling devices. Bowel mobilization and dissection was achieved using either monopolar cautery or ultrasonic shears (when available). With specific reference to right hemicolectomy, all patients had extracorporeal anastomoses following exteriorization of the colon.

Data collection

This was a retrospective chart review of adult patients who underwent elective open or laparoscopic colectomy for cancer between January 1, 2005 and December 31, 2010 at the University Hospital of the West Indies. Emergency procedures and rectal resections were excluded. All included patients had preoperative colonoscopy with confirmation, by biopsy, of a carcinoma. Cases were grouped according to intention-to-treat: laparoscopic cases converted to open were included in the laparoscopic group. The decision to perform laparoscopic or open colectomies was based on the discretion of the attending surgeon. Demographic [age, gender, Charlson comorbidity index score (CCI)], peri-operative, post-operative and oncologic data were collected for each patient. Specific oncologic variables included lymph node yield, pathologic stage, grade, proximal, distal and circumferential margin involvement.

Statistical analysis

Demographic, intra-operative, pathological, and post-operative variables between open colectomies (OC) and laparoscopic colectomies (LC) were analyzed using Fisher's exact (for categorical variables) and Mann-Whitney (for continuous variables). Logistic regression was used to determine if length of stay was significantly different between OC and LC group, controlling for all potential confounding variables. Significance level for all analyses was set at $P < 0.05$.

RESULTS

Charts of one hundred and four patients were included. Of these, 87 persons underwent OC and 17 underwent LC. Neither gender, age, nor CCI significantly differed between OC and LC groups (Table 1).

Only one laparoscopic case was converted. Intra-operative blood loss did not differ significantly between

Table 1 Demographics for open colectomy and laparoscopic colectomy for colonic carcinoma *n* (%)

		OC	LC	*P* value
Gender	Male	36 (41.4)	9 (52.9)	0.429
	Female	51 (58.6)	8 (47.1)	
Age [median, (5Q-75Q)], yr		66 (59-78)	62 (58-72)	0.363
Charlson score	0	7 (8.0)	1 (6.2)	0.501
	1	14 (16.1)	4 (25.0)	
	2	22 (25.3)	4 (25.0)	
	3	18 (20.7)	5 (31.2)	
	4	17 (19.5)	1 (6.2)	
	5	7 (8.0)	0 (0.0)	
	6	1 (1.1)	1 (6.2)	
	7	1 (1.1)	0 (0.0)	

OC: Open colectomy; LC: Laparoscopic colectomy.

Table 2 Intra-operative outcomes for open colectomy and laparoscopic colectomy for colonic carcinoma *n* (%)

		OC	LC	*P* value
Procedure	RH	42 (48.3)	7 (41.2)	0.801
	Extended RH	9 (10.3)	1 (5.9)	
	LH	11 (12.6)	2 (11.8)	
	Extended LH	1 (1.1)	0 (0.0)	
	Transverse colectomy	1 (1.1)	0 (0.0)	
	Sigmoid colectomy	21 (24.1)	6 (35.3)	
	Total colectomy	2 (2.3)	1 (5.9)	
Conversion		NA	1 (5.9)	
Total OR time (min) [median (25Q-75Q)]		165 (128-195)	195 (143-259)	0.075
Intraop blood loss (mL) [median (25Q-75Q)]		300 (200-600)	275 (188-550)	0.512

OC: Open colectomy; LC: Laparoscopic colectomy; RH: Right hemicolectomy; LH: Left hemicolectomy; NA: Not available.

groups (Table 2). Although there was not a significant difference in operating time between LC and OC, there was a trend towards longer operating times in the LC group (P = 0.075; Table 2). This trend is further supported by the fact that 13 patients, all within the OC group, had another procedure along with their OC: cholecystectomy, liver biopsy, axillary dissection, small bowel resection, splenectomy, cystolithotomy, hysterectomy and oophorectomy. Contrarily, only 1 patient had a combined procedure (bilateral inguinal hernia repair) during LC.

There were no significant differences between OC and LC for any of the pathological outcomes (Table 3). These outcomes included lymph node yield (P = 0.619), proximal (P = 0.353) and distal (P = 0.57) resection margin distance and circumferential margin involvement (P = 0.348).

Controlling for potential confounders, there was a trend towards a shorter length of hospital stay in the LC group (P = 0.083; Table 4). However, 30-d morbidity was equivalent between groups (P = 0.774; Table 4). Complications included anastomotic leak, wound infection,

Table 3 Pathological outcomes for open colectomy and laparoscopic colectomy for colonic carcinoma *n* (%)

		OC	LC	*P* value
Grade of differentiation	Well	9 (10.35)	4 (23.5)	0.166
	Moderate	74 (85.1)	10 (58.8)	
	Poor	4 (4.6)	0 (0.0)	
Proximal margin (cm) [median (25Q-75Q)]		10 (5-16)	7 (7-10)	0.353
Distal margin (cm) [median (25Q-75Q)]		8 (4-13)	8 (6-10)	0.570
CRM involved	Yes	9 (10.6)	0 (0.0)	0.348
	No	76 (89.4)	16 (100)	
LN yield [median (25Q-75Q)]		14 (10-17)	14 (10-15)	0.619

OC: Open colectomy; LC: Laparoscopic colectomy; CRM: Circumferential resection margin; LN: Lymph node.

Table 4 Postoperative outcomes for open colectomy and laparoscopic colectomy for colonic carcinoma *n* (%)

		OC	LC	*P* value
30-d morbidity	No	46 (52.9)	8 (47.1)	0.774
	Yes	22 (25.3)	6 (35.3)	
	Not recorded	19 (21.8)	3 (17.6)	
30-d mortality	No	62 (71.3)	14 (82.4)	0.717
	Yes	6 (6.9)	0 (0.0)	
	Not recorded	19 (21.8)	3 (17.6)	
Parenteral narcotic doses [median (25Q-75Q)]		6 (4-9)	5 (4-7)	0.176
LOS (d) [median (25Q-75Q)]		6 (5-7)	5 (4-8)	0.083

OC: Open colectomy; LC: Laparoscopic colectomy.

fascial dehiscence, prolonged ileus, respiratory failure, pulmonary embolus, left ventricular failure, and atelectasis. Anastomotic leakage occurred in 4 (3.8%) patients. The number of post-operative parenteral narcotic doses did not significantly differ between groups (P = 0.176; Table 4). Despite 6 deaths in the OC group, a statistically significant difference in 30-d mortality was not demonstrated (P = 0.717; Table 4).

DISCUSSION

The present study demonstrates no statistical differences between open and laparoscopic colectomy with respect to short term oncologic outcomes (proximal, distal and circumferential margins and lymph node yield). This study represents the first comparative analysis of this nature from a developing country in the English-speaking Caribbean.

Numerous RCTs have demonstrated superior short-term outcomes in favour of laparoscopy with respect to post-operative pain, return of bowel function, length of hospitalization and cosmesis[3-6]. Furthermore, meta-analyses of multiple RCTs have concluded that laparoscopic colectomy for cancer provides superior short-term benefits and equivalent oncologic outcomes compared to

open colectomy[7]. More recent studies have even shown improved 30-day morbidity[7,21] and mortality[21-23] with laparoscopic colectomy, with some authors questioning whether it should be standard of care[24].

Despite this evidence, open colectomy remains the most common approach to colonic resection in developing countries[8]. A previous study from our institution[20] demonstrated that laparoscopic colectomy could safely be performed for colonic neoplasia in a developing country. However, the study did not specifically evaluate perioperative outcomes, including oncologic safety or compare such outcomes to a cohort of open cases. Lohsiriwat *et al*[25] demonstrated equivalent short-term and oncologic outcomes in a retrospective series of patients undergoing open and laparoscopic right hemicolectomy for cancer in Thailand. Those results echo that of the present study where no statistically significant difference was found for positive margins or lymph node yield ($P = 0.08$) between groups[25].

Our results demonstrated a trend towards longer operative time and shorter length of hospital stay in the LC compared to the OC group. Although these findings are consistent with the literature[3-6], our results are likely confounded by the inclusion of patients undergoing concomitant surgical procedures in the analysis. Thirteen of 14 cases with additional procedures occurred in the OC group. As such, this may have skewed results towards even longer operative times and hospital stay in the OC group. The equivalence seen between OC and LC groups regarding 30-d morbidity and mortality rates is consistent with previous literature[3-5]. Similarly, oncologic outcomes for OC and LC groups, including resection margins and lymph node yield are consistent with previous RCTs[3-6].

This study has several limitations. Firstly, like all retrospective chart reviews, data abstraction may be affected by inconsistencies, and is limited to the information contained in patients' charts. Although nothing can be done to address the latter, the former limitation was addressed by having a second abstractor review 10% of patients' charts to ensure accuracy of the information collected. Secondly, although this study provides evidence supporting the safe use of LC in resource-restricted settings, contextual factors imperative for LC implementation, such as availability of equipment and cost, were not considered.

There was a significant difference in the numbers of OC *vs* LC cases. This is a limitation of the study, which will impact on the ability to make definitive conclusions. In addition, the disparity in numbers suggests persistent barriers to the incorporation of laparoscopy in our setting. A recent survey of surgeons in Jamaica suggested that cost and lack of expertise/training were the main barriers of laparoscopy uptake[26]. However, improved short-term outcomes such as shorter hospital stay, faster return to work, and reduced surgical site infection rates, often offset the upfront costs of laparoscopy[27]. In countries already performing laparoscopic cholecystectomy, no additional basic equipment is usually required for colectomy. Institutional investment in reusable bowel graspers and needle drivers would obviate the need for disposables with some cost reduction. Some disposable equipment, however, have no reusable counterpart. As such, the initial cost of these disposables (including energy devices and staplers) to the institution or patient remains a challenge. Manoeuvres to avoid the need for these expensive devices, such as colonic mobilization with extracorporeal anastomoses, and the use of monopolar cautery and clips[13] have been described. Meta-analyses have failed to demonstrate any significant disadvantages to extracorporeal anastomoses for laparoscopic right sided colectomies[28]. Additionally, there is no evidence to suggest that use of energy devices is superior to monopolar cautery for laparoscopic colectomy[29]. The surgical technique employed in the present study utilized reusable instruments and extracorporeal anastomoses in order to reduce costs. Such techniques did not adversely affect outcomes. Future studies should incorporate these contextual factors when describing LC uptake in a resource-restricted setting.

Lack of expertise and training as a limiting factor for LC uptake underscores the need to incorporate LC in residency training[8,30]. The recent opening of a skills laboratory and the further addition of minimally invasive surgical staff to our institution have been methods instituted to address this issue. Unfortunately, these factors were not considered in this study and should be discussed in future work.

There remain many challenges to the use of laparoscopic colectomy for colonic carcinoma in developing countries. The equivalent short-term outcomes demonstrated between open and laparoscopic groups in the present study demonstrate that this is an oncologically safe approach in our environment. Continued strategies to reduce costs and increase surgeon training are essential to the further development of laparoscopic colectomy in developing countries. Only through these strategies can caseload increase allowing for progressive high-quality research in the field in these environments.

COMMENTS

Background

Laparoscopic colectomy for cancer has been proven to have superior short-term benefits to open colectomy with equivalent oncologic outcomes. These findings are based on large-scale studies conducted developed countries. The practice of laparoscopic colectomy in developing countries is limited. To date, few studies have sought to evaluate the benefit and oncologic safety of laparoscopic colectomy for patients in developing countries.

Research frontiers

Laparoscopic surgery has revolutionized the care of patients worldwide, providing advantages of reduced pain, shorter hospital stay, earlier return to normal functioning and improved cosmesis. For developing countries, the research hotspot is the demonstration of similar outcomes as in developed countries, particularly for the use of laparoscopy in cancer cases.

Innovations and breakthroughs

Previous studies on the use of laparoscopic colectomy in developing countries have demonstrated feasibility and safety. These studies are few as the practice of laparoscopic colectomy in these environments is limited, particularly by resource constraints. Very few studies have evaluated the specific effects of laparoscopy on oncologic outcomes of colon cancer in developing countries.

In the present study, authors compared a cohort of patients undergoing open and laparoscopic colectomy for cancer and found that the short-term oncologic outcomes were equivalent between the two groups.

Applications

The study results suggest that laparoscopic colectomy for cancer can be safely performed, with equivalent short-term oncologic outcomes to open colectomy, in developing countries where resources may be limited.

Terminology

Laparoscopy is a minimally invasive surgical technique where abdominal operations are undertaken through small incisions, thus minimizing bowel handling and causing less tissue trauma. Colectomy refers to the surgical excision of the colon or part thereof. Short-term oncologic outcomes related to colon cancer include proximal, distal and circumferential margin involvement and the numbers of lymph nodes harvested at the time of surgery.

Peer review

The authors present a comparative study between open and laparoscopic approaches for colectomies in a developing country. They should be congratulated for addressing this relevant topic.

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BRIEF ARTICLE

Drainage *vs* no drainage in secondary peritonitis with sepsis following complicated appendicitis in adults in the modern era of antibiotics

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Abstract

AIM: To compare the profile of postoperative outcome in secondary peritonitis with sepsis due to complicated appendicitis in two cohorts (drainage *vs* no-drainage) after appendicectomy in adults in the modern era of effective antibiotics.

METHODS: A retrospective review of all adult patients who were operated for secondary peritonitis with sepsis due to complicated appendicitis was carried out. Total of 209 patients were identified from May 2005 to April 2009 with operative findings of gangrenous or perforated appendix. The patients were divided into two cohorts, those where prophylactic drainage was established (n = 88) and those where no drain was used (n = 121). Abdominal drain was removed once the drainage ceased or decreased (< 10-20 mL/d in closed system of drainage or when once daily dressing was minimally soaked in open system). Broad spectrum antibiotics to cover the gut flora were started in both cohorts at diagnosis and were stopped once septic features resolved. Peritoneal fluid for aerobic culture and sensitivity were routinely obtained intra operatively; however antibiotic regimens were not changed unless patient failed to respond to the antibiotics based on the institutional protocol. The co-morbidities and their influence on primary end points were noted. Immunocompromised patients, appendicitis complicated by inflammatory bowel disorder and tumors were excluded from the study.

RESULTS: Disease stratification and other demographic features were comparable in both cohorts. There was zero mortality in drainage group while as one patient (0.82%) died in the non-drainage group. The median duration (in days) of hospital stay (6.5 *vs* 4); antibiotic use (5 *vs* 3.5); regular parental analgesic use (5 *vs* 3.5) and paralytic ileus (2.5 *vs* 2) was more common in the drainage group. Incidence of major wound infection in patients 14 (15.9%) *vs* 22 (18.18%) and residual intra-abdominal sepsis (inter loop collection/abscess) -7 (8%) *vs* 13 (10.74%) requiring secondary intervention was not significantly different in drainage and non-drainage cohorts respectively. One patient in the drainage cohort had faecal fistula (1.1%).

CONCLUSION: The complicated appendicitis in the modern era of antibiotics does not necessitate the use of prophylactic drain placement which at times may even prove counterproductive.

Key words: Appendicitis; Antibiotics; Drainage; Gangerenous; Peritonitis

Core tip: The routine placement of the drain after appendicectomy irrespective of the severity of the appendicitis increases both the morbidity and the cost of treatment. The surgeons need to do away with the habits of riding on drains perhaps as a soup to their consciences. Post-operative management of the patient with the drain as compared to those without drain is troublesome, requiring increased work and manpower for the hospital.

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INTRODUCTION

The untruthful trust on the functioning of drains as an agent in preventing the intra-abdominal sepsis is deeply seated in the minds of the surgeons. This belief is usually imbibed by the surgeons from their predecessors during their training period and the practice persists from one generation-surgeons to another. Robinson[1] aptly classified surgeons into three categories based on their use of drains: those who believe that all intraperitoneal operations should be drained, those who feel that drain is useless and those who sit on the fence and insert a drain as a safety valve or perhaps as a sop to their consciences. Even though there is enough evidence to discourage the use of prophylactic drains in different areas of gastrointestinal surgery[2] the literature for or against the use of drain after the complicated appendicitis is small and historical. Drainage following "simple" appendicitis has been assessed by two randomized trials[3,4] which do not favour the placement of drains.

There have been only few randomized trials so for to evaluate the role of drains when the appendix was eithe perforated or gangrenous[3-6]. However three of these studies have been reported in 1970s. Though the meta-analysis based on these studies by Petrowsky *et al*[7] did not recommend the use of intraperitoneal drains, no evidence exist as to whether this approach should be extrapolated in adult patients; and in the new era of antibiotics. Although, there is no universally accepted antibiotic regimen, however broad spectrum coverage with multiple drugs has been advocated[8-10].

MATERIALS AND METHODS

The retrospective analysis of the medical records of adult patients who underwent open appendicectomy for complicated appendicitis (gangrenous and perforated appendix) at Sher-i-Kashmir institute of medical sciences Srinagar from May 2005 to April 2009 was done. The total number of patients encountered was 209. Prophylactic drainage was established in 88 patients while as in 121 patients no drain was used. Abdominal drain was removed once the drainage ceased or decreased (< 10-20 mL/d in closed system of drainage or when once daily dressing was minimally soaked in open system). Broad spectrum antibiotics to cover the gut flora were used in both cohorts at diagnosis and were stopped once sepsis got resolved. Peritoneal fluid for aerobic culture and sensitivity were routinely obtained intra operatively. The co-morbidities and their influence on primary end points were noted. Laparoscopic appendicectomy, immunocompromised patients and appendicitis complicated by inflammatory bowel disorder were excluded from the study. The fluid and electrolyte correction was done wherever necessary before surgery. The patients were put on 3rd generation cephalosporin with or without sulbactum plus metronidazole 7.5 mg/kg q8H at the time of diagnosis of complicated appendicitis. Postoperatively parenteral antibiotics were switched to oral therapy for 5 to 7 d when: (1) baseline signs and symptoms of infection were resolving or resolved; (2) resolution of fever (≤ 37.8 ℃) or hypothermia; (3) leukocytosis, leucopoenia resolving or normal; and (4) subjects able to maintain oral intake.

Patients were operated by one of the Registrars (advanced trainees) in 24 h-emergency theatre without much delay after the assessment by a senior consultant. Right iliac fossa standard muscle splitting/cutting transverse or oblique incision was utilised usually for localised peritonitis or for documented case of appendicitis. A right lower lateral para-median incision was usually used for generalised peritonitis or when diagnosis was in question. After appendicectomy stump burial was an individual preference of surgeon. A liberal lavage was performed by luke warm 0.9% normal saline. Drain placement was largely influenced by the surgeons own preference, understanding of the subject and belonging to a particular school of thought. No rigid departmental protocol has been formulated in this context. Drain was placed either in right para-colic gutter or in pelvis. All wounds were closed primarily after a thorough wound wash. Abdominal drain was removed once the drainage has ceased or decreased (< 10-20 mL/d in closed system of drainage or when once daily dressed was minimally soaked in open system).

In the post-operative period patients who failed to improve over a period of time underwent radiological evaluation (ultrasonography and/or computed tomography) of the abdomen and antibiotics were changed as per the culture sensitivity reports wherever necessary. Though only aerobic culture was obtained often but not routinely at the time of primary surgery. Subsequent cultures were drawn from the potential sources (infected wound or intra-abdominal collection) only if patients failed to respond to initial therapy.

RESULTS

Over a period of 4 years there were a total of 209 adult patients who underwent open appendicectomy for com-

Table 1 Preoperative status of the patients

Patient characteristics	Drainage cohort (*n* = 88)	Non-drainage cohort (*n* = 121)
Age[1] (yr)	29 (14-93)	26 (14-78)
Sex[2] (male: female)	1:1.2	1.3:1
Duration of symptoms[2] (d)	2.5 ± 1.3	2.1 ± 1.5
WBC count[2] (× 109/L)	16.8 ± 4.9	16.1 ± 5.3
Febrile %age (> 37.80 C)	68 (77%)	91 (75%)

[1]Expressed as median (years); [2]Expressed as an average with the standard deviation.

Table 2 Postoperative status of the patients *n* (%)

Post operative outcome	Drainage cohort (*n* = 88)	Non-drainage cohort (*n* = 121)
Hospital stay[1]	6.5 (4-8)	4.0 (3-8)
Antibiotic use (parenteral)[1]	5.0 (4-9)	3.5 (3-6)
Regular analgesic use[1]	5.0 (4-9)	3.5 (3-6)
Paralytic ileus[1] (passing of flatus)	2.5 (1-5)	2.0 (1-4)
Major wound infection	14.0 (15.9)	22.0 (18.18)
Residual intra-abdominal collection	7.0 (8)	13.0 (10.74)
Subacute intestinal obstruction	3.0 (3.4)	5.0 (4.13)
Faecal fistula	1.0 (1.1)	-
Incisional hernia	2.0 (2.2)	2.0 (1.6)
Mortality	1.0 (0.82)	

[1]Are expressed as median (d). $P > 0.05$ (insignificant).

plicated appendicitis. All the patients gave history of fever, vomiting and pain which had started initially in the umbilical area and later shifted to right iliac fossa. All the patients were febrile and had a pulse rate of more than 100/min. There was severe tenderness in the right iliac fossa with positive Mcburney's sign. All the patients had leukocytosis with neutroplilia. The patient demographics and disease parameters were not statistically different in drainage and non-drainage cohorts (Table 1). The post-operative outcome in two cohorts is shown in Table 2. Data was analyzed using SPSS version 10 using χ^2 test. A *P* value below 0.05 was considered statistically significant. The hospital stay in the two cohorts was significantly different, with a median of 6.5 and 4 d in the drainage and non-drainage cohorts respectively. The antibiotic use was longer in the drainage cohort as compared to the non-drainage cohort, *i.e.*, median of 5 d (range 4-29) *vs* 3.5 d (range 3-26) respectively. Similarly the regular analgesic use was also prolonged in the drainage cohort as compared to non-drainage cohort, *i.e.*, median of 5 d (range 2-17) *vs* 3.5 d (range 2-14). One 76-year-old obese female patient with a body mass index of 37.4, with diabetes and hypertension in the non-drainage cohort was operated with a delay of 4 d because of subclinical signs and symptoms. After appendicectomy patient continued to be in sepsis and underwent multiorgan dysfunction syndrome which ultimately resulted in death on 28th post-operative day. One 31-year-old male patient in the drainage cohort had a faecal fistula through the main wound after the removal of the drain on the 5th post operative day.

Table 3 Clinico-pathological profile of patients requiring second surgery *n* (%)

Indications	Duration[1] (*n* = 88)	Drainage cohort (*n* = 121)	Non-drainage cohort
Subacute intestinal obstruction	28-35 d	1 (1.1)	1 (0.82)
Incisional hernia	6-11 mo	2 (2.2)	2 (1.60)

[1]Period after the primary surgery.

Patient was managed conservatively and his fistula healed completely after 35 d. Residual intra-abdominal collection was noted in 7 (8%) patients and 13 (10.74%) patients in drainage and non-drainage cohorts respectively on USG and/or CECT abdomen.

Two patients in each cohort required radiological guided drainage and one patient in the non-drainage cohort drained spontaneously through the main wound. The patients who do not show clinical deterioration or whose intra-abdominal collections were not significant enough to be drained radiologically/surgically were managed conservatively. The clinico-pathological profile of the patients who require second surgery is shown in Table 3. One patient in each cohort failed to the conservative management and required multiple admissions for sub acute intestinal obstruction. Adhesinolysis was all that was required and patients were symptom free thereafter. Mesh hernioplasty was done in a patient with incisional hernia.

DISCUSSION

Hippocrates[11] ever since he first reported the use of an abdominal drain in empyema gallbladder, its usage has been extended to almost all surgical procedures. The very purpose of the drains, to reduce the potential source of infection, detect post-operative bleed and anastomotic leakage or to establish the tract for the drainage of the collected material even after its removal may not be always served. Likewise drainage following appendicectomy (one of the commonest gastrointestinal operation) is usually determined by whether the underlying appendicitis is simple/complicated and largely determined by the surgeons' belief.

In the absence of any universally accepted antibiotic regime for appendicitis, traditionally broad spectrum antibiotic coverage is routinely adopted[8-10]. However the choice of antibiotics in complicated appendicitis is largely influenced by the institutional protocols[12]. A commonly followed guideline[9] recommends triple antibiotics. However there has been a recent trend towards single or dual drug regimes in children[12,13], in order to reduce the cost and simplify dosing schedules. While these paediatric trials are not adequately powered[13-16], the randomised trials in adults have failed to show any difference in antibiotic regimes[17]. We have adopted a cost effective policy of two/three drug regimens (3th generation cephalosporin with or without salbactum plus metronidazole 7.5 mg/kg

q8H), which was instituted at the time of diagnosis of complicated appendicitis. It has been seen that post-operative abscesses occurred in patients who had organisms on culture that were sensitive to the treatment antibiotics[18,19]. Unlike Kokoska *et al*[19], Ong *et al*[18] found that culture of the postoperative abscess did correlate with the initial peritoneal culture, although this does not alter management. Contrary to the commonly held belief, recently, the natural history of immunological mechanisms of the peritoneum has been better understood and its natural defence mechanisms to clear the infection have been elucidated[20-23]. These studies highlight the importance of the peritoneal fluid, and its drainage can even prove counterproductive.

Two randomized controlled trials (RCT) investigated the value of prophylactic drainage after open appendicectomy for acute/simple appendicitis[4,24]. Although both arms (drainage, no-drainage) of the trials had a relatively large sample size (> 90 patients each group), the studies were performed without a power and sample size calculation and were therefore ranked as level 2b. One study reported a significantly higher wound infection rate in drained patients with acute/simple appendicitis[23], whereas the other study found similar wound and intra-abdominal infection rates in drained and non-drained patients[4].

In complicated appendicitis (gangrenous/perforated), the role of prophylactic drainage has been studied in five RCTs. Because of the same reasons mentioned above, the level of evidence was classified as 2b in each RCT. The results showed higher wound infection rates in drained patients (range 43%-85%) than in non-drained patients (29%-54%). The pattern of intra-abdominal infection was not uniform among the studies, as two studies reported slightly higher intra-abdominal infection rates in non drained patients[24,25], one study a higher rate in drained patients[4], and another a similar rate in both groups[6]. Interestingly, the development of fecal fistulas was only observed in drained patients with a rate ranging from 4.2% to 7.5%.

Petrowsky *et al*[7] performed meta-analysis including series of gangrenous or perforated appendicitis only. Four RTCs (all level 2b) were included in the meta-analysis with the end point wound infection, whereas data from 3 RTCs were available for the end points intra-abdominal infection and fecal fistula. The analysis calculated an odds ratio for wound infection of 1.75 (CI: 0.96-3.19). The odds ratio for fecal fistula of 12.4 (CI: 1.14-1.35) favours the no drainage group; whereas the odds ratio for the end point intra-abdominal infection of 1.43 (CI: 0.39-5.29) favours neither group.

We observed almost similar incidence of major wound infection in patients in the drainage (15.9%) and non-drainage (18.18%) cohorts which is not statistically significant ($P > 0.05$). Dandapat *et al*[5] also showed that peritoneal drainage does not prevent wound infection. The author believes that protection of the wound during the primary surgery is of utmost priority, and the effective antibiotics compliment to the aseptic precautions in reducing the incidence of wound infection. Ciftci *et al*[15] observed that the most crucial point to avoid the wound infection is the application of antibiotics with aerobic and anaerobic coverage. In our study all the wounds were closed primarily in both the cohorts. There is an apprehension that primary closure of surgical incision after appendicectomy for complicated appendicitis may result in increased incidence of surgical site infection[26,27]. These incisions are often managed with delayed closure. However Rucinski *et al*[28] did a meta-analytic study of 2532 patients with gangrenous and perforated appendicitis. They concluded that primary closure of the skin and subcutaneous tissue after appendicectomy for gangrenous or perforated appendicitis, combined with the use of antibiotics in the perioperative period, is not associated with an increased risk of incision infection when compared with delayed closure.

On the one hand there seems to be a tendency on the part of the treating physician to continue the parental antibiotics and analgesics longer in the drainage cohort than in the non-drainage cohort and thus delay the discharge of the former[29,30]. On the other hand there seems to be tendency on the part of the patient to continue to assume the sick role until the drains are removed. Furthermore the post-operative care of the patients with the drain as compared to those without drain is troublesome, requiring increased work and manpower for the hospital. We had one patient (1.1%) in the drainage cohort whose postoperative course was complicated by the fecal fistulae. The exact cause of the fistulae remained unsolved in our series. However, these drains themselves are also a potential source of infection; may induce anastomotic leakage and may cause damage by mechanical pressure and suction[31,32].

The incidence of paralytic ileus and intra-abdominal collection in the two cohorts is not statistically different in our series. Also the incidence and indications of the second operation is not significantly different in the two cohorts in our series.

In a conclusion, the routine placement of the drain after appendicectomy is not indicated regardless of the severity of the appendicitis. It not only increases the morbidity, but is also not a cost effective method. The surgeons need to shun away the deeply inculcated habits of riding on drains perhaps as a soup to their consciences. The criticism of the study is that it is not a randomised controlled prospective trial and thus cannot generate the level 1 evidence. The results cannot be translated completely into the laparoscopic era, where the profile of postoperative outcome would be certainly different. However the author maintains that these patients were diagnosed and operated as secondary peritonitis with sepsis where the role of laparoscopy is still not fully defined. But the power of the study is adequate enough to validate the end points of the study.

COMMENTS

Background

Although there is lot of evidence that discourages the use of prophylactic drains in different types of gastrointestinal surgeries, enough studies have not been

conducted that would favour or disfavour the use of drain after the complicated appendicitis.

Research frontiers

The principal aim of the study was to compare the postoperative outcome in secondary peritonitis with sepsis due to complicated appendicitis in two groups of patients, one with drainage and another without drainage, after appendicectomy in adults in the modern era of effective antibiotics.

Innovations and breakthroughs

Regardless of the severity of the appendicitis, the routine use of the drain after appendicectomy is not indicated. It not only increases the morbidity, but is also not a cost effective method.

Applications

In the modern era when wide range of antibiotics with a very broad spectrum of action are available, the patients with peritonitis secondary to appendicitis does not necessitate the use of prophylactic drain, rather it may at times may even prove counterproductive.

Peer review

The authors have conducted the present study to evaluate the effectiveness of drain in patients with complicated appendicitis. The results are interesting and may form the basis of further study.

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CASE REPORT

Hemophagocytic lymphohistiocytosis caused by primary Epstein-Barr virus in patient with Crohn's disease

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Abstract

We present a case of a 19-year-old man with a 6-year history of Crohn's disease (CD), previously treated with 6-mercaptopurine, who was admitted to our department for Epstein-Barr virus (EBV) infection and subsequently developed a hemophagocytic lymphohistiocytosis (HLH). HLH is a rare disease which causes phagocytosis of all bone marrow derived cells. It can be a primary form as a autosomic recessive disease, or a secondary form associated with a variety of infections; EBV is the most common, the one with poorer prognosis. The incidence of lymphoproliferative disorders was increased in patients with inflammatory bowel disease (IBD) treated with thiopurines. Specific EBV-related clinical and virological management should be considered when treating a patient with IBD with immunosuppressive therapy. Moreover EBV infection in immunosuppressed patient can occur with more aggressive forms such as encephalitis and diffuse large B cell lymphoma. Our case confirms what is described in the literature; patients with IBD, particularly patients with CD receiving thiopurine therapy, who present 5 d of fever and cervical lymphadenopathy or previous evidence of lymphopenia should be screened for HLH.

Key words: Crohn's disease; Hemophagocytic lymphohistiocytosis; Epstein-Barr virus infection; Immunosuppressive therapy; Thiopurines

Core tip: About the case we're presenting, a literature review showed how this rare disease is often lethal and how low is the percentage of patients who have successful treatment. We show our case history and our management which has permitted to discharge the patient with disease regression.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and often fatal disease which causes phagocytosis of all bone marrow derived cells. It can be a primary form as a autosomic recessive disease, or a secondary form associated with a variety of infections; Epstein-Barr virus (EBV) is the most common, the one with poorer prognosis. Patients with inflammatory bowel disease (IBD) are a greater risk of developing secondary HLH due to chronic systemic inflammation condition as well as exposure to immunosuppressive medications[1].

CASE REPORT

A 19-year-old man was moved to our Hospital from a local hospital in London, where he was admitted 10 d

Table 1 Current diagnostic criteria for hemophagocytic lymphohistiocytosis[7]

The diagnosis of HLH may be established by[1]
A molecular diagnosis consistent with HLH (for example, pathologic mutations of *PRF1*, *UNC13D* or *STX11* are identified) or
Fulfillment of five out of the eight criteria listed below:
Fever
Splenomegaly
Cytopenias (affecting at least two of three lineages in the peripheral blood):
Hemoglobin < 9 g/100 mL (in infants < 4 wk: hemoglobin < 10 g/100 mL)
Platelets < 100-103/mL
Neutrophils < 1-103/mL
Hypertriglyceridemia (fasting, 265 mg/100 mL) and/or hypofibrinogenemia (150 mg/100 mL)
Hemophagocytosis in BM, spleen or lymph nodes
Low or absent NK cell activity
Ferritin 500 ng/mL
Soluble CD25 (that is, soluble IL-2 receptor) > 2400 U/mL (or per local reference laboratory)

[1]In addition, in the case of familial HLH, no evidence of malignancy should be apparent. HLH: Hemophagocytic lymphohistiocytosis; NK cell: Natural killer cell; CD: Crohn's disease; IL-2: Interleukin-2; *PRF1: Pore Forming Protein* gene; *UNC13D*: *Unc-13 homolog D* gene; *STX11*: *Syntaxin 11* gene.

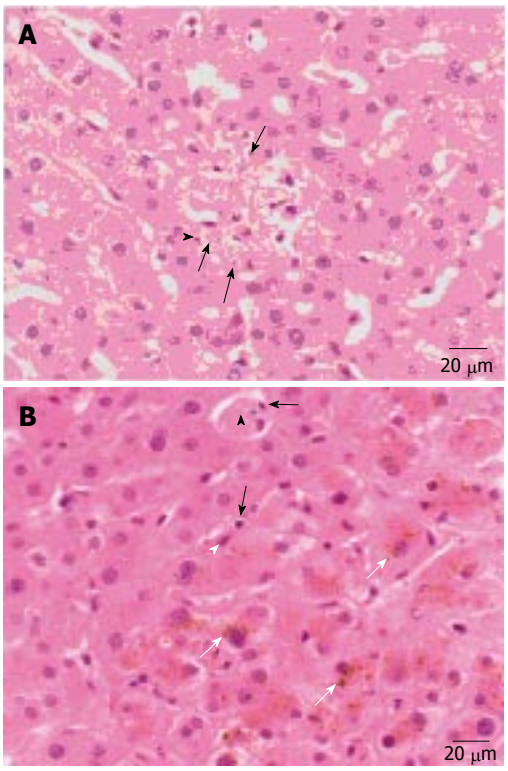

Figure 1 Active Epstein-Barr virus infection with hemophagocytosis not with lymphoma. A: Large histiocytes showing erythrophagocytosis (arrows) and leucophagocytosis (black arrowhead); B: A Kupffer cell (white arrowhead) and a large histiocyte (arrowhead) have phagocytosed a lymphocyte (arrow), moderate cholestasis is present (white arrow).

before with a history of fever, jaundice and weakness on a background of Crohn's disease (CD), which was diagnosed 5 years before and was previously treated with 6-mercaptopurine (6-MP). Diagnosis of EBV infection was performed by serologic exams. During his inpatient stay he developed a progressive pancytopenia (white blood cell 0.5 × 10^9/L, neutrophils 0.7 × 10^9/L, hemoglobin 66 g/L, platelets 236.000/mm^3), 6-MP therapy was therefore suspended and replaced with steroids. On clinical examination a continuous fever of up to 39 ℃ was reported. A bone-marrow biopsy was performed to clarify the cause of pancytopenia and it was positive for HLH; diagnosis was thus confirmed matching the diagnostic criteria for HLH (Table 1). Supportive treatment with granulocyte-colony stimulating factor and antibiotics was started. He had been transfused with packed red cells as necessary.

During his recover in our hospital he developed perirectal bleeding and a flexysigmoidoscopy showed multiple ulcers but a non specific point of bleeding. Due to this, a computed tomography (CT) angiogram was performed and at that time a bleeding point was identified at the splenic flexure. Hepatosplenomegaly was also noted. Consequently embolization of mesenteric artery was attempt but superior and inferior mesenteric arteries runs did not demonstrate any active bleeding. Moreover, a liver biopsy to exclude other liver diseases has been performed and it showed features consistent with active EBV infection with evidence of hemophagocytosis and no evidence of lymphoma (Figure 1). CT chest was performed and it showed diffuse adenopathy (mediastinal, supraclavicular, bilateral axillary). A right axillary core biopsy showed no evidence of lymphoma. HLH 2004 protocol with Etoposide and Rituximab was therefore started ten days after his admission in our Hospital.

The patient clinically improved from a HLH point of view whilst on the HLH 2004 protocol. However increasing cervical lymphadenopathy was noted and a subsequent biopsy demonstrated diffuse large B cell lymphoma (DLBCL) secondary to EBV. He was therefore started on Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone chemotherapy. The patient was noted to have two tonic clonic seizures on the ward, one of which resulted in aspiration pneumonia; transfer in intensive treatment unit for intubation and ventilation was required.

CT head was required to exclude any brain damage

The CT head reported multifocal low attenuation areas of the brain (Figure 2); radiologist report showed as these lesions could have represented central nervous system (CNS) infiltration by the HLH process. However the patient neurological condition was discussed with neurological team and a diagnosis of EBV encephalitis was made. This was treated with Rituximab, Methotrexate, Hydrocortisone and supportive care. His neurological condition improved and the most recent magnetic resonance imaging head showed significant disease improvement. Patient was discharge three months after his admission date.

DISCUSSION

HLH is a rare, often fatal disease in which macrophages

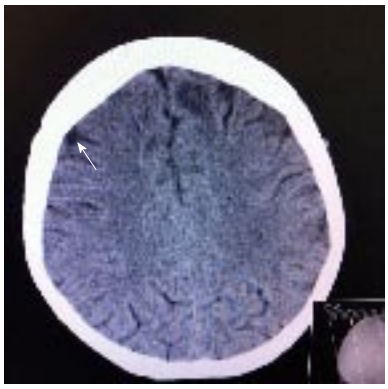

Figure 2 Focal lesion anteriorly in the left parietal lobe.

are inappropriately activated resulting in phagocytosis of all bone marrow derived cells[1].

There are two presentation forms: the first, primary, is an autosomic recessive disease; the second is a secondary HLH which can present at any age and has been documented in association with a variety of infections. While there are a wide variety of micro organisms related to the development of HLH, EBV is the most common, the one with poorer prognosis, and the one benefiting most from early treatment with etoposide[2].

The literature review shows how the incidence of lymphoproliferative disorders was increased in patients with IBD treated with thiopurines[3].

However, thiopurines may interfere with the host's response to a primary EBV infection[1].

EBV can induce HLH; case reports describing HLH and/or lymphoma in patients with CD have also been published[4].

Biank *et al*[1] described 11 additional cases in the literature of HLH in patient with IBD and only 3 of 11 cases reported were associated with an EBV infection. A new review of literature identified 3 further cases; therefore our case is potentially the seventh described in literature. Our patient met diagnostic criteria for HLH (Table 1).

Moreover he developed CNS symptoms with lesions on the CT head which could represent CNS infiltration by the disease process. CNS symptoms occurs in 35%-49% of patients with HLH[5].

In the case we have reported the patient started etoposide 20 d after his first admission. Etoposide may be life-saving, especially in patients with HLH due to EBV infection; mortality was 14 times higher for patients with EBV-associated HLH who did not receive etoposide within the first 4 wk[6].

Our patient also developed a DLBCL secondary to EBV; in literature we founded only one case involving hepatosplenic lymphoma, HLH and EBV infection in a patient with CD undergoing thiopurine and infliximab therapies[3].

Secondary HLH in patients with IBD is often due to EBV infection. Specific EBV-related clinical and virological management should be considered when treating a patient with IBD with immunosuppressive therapy[4].

Particularly, patients treated with thiopurine have greater risk to develop EBV infection, due to inadequate immune system response. Our case confirms what is described in the literature; patients with IBD, particularly patients with CD receiving thiopurine therapy, who present five days of fever and cervical lymphadenopathy or previous evidence of lymphopenia should be screened for HLH[1].

Moreover EBV infection in immunosuppressed patient can occur with more aggressive forms such as encephalitis and DLBCL.

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CASE REPORT

Malignant pheochromocytoma: Hepatectomy for liver metastases

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Abstract

Malignant pheochromocytoma accounts for approximately 10% of pheochromocytoma cases. The main site of distant metastasis is the liver. Hypertensive crisis due to catecholamine oversecretion is potentially fatal. We present a case of malignant pheochromocytoma with multiple liver metastases. A 60-year-old female with repeated hypertensive episodes was diagnosed with malignant pheochromocytoma. She underwent a left adrenalectomy and partial hepatectomy with resection of segment 6. Catecholamine levels remained high after surgery and she received repeated cycles of chemotherapy. Four months after surgery, multiple liver metastases were detected. In spite of ongoing chemotherapy, catecholamine levels eventually became uncontrollable. Serum and urine noradrenaline and vanillylmandelic acid levels increased, but adrenaline and dopamine levels stayed within the normal range. Preoperative liver imaging revealed multiple metastases in all segments except segment 4. Percutaneous transhepatic portal vein embolization (PTPE) of the right and lateral branches of the portal vein was performed. The functional liver volume of segment 4 increased after PTPE. Right hepatectomy, lateral segmentectomy and partial resection of segment 1 were performed 10 mo after the initial surgery. Intraoperative ultrasonography detected two small tumors in segment 4, which were treated with intraoperative microwave coagulation therapy. Noradrenaline levels normalized immediately after the second hepatectomy. As there was increased telomerase activity in the resected specimen, she received adjuvant chemotherapy. She remained in good health for 2 years. However, further metastases eventually occurred and she subsequently died due to a brain hemorrhage. Hepatectomy may be a therapeutic option for reduction of tumor mass in pheochromocytoma with liver metastases.

Key words: Malignant pheochromocytoma; Liver metastasis; Mass reduction; Percutaneous transhepatic portal vein embolization; Hepatectomy

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INTRODUCTION

Pheochromocytoma is an endocrine tumor. Malignant

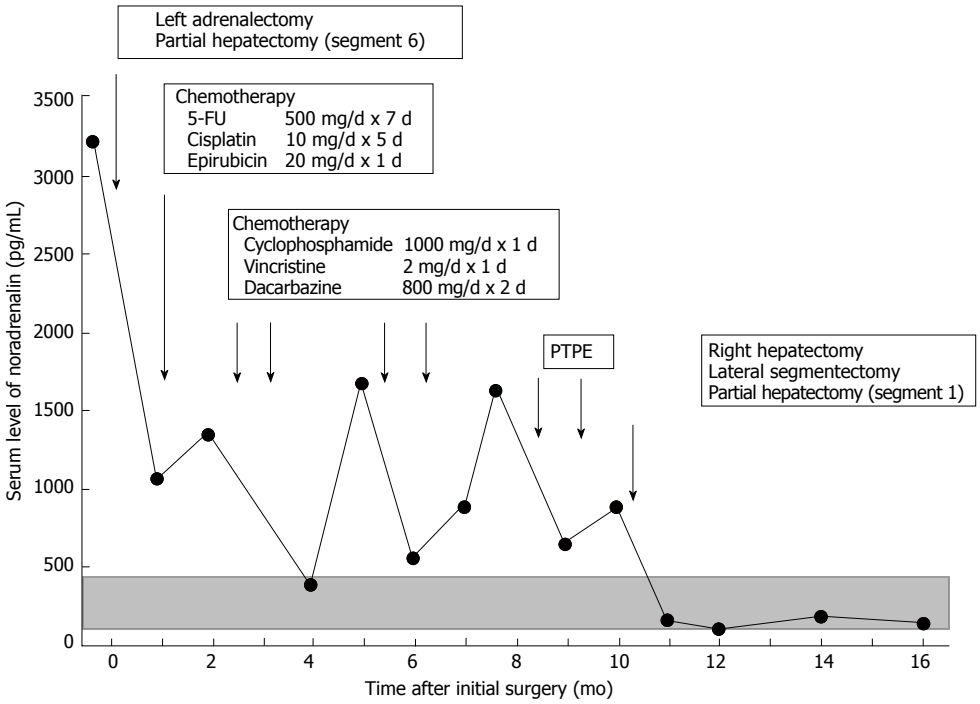

Figure 1 Serum catecholamine levels before and after treatments. Serum catecholamine levels are shown in relation to surgery, chemotherapy and preoperative percutaneous transhepatic portal vein embolization. The shaded area represents the normal range (100-450 pg/mL). PTPE: Percutaneous transhepatic portal.

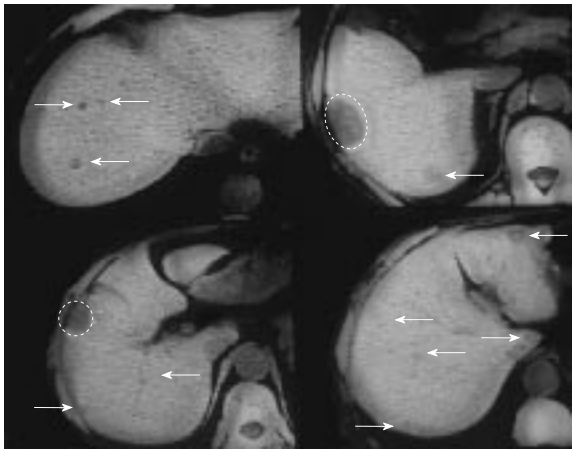

Figure 2 Angio-computed tomography findings. Preoperative image study revealed multiple liver metastases (white arrows) except for segment 4. She underwent the partial hepatectomy of segment 6 at initial surgery (white dotted circle).

pheochromocytoma is diagnosed if a distant metastasis is detected, which occurs in approximately 10% of cases. Hence, pheochromocytoma is commonly called a "10% disease". Hypertension due to the oversecretion of catecholamines may be fatal[1,2]. The main site of distant metastasis is the liver. We present a case of malignant pheochromocytoma treated by hepatectomy to reduce tumor mass. To our knowledge, this is the first case of aggressive hepatectomy for liver metastases requiring preoperative percutaneous transhepatic portal vein embolization (PTPE).

CASE REPORT

A 60-year-old female with repeated hypertensive episodes was diagnosed with malignant pheochromocytoma. She underwent a left adrenalectomy and partial hepatectomy with resection of segment 6. Since her catecholamine levels stayed high after surgery, she received repeated cycles of chemotherapy (5-FU, cisplatin and epirubicin, followed by cyclophosphamide, vincristine and dacarbazine) (Figure 1). Four months later, multiple liver metastases were detected (Figure 2). Even with ongoing cycles of chemotherapy (cyclophosphamide, vincristine and dacarbazine), catecholamine levels eventually became uncontrollable. She was admitted to our institution for surgical therapy. Angio-computed tomography and magnetic resonance imaging findings were consistent with liver metastases, with the tumors showing uptake on meta-iodobenzylguanidine scintigraphy. Serum and urine levels of noradrenaline and vanillylmandelic acid increased, but adrenaline and dopamine levels stayed within the normal range. As preoperative imaging studies revealed multiple metastases in all liver segments except segment 4, PTPE of the right and lateral branches of the portal vein was performed. The functional liver volume of segment 4 increased after PTPE (Figure 3). She underwent a right hepatectomy with lateral segmentectomy and partial resection of segment 1 (Spiegel lobe) at 10 mo after her initial surgery (Figure 4A). Intraoperative ultrasonography detected two small nodules in segment 4, which were treated with intraoperative microwave coagulation therapy (Figure 4B). Intraoperative examination did not detect tumor in the right adrenal gland. Histopathological examination of the surgical specimens was consistent with pheochromocytoma (Figure 5A). The patient's noradrenaline level normalized immediately after the second operation. Telomerase activity in the resected tumor, measured by a modified telomeric repeat amplification protocol, was clearly elevated (Figure 5B).

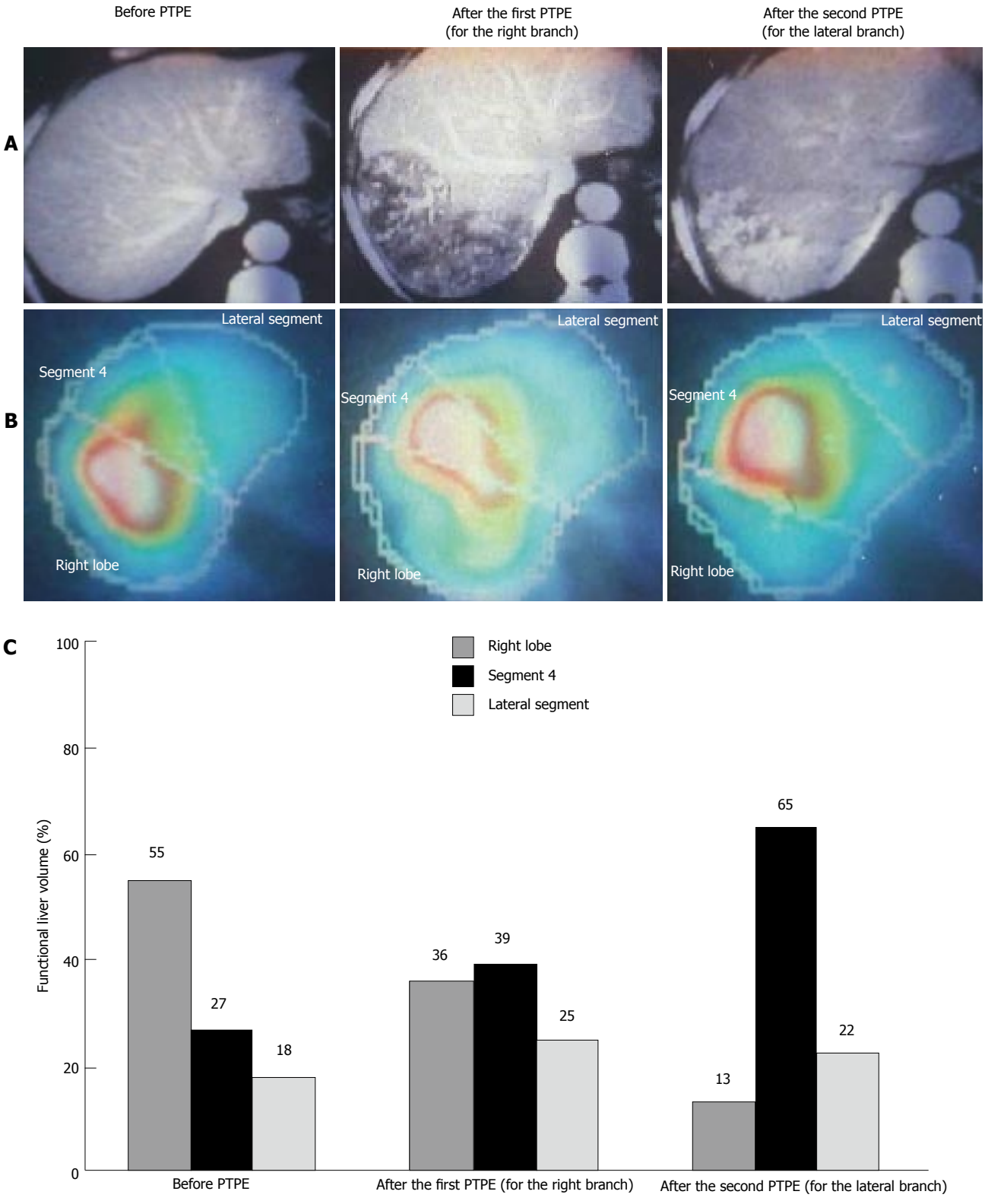

Figure 3 Changes in functional hepatic volume after percutaneous transhepatic portal vein embolization. The angio-computed tomography findings (A), technetium-99m diethylenetriamine pentaacetic acid galactosyl human serum albumin scintigraphy for asialoglycoprotein receptor (B) and the functional hepatic volume (C) were shown in each lobe/segment before and after percutaneous transhepatic portal vein embolization. Functional hepatic volume of each lobe/segment was calculated as a percentage of whole liver volume. PTPE: Percutaneous transhepatic portal.

She received adjuvant chemotherapy (5-FU, cisplatin and epirubicin) and was able to return to her normal physical and social activities. She remained in good health for 2 years after the second operation. However, she eventually developed further distant metastases. The metastatic tumors enlarged and catecholamine levels increased in

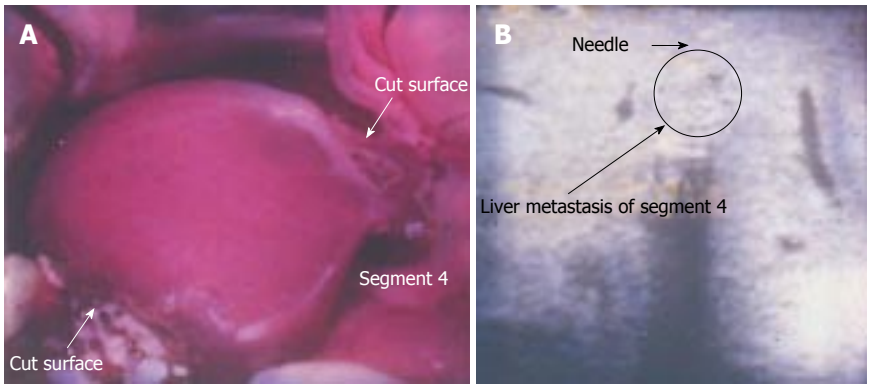

Figure 4 Intraoperative findings. A: She underwent right hepatectomy with lateral segmentectomy and partial resection of segment 1. B: Intraoperative ultrasonography detected two small nodules in segment 4, which were treated with intraoperative microwave coagulation therapy.

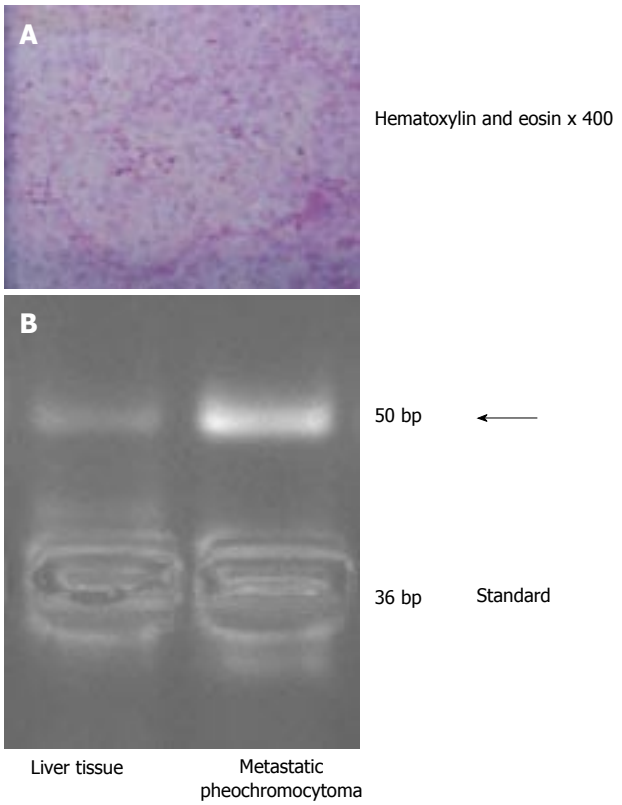

Figure 5 Histopathological finding and telomerase activity in the resected tumor. A: Histopathological examination of the surgical specimens was consistent with pheochromocytoma; B: Real-time polymerase chain reaction clearly revealed increased telomerase activity (arrow) in the resected tumor tissue compared with liver tissue.

spite of ongoing cycles of chemotherapy (cyclophosphamide, vincristine and dacarbazine). She finally died due to a brain hemorrhage triggered by a hypertensive crisis 3 years after the second operation.

DISCUSSION

Pheochromocytoma is an endocrine tumor arising from the chromaffin cells of the adrenal medulla[1]. Distant metastasis occurs in approximately 10% of cases, resulting in a diagnosis of malignant pheochromocytoma. It is important to consider the possibility of malignant disease even if imaging only detects a primary tumor, but it is difficult to predict malignant potential[3,4]. A previous report documented that the expression of telomerase activity clearly suggests malignant behavior of the component cells[3]. We speculate that analysis of telomerase activity in the biopsy or resected specimens may predict the disease course and may be useful for deciding therapeutic strategies, including surgical procedures and postoperative therapy. We understand that liver metastasis should be considered as the systemic disease. We speculate that more aggressive adjuvant chemotherapy will be required in cases with increased telomerase activity, even in the pheochromocytoma without distant metastasis.

Pheochromocytoma may lead to a fatal hypertensive crisis during anesthesia and other stresses[5]. Surgery to resect tumors can cause unexpected oversecretion of catecholamines and severely raise systolic blood pressure[2,5,6], and it is important to try to avoid such hypertension. In our institution, the drainage vein (*i.e.*, the adrenal vein) is ligated as soon as possible during surgery, followed by ligation of the adrenal artery. We suggest that this isolation technique is useful for the prevention of hypertension and in this case, systolic blood pressure stayed less than 200 mmHg.

Close follow-up is crucial for adequate induction of additional therapies after surgery[2,3]. In our institution, catecholamine levels are checked monthly and image studies are scheduled every three months. In this case, we followed this patient more closely, based on the expression of telomerase activity. Malignant potential based on the expression of telomerase activity may be informative for the follow-up schedule in each case.

The fatal manifestation of pheochromocytoma is hypertension due to the oversecretion of catecholamines[1,2]. Current therapies for pheochromocytoma and close long-term follow-up can result in good survival rates[6-8], even although patients with recurrence eventually die due to hypertensive crisis. The liver is the most common site of pheochromocytoma metastasis. Safe techniques for extended hepatectomy and preoperative PTPE are well established. Hepatectomy is a therapeutic option for reduction of tumor mass in patients with liver metastases, even if preoperative PTPE is required for postoperative safety, and may prolong survival or the symptom-free period.

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5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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