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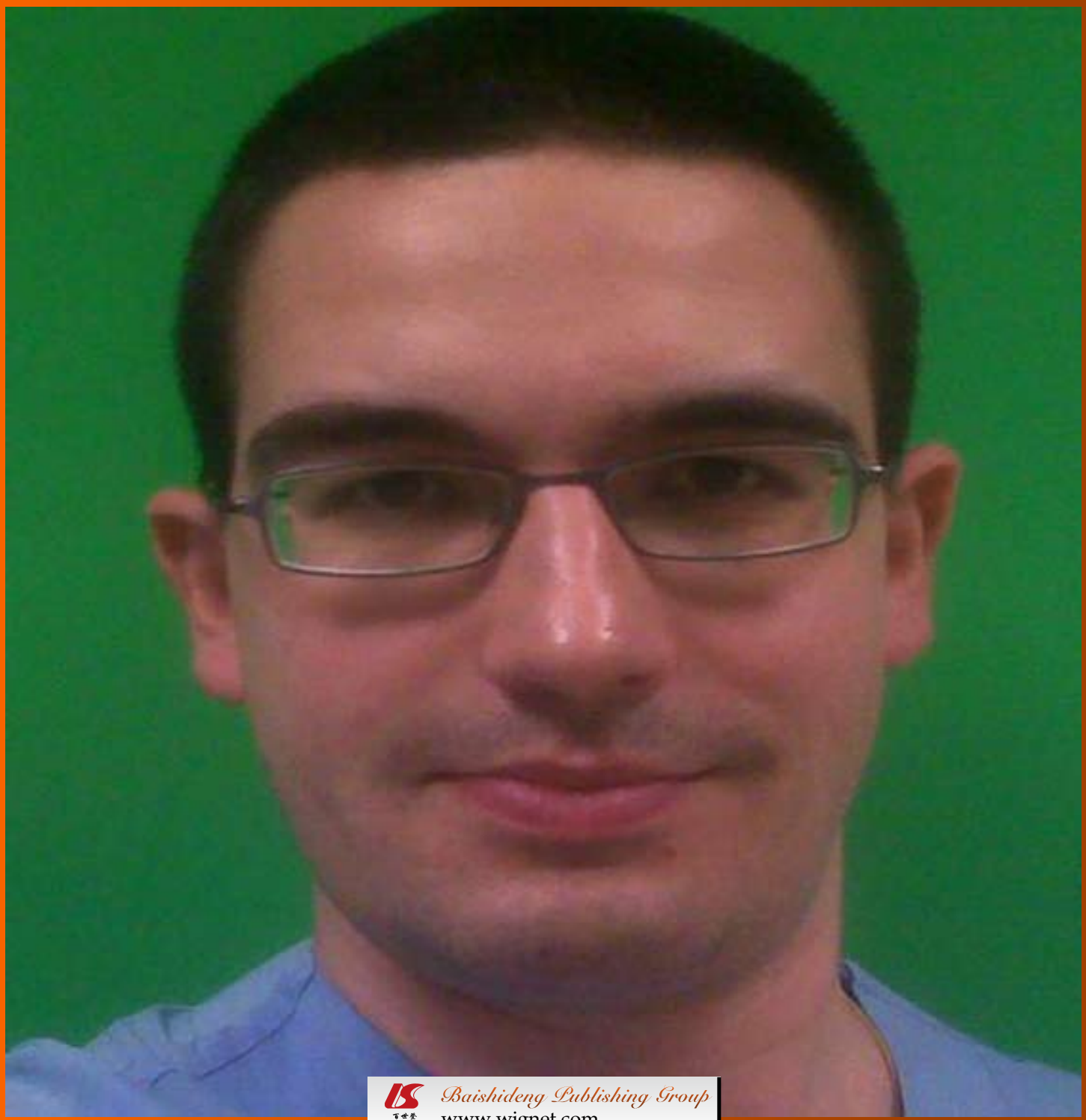

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MINIREVIEWS

Multimodal treatment of gastric cancer

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Abstract

Gastric cancer is the second leading cause of death from malignant disease worldwide. Although complete surgical resection remains the only curative modality for early stage gastric cancer, surgery alone only provides long-term survival in 20% of patients with advanced-stage disease. To improve current results, it is necessary to consider multimodality treatment, including chemotherapy, radiotherapy and surgery. Recent clinical trials have shown survival benefit of combining different neoadjuvant or adjuvant protocols compared with surgery with curative intent. Furthermore, the implementation of chemotherapy with novel targeted agents could play an important role in the multimodal management of advanced gastric cancer. In this paper, we focus on a multidisciplinary approach in the treatment of gastric cancer and discuss future strategies to improve the outcome for these patients.

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Key words: Gastric cancer; Gastrectomy; Lymphadenectomy; Multimodal treatment; Adjuvant therapy; Neoadjuvant therapy; Chemotherapy; Radiotherapy; Targeted therapy

Core tip: It is necessary to consider multimodality treatment, including chemotherapy, radiotherapy and surgery, to improve current results of gastric cancer treatment. Recent clinical trials have shown survival benefit combining different neoadjuvant or adjuvant protocols compared with curative surgery. Furthermore, the implementation of chemotherapy with novel targeted agents could play an important role in the multimodal management of advanced gastric cancer. In this paper, we focus on a multidisciplinary approach in the treatment of gastric cancer and discuss future strategies to improve the outcome for these patients.

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INTRODUCTION

Gastric cancer is one of the most common cancers worldwide and the second leading cause of death from malignant disease. This mortality data is explained by a late diagnosis. The incidence justifies screening programs only in Asia; in other parts of the world, gastric cancer remains a healthcare dilemma. In fact, in Japan and South Korea, the diffusion of endoscopy for gastric cancer resulted in 50% of patients with early disease (*i.e.*, T1 tumors). Conversely, in Europe and the United States, more

than two thirds of gastric cancers are found in advanced stages and most of these patients have a locally advanced resectable disease. Surgery with D2 nodal dissection is the primary treatment for patients with resectable cancer, with only a-5-year survival rate of 25.7% in locally advanced disease in these countries. To improve survival multimodal treatment has been used as an adjunct to surgery in recent years. In this review, we present a short analysis of high evidence level contributions published in the literature (phase-Ⅲ randomized controlled trials) on this topic.

POSTOPERATIVE THERAPY: CHEMORADIOTHERAPY

The role of adjuvant chemoradiotherapy (CRT) was established by the SWOG 9008/INT-0116 trial[1]. In this study, patients with completely resected gastric and esophagogastric junction (EGJ) adenocarcinoma were randomized to receive surgery alone or surgery plus postoperative chemoradiation [bolus 5-fluorouracil (5-FU) and leucovorin before and after chemoradiation with the same combination]. Overall survival was 27 mo in the group that received surgery alone and 36 mo in the group that received adjuvant CRT. After ten years follow-up, overall survival advantage is confirmed in favor of adjuvant CRT[2]. This trial has been criticized because the surgical procedure was considered inadequate since only 10% of patients had the recommended extended lymph node dissection (D2) and the combined modality arm reported a high rate of acute toxicity, probably due to the large field of irradiation and to the RTX technique used.

In the CALGB 80101 trial[3], postoperative CRT with epirubicin, cisplatin and 5fluorouracil (ECF) before and after CRT with concurrent infusional fluorouracil did not improve survival compared to bolus 5-FU-LV before and after 5-FU-RT (INT regimen).

More recently, the role of adjuvant CRT has not been confirmed. In the ARTIST trial[4], the authors investigated the role of postoperative CRT in addition to chemotherapy (cisplatin, capecitabine) in patients with curatively resected gastric cancer with D2 lymph node dissection. In this study, CTR did not significantly reduce recurrence compared to chemotherapy alone. Stratified analysis showed that the 3 year disease free survival rate was better in the CRT group in patients with positive lymph nodes.

Pending the results of ongoing clinical trials, we can conclude that while postoperative CRT is considered a standard therapy in the United States, in Europe it remains an effective and preferred treatment after D0 or D1 dissection and R1 resection, but not after D2 dissection[5], when the role of adjuvant chemotherapy is demonstrated.

POSTOPERATIVE THERAPY: CHEMOTHERAPY

The role of adjuvant therapy in GC has been studied during the past three decades in an attempt to improve the prognosis of patients who have undergone curative surgery. A recent meta-analysis[6] suggested a survival benefit with adjuvant chemotherapy based on fluorouracil regimens (HR = 0.82, 95%CI: 0.75-0.9, $P < 0.001$).

These results were recently confirmed by the CLASSIC and the ACTC-GC trial. The ACTS-GC study conducted in Japan demonstrated that adjuvant chemotherapy with 1 year treatment of S-1, an oral fluoropyrimidine, showed a significant benefit for gastric cancer with stage II and III who underwent gastrectomy with extended (D2) lymph node dissection, with a 3-year-overall survival (OS) for S-1 group of 80.1% compared with 70.1% for controls. The study was prematurely stopped by the Data and Safety Monitoring Committee because active treatment exceeded the efficacy threshold. The comparison of this study with those done in Western countries is difficult because of differences in survival rates, early detection rates and surgical techniques between Western and Asian countries.

Furthermore, S-1 remains an investigational agent in North America due to biological differences of how the drug is metabolized between patient populations[7].

In the CLASSIC trial[8] conducted in South Korea, China and Taiwan, patients with stage Ⅱ-ⅢB gastric cancer who underwent curative gastrectomy (D2 dissection) were randomized to surgery alone or postoperative chemotherapy with capecitabine and oxaliplatin (XELOX). The primary endpoint of the 3 year disease free survival (DSF) rate was 74% in the XELOX group and 59% in the surgery only group (HR = 0.56); stratified analysis revealed a significant difference between the two groups in stage Ⅲ disease.

However, there is no currently recognized standard regimen, particularly in countries where D2 dissection is a routine procedure.

The ITACA-S trial[9] was published during the last year in which the authors assessed whether a more intensive postoperative chemotherapy than fluoropyrimidine improves effectiveness. Patients radically resected for gastric or GEJ (≥ D1 node dissection) pN0 with pT > 2b or pN+ were randomized to receive CPT-11, LV, 5-FU for 4 cycles (FOLFIRI regimen) followed by docetaxel, cisplatin for 3 cycles or to LV, 5-FU (De-Gramont regimen) for 9 cycles. With a median follow-up of 49 mo, the use of an intensive treatment did not result in a significant prolongation of DFS and OS when compared to the De-Gramont regimen.

In conclusion, adjuvant chemotherapy with fluoropyrimidine is associated with improvement in overall survival and is recommended after complete resection in patients with stage ≥ I B who have not received perioperative treatment. The data seem to also confirm this benefit in patients treated with extended lymph node dissection.

PERIOPERATIVE THERAPY: NEOADJUVANT CHEMOTHERAPY

Neo-adjuvant chemotherapy (CHT) has been shown to

increase the rate of complete tumor resection, to reduce the incidence of systemic metastases and, probably, to prolong survival. Overall, the data indicate that neo-adjuvant CHT is feasible, does not increase post-operative morbidity and mortality, and is able to increase the rate of R0 resection.

The MAGIC trial[10] evaluated the efficacy of a perioperative CHT. Five hundred and three patients with potentially resectable GC were randomly assigned to both preoperative and postoperative cisplatin, epirubicin and 5-FU (ECF) CHT versus surgery alone. The results evidenced a statistically significant improvement of the ECF arm in progression free survival (PFS) (HR = 0.66; 95%CI 0.53-0.81) and OS (HR = 0.75; 95%CI: 0.60-0.93; 5 year OS 36% *vs* 23%). The resected tumors were significantly smaller and less advanced in the perioperative CHT group.

The two groups had a similar incidence of postoperative complications and mortality rates and, additionally, the completion rate of 3 course preoperative CHT was 86%, while only 42% of the patients completed postoperative ECF therapy.

Recently, in the FNCLCC/FFCD TRIAL[11], 224 patients with resectable adenocarcinoma of the lower esophagus, GEJ or stomach were randomized to either perioperative chemotherapy with cisplatin and 5fluorouracil continuous intravenous infusion plus surgery or surgery alone. The multimodal treatment significantly increased the curative resection (84% *vs* 74%; $P = 0.04$), disease free (5 year rate: 34% *vs* 19%; $P = 0.003$) and overall survival (5 year rate: 38% *vs* 24%; $P = 0.02$) rates.

We are awaiting the results of the ongoing CRITICS trial that compares three cycles of preoperative polychemotherapy followed by surgery and then randomised between adjuvant chemotherapy and CRT.

In our institution, we are involved in the multicentric randomized phase Ⅲ study ITACA-S-2 that compares the efficacy of a perioperative versus a postoperative CHT treatment in patients with operable gastric cancer and assesses the benefit of a postoperative CRT.

According to published data, perioperative chemotherapy is considered the preferred option in most of Europe and the United Kingdom, but we believe that each patient should be assessed within a multidisciplinary team, waiting the pending data of ongoing trials.

MOLECULAR TARGETED AGENTS

Recently, new elements have emerged which have shown the benefit of molecular targeted agents (MTA) in the treatment of advanced gastric cancer. human epidermal growth factor receptor 2 (HER2) overexpression has been reported in 13%-20% of gastric cancer specimens and is associated with a poor prognosis. Trastuzumab is a humanized monoclonal antibody that selectively blinds to the human epidermal growth factor receptor type 2. Based on results obtained in the treatment of HER2 positive breast cancer, the role of trastuzumab has also been studied in gastric cancer. The ToGA trial[12] randomised 594 patients with HER2 positive locally advanced, recurrent and metastatic gastric and EGJ cancer to receive trastuzumab, plus chemotherapy (cisplatin and fluorouracil or capecitabine) or CHT alone. Overall survival was 11.1 mo in patients who received chemotherapy alone and 13.8 mo in patients who received chemotherapy plus trastuzumab. This result established trastuzumab in combination with chemotherapy as the standard of care for first line treatment of HER2 positive advanced gastric cancer. According to the results obtained in metastatic settings, further clinical trials should be undertaken to evaluate the role of MTA in the perioperative setting.

Conversely, anti epidermal growth factor receptor and vascular endothelial growth factor antibodies that are widely used in advanced colon cancer have failed to improve overall survival of patients in association with chemotherapy.

CONCLUSION

The management of gastric cancer has been evolving during the last years. Clinical data demonstrated that a multimodal approach is mandatory to achieve maximum clinical benefit; therefore, it is desirable that each center has a multidisciplinary team which should include a surgeon, gastroenterologist, medical and radiation oncologist and pathologist. An adequate selection of the patients is mandatory to optimize clinical results. To obtain this endpoint, it is critical to make an accurate and strict patient selection by a correct staging of the disease, which has to take laparoscopy into account.

We recognize that increasing numbers of patients in controlled clinical trials is essential to improve our knowledge about the best clinical practice.

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RETROSPECTIVE STUDY

Short-term efficacy of laparoscopy-assisted *vs* open radical gastrectomy in gastric cancer

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Abstract

AIM: To investigate the short-term benefits of laparoscopic radical gastrectomy (LARG) and open radical gastrectomy (ORG) in patients with gastric cancer.

METHODS: A total of 400 patients with gastric cancer aged ⩽ 65 years who were treated at General Hospital of Lanzhou Military Region were enrolled. Among these, 200 patients underwent LARG between October 2008 and August 2012 (LARG group); and 200 patients underwent ORG between March 2000 and September 2008 (ORG group). The short-term therapeutic benefits between the two groups were analyzed.

RESULTS: The LARG procedure offered significantly better benefits to the patients compared to the ORG procedure, including less intraoperative blood loss (103.1 ± 19.5 mL *vs* 163.0 ± 32.9 mL, $P < 0.0001$), shorter postoperative hospital stay (6.8 ± 1.2 d *vs* 9.5 ± 1.6 d, $P < 0.0001$), less frequent occurrence of postoperative complications (6.5% *vs* 13.5%, $P = 0.02$), shorter time to mobilization (1.0 ± 0.3 *vs* 3.3 ± 0.4 d, $P < 0.0001$), shorter time to bowel opening (3.3 ± 0.7 d *vs* 4.5 ± 0.7 d, $P < 0.0001$), and shorter time to normal diet (3.0 ± 0.4 *vs* d 3.8 ± 0.5 d, $P < 0.0001$). However, LARG required a longer time to complete than the ORG procedure (192.3 ± 20.9 min *vs* 180.0 ± 26.9 min, $P < 0.0001$).

CONCLUSION: Compared to ORG, LARG is safer, more effective, and less invasive for treating gastric cancer, with better short-term efficacy.

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Key words: Laparoscopic surgery; Gastric cancer; Short-term efficacy; Open surgery

Core tip: We compared patients who underwent laparoscopic-assisted radical gastrectomy (LARG) with those who underwent open radical surgery (ORG) in terms of intra- and postoperative benefits. LARG was successfully completed without needing to convert to laparotomy in all patients, and no residual cancerous tissues were noted in the surgical margins. LARG offered the patients several better short-term benefits compared to the ORG procedure, such as less intraoperative blood loss, shorter hospitalization time, shorter time to mobilization, and shorter time to bowel opening. Additionally, LARG was also associated with fewer postoperative complications.

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INTRODUCTION

Gastric cancer is one of the most common malignant tumors worldwide, with a yearly incidence of about 900000. In China, > 400000 cases of gastric cancer are diagnosed annually, and the mortality rate is estimated to be 25.2/100000, which accounts for 23.3% of cancer-related mortality[1]. The 5-year survival rate is about 95% for early gastric cancer but, in patients with advanced gastric carcinoma, the 5-year survival falls to < 50%[2]. In China, > 90% of gastric cancer patients are diagnosed at an advanced stage when they first present[1].

At the present time, radical surgery is the only effective treatment for early gastric cancer with a potential to cure the disease[3]. Since its seminal application in patients with advanced gastric cancer in 1991 by a group of Japanese surgeons[4], laparoscopic radical gastrectomy (LARG) has been increasingly used as a promising approach for the management of gastric cancer because of its minimal invasiveness and its potential to treat successfully patients with lymph node metastasis[5,6]. However, LARG is technically demanding and requires a long learning curve[4,7].

Although LARG and laparoscopic D2 gastrectomy have now been widely used in the treatment of gastric cancer, including advanced gastric carcinoma, the short- and long-term benefits are unclear. The short-term outcomes of LARG have recently been reported, although these studies were based on small samples.

In the current study, we compared the short-term outcomes between LARG and open radical gastrectomy (ORG) in patients with gastric cancer in our department.

MATERIALS AND METHODS

Patient selection criteria

A total of 200 patients with gastric cancer who were treated with LARG after 2008 were randomly selected (LARG group). Tumors were located in the antrum (n = 95), cardia-fundus (n = 56), and corpus (n = 49) of the stomach. Pathological diagnosis of gastric cancer was confirmed in all patients using gastroscopic biopsy specimens. These samples included adenocarcinoma (n = 156), signet ring cell carcinoma (n = 15), adenosquamous carcinoma (n = 6), squamous cell carcinoma (n = 8), carcinoid (n = 4), and undifferentiated carcinoma (n = 11). The pathological classification was based on the 2010 World Health Organization (WHO) classification[8].

We also randomly selected 200 patients with gastric cancer who were treated with ORG between 2000 and 2008 (ORG group). Within this group, tumors were located in the antrum (n = 91), cardia-fundus (n = 58), and corpus (n = 51) of the stomach. Pathological diagnosis was confirmed in all patients using gastroscopic biopsy specimens, including adenocarcinoma (n = 162), signet ring cell carcinoma (n = 10), adenosquamous carcinoma (n = 7), squamous cell carcinoma (n = 6), carcinoid (n = 7), and undifferentiated carcinoma (n = 8), based on the 2010 WHO classification[8].

Surgical procedures

Patients fasted for 24 h prior to surgery. Following general anesthesia and endotracheal intubation, patients were placed in the supine position with their legs apart. A small subumbilical arc incision of 1 cm was made, and a pneumascos needle was inserted to generate CO_2 pneumoperitoneum, which was maintained at 12-14 mmHg during surgery. A 10-mm trocar was inserted into the same incision, and laparoscopy-assisted examination was performed to assess visually the extension, diameter, and location of the lesion. Tumor metastasis, serous layer invasion, adhesion to adjacent tissues, and organs were also carefully examined to determine the best angle of approach. A 12-mm trocar was inserted at the junction of the left lower costal margin and anterior axillary line to conduct the operation. Three 5-mm trocars were inserted through the abdominal wall; one at the level of the umbilicus at the left midclavicular line; one at the junction of the right lower costal margin and right midclavicular line; and one at the junction of the right lower costal margin and anterior axillary line. The operator was standing on the left side of the patient, while one assistant was standing on the right side, and another assistant who was holding the laparoscope was standing between the patient's legs. Blocking glue was used at the serous layer of the tumor to prevent implantation metastasis, and biological glue was used to seal the anastomosis after the tumor was removed completely to prevent the formation of anastomotic leakage or stump fistula.

Radical distal subtotal gastrectomy

The greater omentum was resected off the transverse colon using an ultrasonic knife along the border of the transverse colon. The dissection was continued to the left toward the splenic flexure, and to the right toward the origin of right gastroepiploic artery. The anterior lobe of the transverse mesocolon and pancreatic capsule were also resected, and lymph nodes along the middle colic artery were removed. The right gastroepiploic artery and the right gastro-omental vein were isolated and resected after ligation using titanium clips, and lymph nodes (Group 6) were removed. The greater omentum was pulled to the front of the stomach, and the stomach was gently picked up. The common hepatic artery, splenic artery, and left gastric artery were dissected, and the lymph nodes of Groups 8, 11, 7 and 9 were removed. The left gastric artery was ligated by two titanium clips and resected. The hepatogastric ligament and right gastric artery were resected along the lesser curvature, and the lymph nodes of Groups 5, 12, 3, 1 and 4 were removed. A longitudinal incision of 5 cm was made in the center of the upper abdomen. After an incision protective layer

Table 1 Patients characteristics *n* (%)

	LARG	ORG	*P* value
Sex (male/female)	109/91	112/88	0.84
Age (yr)	58.3 ± 6.5	58.6 ± 6.3	
Pathological type			
Well-differentiated adenocarcinoma	49 (24.5)	38 (19.0)	0.32[1]
Moderately-differentiated adenocarcinoma	23 (11.5)	31 (15.5)	
Poorly-differentiated adenocarcinoma	115 (57.5)	122 (61.0)	
Signet ring cell carcinoma	13 (6.5)	9 (4.5)	
Classification (T)			
T1	18 (9.0)	15 (7.5)	0.86[2]
T2	89 (44.5)	91 (45.5)	
T3	93 (46.5)	94 (47.0)	
Lymph node metastasis			
N0	13 (6.5)	11 (5.5)	0.90[3]
N1	88 (44.0)	91 (45.5)	
N2	99 (49.5)	98 (49.0)	
Clinical stage			
Ⅰ + Ⅱ	91 (45.5)	89 (44.5)	0.92
Ⅲ + Ⅳ	109 (54.5%)	111 (55.5)	

[1]Well-differentiated adenocarcinoma group of LARG and ORG; [2]T1 group of LARG and ORG; [3] Ⅰ + Ⅱ group of LARG and ORG. LARG: Laparoscopic radical gastrectomy; ORG: Open radical gastrectomy.

was placed, the stomach was pulled out of the abdominal cavity, and the distal part of the stomach was resected. A Billroth Ⅰ or Ⅱ reconstruction was then performed. The abdominal cavity was perfused with low-permeability, warm sterilized distilled water for 30 min. The distilled water was discarded, and the peritoneal cavity was perfused with 1 g Tegafur and 0.3 g leucovorin in 250 mL saline. The abdomen was closed after drainage tubes were placed.

Radical proximal subtotal gastrectomy

The greater omentum, anterior lobe of the transverse mesocolon, and pancreatic capsule were isolated along the border of the transverse colon to the splenic flexure, and the right gastroepiploic hemal arch was kept intact at the distal greater curvature. The lymph nodes of Groups 6 and 4 were removed. The splenic flexure was isolated, and the left gastroepiploic artery and vein were dissected. The short gastric vessel was resected at the origin. The splenic artery was isolated and the lymph nodes of Groups 11 and 10 were removed. The stomach was isolated from the gastric fundus and posterior stomach, and the lymph nodes of Groups 8, 9 and 7 were removed. The lesser omentum was isolated along the inferior border of the liver, 5 cm of the esophagus was exposed, and the cardia was dissected. The anterior and posterior vagal trunks were resected, and the lymph nodes of Groups 1-3 were removed. A longitudinal incision of 5 cm was made in the center of the subcostal area. The same procedures to protect the incision were performed as for radical distal subtotal gastrectomy as described above, and the stomach was pulled out of the abdominal cavity. After the proximal part of the stomach was resected, the anterior wall of the residual stomach was resected, and staples were placed. The esophagus and residual stomach were anastomosed, and the anterior wall of the stomach was stitched. The abdominal cavity was perfused with low-permeability, warm sterilized distilled water for 30 min. The distilled water was discarded, and peritoneal perfusion with chemotherapy drugs was performed. The abdomen was closed after drainage tubes were placed.

Radical total gastrectomy

The veins and lymph nodes were isolated and removed in the same way as in subtotal gastrectomy. A longitudinal incision of 5-7 cm was made in the center of the upper abdomen. The same procedures were performed to protect the incision as in radical distal subtotal gastrectomy, and the stomach was pulled out of the abdominal cavity. The cardia was then resected, and the whole stomach and lymph nodes around the omentum were removed. Roux-en-Y reconstruction was performed. The abdominal cavity was perfused with low-permeability, warm sterilized distilled water for 30 min. The distilled water was discarded, and peritoneal cavity was perfused as described above. The abdomen was closed after drainage tubes were placed.

ORG

The operation was carried out under general anesthesia with endotracheal intubation. Patients were placed in the supine position. An incision of 15-20 cm was made in the center of the upper abdomen. Radical gastrectomy was performed as described above.

Outcomes

The readout outcomes selected to assess the therapeutic efficacy were: operation time, number of lymph nodes dissected, intraoperative blood loss, length of hospital stay, time to mobilization, time to bowel opening, and time to normal diet.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 (SPSS Inc., Chicago, IL, United States). Continuous data are presented as mean ± SD, and were analyzed using Student's *t* test. Categorical data are presented as proportions, and were analyzed using the χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

A total of 200 patients, including 109 men and 91 women with a mean age of 56.1 years (range: 23-63 years) were included in the LARG group. In the ORG group, there were 112 men and 88 women with a mean age of 56.3 years (range: 21-65 years). No significant differences were observed between the two groups in terms of age, sex, pathological type of tumor, depth of tissue invasion, lymph node metastasis, and clinical stage (Table 1).

Table 2 Comparison of surgical outcomes between laparoscopic radical gastrectomy and open radical gastrectomy groups

Outcomes	LARG	ORG	*P* value
Operation time (min)	192.3 ± 20.9	180.0 ± 26.9	< 0.0001
No. of lymph nodes removed	28.5 ± 4.5	28.3 ± 3.4	0.62
Intraoperative blood loss (mL)	103.1 ± 19.5	163.0 ± 32.9	< 0.0001
Bedbound time (d)	1.0 ± 0.3	3.3 ± 0.4	< 0.0001
Time to bowel opening (d)	3.3 ± 0.7	4.5 ± 0.7	< 0.0001
Length of incision (cm)	5.2 ± 0.7	17.8 ± 1.0	< 0.0001
Time to normal diet (d)	3.0 ± 0.4	3.8 ± 0.5	< 0.0001
Total hospital stay (d)	6.8 ± 1.2	9.5 ± 1.6	< 0.0001

LARG: Laparoscopic radical gastrectomy; ORG: Open radical gastrectomy.

Table 3 Comparison of postoperative complications between the two groups *n* (%)

Postoperative complications	LARG	ORG	*P* value
Decreased gastrointestinal motility	3 (1.5)	7 (3.5)	0.2
Anastomotic leakage/stump fistula	7 (3.5)	15 (7.5)	0.08
Poor incision healing	5 (2.5)	16 (8.0)	0.01
Pulmonary infection	4 (2.0)	19 (9.5)	0.001
Acute liver/kidney failure	1 (0.5)	4 (2.0)	0.18
Total	13[1] (6.5)	27[1] (13.5)	0.02

[1]Some patients had two or more concomitant complications. LARG: Laparoscopic radical gastrectomy; ORG: Open radical gastrectomy.

Major intraoperative characteristics and outcomes

LARG was successfully performed in the 200 patients without conversion to laparotomy. ORG was also successfully performed in 200 patients. No malignant tissues were found at the lower or upper resection margin in any of the patients.

Table 2 shows the treatment characteristics between the two groups. Longer time was needed for LARG than for ORG (192.3 ± 20.9 min *vs* 180.0 ± 26.9 min, respectively, $P < 0.0001$). A similar number of lymph nodes was removed by both approaches ($P = 0.62$). The LARG procedure was superior to ORG for several outcomes, including: less intraoperative blood loss (103.1 ± 19.5 mL *vs* 163.0 ± 32.9 mL, $P < 0.0001$); less bedbound time (1.0 ± 0.3 d *vs* 3.3 ± 0.4 d, $P < 0.0001$); less time to bowel opening (3.3 ± 0.7 d *vs* 4.5 ± 0.7 d, $P < 0.0001$); less time to normal diet (3.0 ± 0.4 d *vs* 3.8 ± 0.5 d, $P < 0.0001$); and shorter hospital stay (6.8 ± 1.2 d *vs* 9.5 ± 1.6 d, $P < 0.0001$). In addition, the incision length was shorter in the LARG group than in the ORG group (5.2 ± 0.7 *vs* 17.8 ± 1.0 cm, $P < 0.0001$), and fewer patients required special pain control in the LARG group than in the ORG group (39.5% *vs* 56.5%, $P = 0.0007$).

Postoperative complications

As shown in Table 3, significantly fewer patients in the LARG group suffered from poor incision healing (2.5% *vs* 8.0%, $P = 0.01$) and pulmonary infection (2.0% *vs* 9.5%, $P = 0.001$). Fewer patients experienced anastomotic leakage or stump fistula in the LARG group than ORG group, although the difference was not significant (3.5% *vs* 7.5%, $P = 0.08$). No difference was observed in the incidence of decreased gastrointestinal motility and acute organ (liver or kidney) failure between the LARG and ORG groups ($P > 0.05$). Overall, the LARG group was associated with less frequent complications than the ORG group was (13% *vs* 27%, $P = 0.02$).

DISCUSSION

We compared 200 patients who underwent LARG and 200 who underwent ORG in terms of their intra- and postoperative benefits. The laparoscopic procedures were successfully completed without needing to convert to laparotomy in all patients in the LARG group, and no residual cancerous tissues were noted in the surgical margins. Despite a significantly longer operation time with LARG, this approach offered the patients several better short-term benefits compared to the ORG procedure, such as less intraoperative blood loss, shorter hospitalization time, shorter time to mobilization, shorter time to bowel opening, and shorter time to normal dietary intake. Additionally, LARG was also associated with fewer postoperative complications.

Well-exposed surgical fields could help reduce blood vessel damage and reduce intraoperative blood loss. A satisfactory surgical field can be obtained using laparoscopy with the assistance of an ultrasonic knife and titanium clips, and this could greatly reduce intraoperative blood loss. Currently, the same surgical processes used in traditional radical gastrectomy are still used in LARG, including blood vessel ligation at the origin, excessive margin resection, and removal of perigastric lymphoid tissues. However, because LARG is performed with laparoscopic instruments inside the abdominal cavity, mechanic organ damage by direct contact with the stomach during surgery can be minimized.

The indications for LARG in the treatment of patients with gastric cancer vary among different centers. For example, Kitano *et al*[9] have suggested that LARG could be indicated for patients with advanced-stage gastric carcinoma with an invasion depth lower than T2[9,10], whereas Huscher *et al*[11] have suggested that LARG is the best choice for patients with advanced gastric carcinoma in whom tumor invasion has reached T3[11]. Based on our study, we believe that LARG is a safe, effective, and minimally invasive approach for treatment of gastric cancer, as previously reported[7,12,13]. The long-term efficacy of LARG in patients with gastric cancer has also been reported[10]. In this long-term follow-up study, no significant difference in the 5-year survival rate was observed between 136 patients with gastric cancer who underwent LARG and 120 who underwent ORG.

Currently, CO_2 pneumoperitoneum is widely used in LARG procedures. However, the use of CO_2 pneumoperitoneum could result in inhibition of the immune response in the abdominal cavity. In an animal experiment[14], a significant decrease in the number of CD4/CD8 cells was observed after the induction of CO_2 pneu-

moperitoneum. CO_2 pneumoperitoneum was also shown to inhibit macrophage activation in the abdominal cavity, and thus inhibit the release of tumor necrosis factor (TNF)-α and interleukin-1 by macrophages. Both macrophages and TNF-α play a potent role in the antitumor activity in the abdominal cavity[15].

During the treatment of malignant tumors using laparoscopy-assisted approaches, potential tumor implantation induced by the operation has been a major concern. Based on our study, the possible impact of CO_2 pneumoperitoneum on immune disturbance and possible implantation metastasis could not be determined. However, previous studies have reported no significant increase in metastasis implantation after LARG, and the rate of incision metastasis did not differ between patients who underwent and those who did not undergo CO_2 pneumoperitoneum during surgery[16]. Similarly, no implantation metastasis was found in patients treated with LARG in our study. We believe that gentle surgical maneuver without squeezing the tumor tissues, and withdrawal of the laparoscopic instruments only after the intra-abdominal gas is completely removed, are important.

In conclusion, LARG is a safe, effective, and minimally invasive approach for the treatment of gastric cancer. LARG may offer better short-term benefits to patients than ORG offers. Further studies are needed to investigate the long-term efficacy of the LARG approach.

COMMENTS

Background

Gastric cancer is one of the most common malignant tumors worldwide, with a yearly incidence of about 900000. Laparoscopic radical gastrectomy (LARG) has been increasingly used as a promising approach for the management of gastric cancer because of its minimal invasiveness and a potential to treat successfully patients with lymph node metastasis. Although LARG and laparoscopic D2 gastrectomy have now been widely used in the treatment of gastric cancer, including advanced gastric carcinoma, the short- and long-term benefits are unclear. The short-term outcomes of LARG have recently been reported, although these studies were based on small samples. In the current study, authors compared the short-term outcomes between LARG and open radical gastrectomy (ORG) performed in patients with gastric cancer in our department.

Research frontiers

LARG and laparoscopic D2 gastrectomy have now been widely used in the treatment of gastric cancer, including advanced gastric carcinoma. The research hotspot is how to investigate the short-term benefits of LARG and ORG in patients with gastric cancer.

Innovations and breakthroughs

Based on this study, authors believe that LARG is a safe, effective, and minimally invasive approach for the treatment of gastric cancer, as previously reported. The long-term efficacy of LARG in patients with gastric cancer has also been reported. In this long-term follow-up study, no significant difference in the 5-year survival rate was observed between 136 patients with gastric cancer who underwent LARG and 120 patients who underwent ORG. Well-exposed surgical fields could help reduce blood vessel damage and reduce intraoperative blood loss. A satisfactory surgical field can be obtained using laparoscopy with the assistance of an ultrasonic knife and titanium clips, and this could greatly reduce intraoperative blood loss. Currently, the same surgical processes used in traditional radical gastrectomy are still used in LARG, including blood vessel ligation at the origin, excessive margin resection, and removal of perigastric lymphoid tissues. However, because LARG is performed with laparoscopic instruments inside the abdominal cavity, mechanical organ damage by direct contact with the stomach during surgery can be minimized.

Applications

The results suggest that LARG is a safer, more effective, and less-invasive approach for treating gastric cancer with a better short-term efficacy.

Terminology

LARG: LARG is a novel minimally invasive surgical technique. It is associated with such advantages as less injury, reduced postoperative pain, lower impact on immune function, rapid recovery of gastrointestinal function, and short hospital study.

Peer review

The authors have performed a well-designed study and submitted a full detailed manuscript. The overall body of the article is fine and they have presented the results and discussion well.

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CASE REPORT

Pancreatic recurrence of intrahepatic cholangiocarcinoma: Case report and review of the literature

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Abstract

Intrahepatic cholangiocarcinomas (ICC) are malignant tumors arising from the intrahepatic bile ducts that frequently recur after resection. The main sites of recurrence are the remnant liver, lymph nodes and lungs. Metastasis to the pancreas has never been reported. This case describes a 24-year-old woman who underwent a hepatic lobectomy in 2008 for an ICC. Almost 4 years after her surgery she presented with a pancreatic mass and lung nodules. An endoscopic ultrasound guided fine needle aspiration of the pancreatic mass and a video-assisted thoracoscopic surgery resection for the lung nodules were performed for diagnostic purposes. Pathological analyses of specimens revealed recurrence of her primary ICC in both pancreas and lungs. Subsequently, the patient received systemic chemotherapy. The patient is currently off chemotherapy and remains well. Moreover, she is pregnant. This is the first report of an ICC with pancreatic metastasis.

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Key words: Intrahepatic cholangiocarcinoma; Recurrence; Liver resection; Pancreatic metastasis; Pulmonary metastasis

Core tip: Intrahepatic cholangiocarcinoma (ICC) is characterized by its high potential to metastasize. Most frequent sites for metastases are the remnant liver, lymph nodes and lungs. Metastasis to the pancreas has never been described. Although this may happen exceedingly rarely, hepatobiliary surgeons should be made aware that ICC can also metastasize to the pancreas.

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INTRODUCTION

Cholangiocarcinomas are malignant tumors arising from the biliary tree. They account for about 3% of all digestive cancers and are the second most common primary liver tumors following hepatocellular carcinoma. In the United States approximately 5000 new cases are diagnosed each year[1] but the frequency considerably varies worldwide[2,3]. There are well-established risk factors as well as controversial ones. The former include primary sclerosing cholangitis, parasitic infections and biliary anomalies whereas the latter include inflammatory bowel diseases, obesity, diabetes, smoking and liver inflammatory conditions such as cirrhosis, hepatitis C and hepatitis B (HBV)[2-4]. Cholangiocarcinomas are divided into three different types according to their anatomic location along the biliary tree: intrahepatic cholangiocarcinomas (ICC),

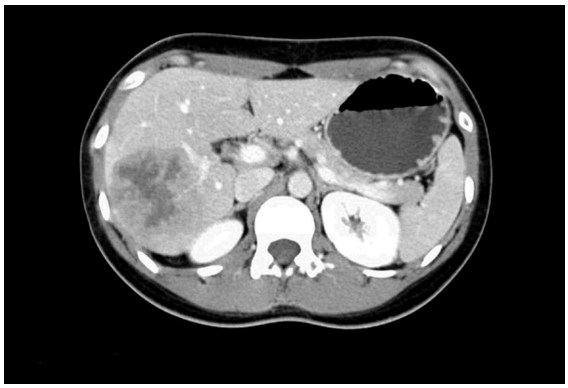

Figure 1 A computed tomography scan with nonionic contrast confirmed a mass located in the posterior right lobe within segments VI-VII and measuring 7.2 cm × 6.0 cm. The lesion demonstrated peripheral enhancement with central necrosis but no evidence for portal vein invasion. The hepatic veins were patent and no biliary dilatation was observed. No pulmonary lesion was highlighted.

perihilar or Klatskin tumor (PCC) and distal extrahepatic cholangiocarcinoma[5]. Tumor features and behavior seem to vary according to its type, thus, the importance of a precise classification that will influence the management and eventual outcomes. ICC are located above the second-order bile duct that represents the segregation point from PCC. They account for approximately 10%-20% of all primary liver cancers)[2-4] and their incidence has been reported to increase disturbingly, especially within Western countries[6-8]. It is also characterized by its poor prognosis despite liver resection although surgery is considered as the only curative treatment. Studies have reported a 3-year survival rate of 22%-55% after extended surgery[9-13] whereas survival rate without surgical treatment was much poorer at 7%-21%[8,9,12]. The reason for this could be that ICC are longer clinically silent being often diagnosed at an advanced stage but also their strong tendency to recur. Postoperative recurrences were mainly located in the remnant liver whereas extrahepatic recurrences especially involved lymph nodes, lungs and peritoneum[9,14]. To our knowledge there is no case of pancreatic metastasis from ICC being reported in the literature. Thus, this case report is the first to address this interesting issue.

CASE REPORT

In May 2008 a healthy 24-year-old Chinese woman longtime immigrant was referred to our Division for the investigation of a liver mass revealed by an ultrasound at an outside hospital, as part of her regular follow up for chronic hepatitis B. A computed tomography (CT) scan with nonionic contrast confirmed a mass within segments VI-VII measuring 7.2 cm × 6.0 cm. No lesion was observed in the lungs and her pancreas appeared normal (Figure 1). The patient had no health issue beside HBV, received no medication and had not undergone any surgery so far. Her brother also had HBV but her family history for liver cancer was negative. She presented without symptoms and was not icteric. Abdominal palpation was

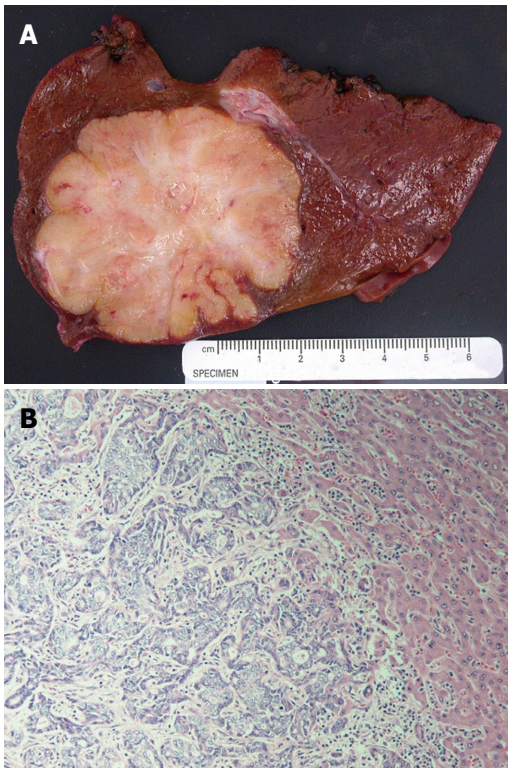

Figure 2 Photograph. A: Right lobe liver resection specimen showing a 6.0 cm × 5.5 cm × 5 cm well-circumscribed tumor with a firm, heterogeneous, yellow tan and white cut surface with areas of fibrosis. The surrounding liver is unremarkable; B: Representative photomicrograph of the tumor shows anastomosing glandular structures composed of highly pleomorphic epithelial cells in a desmoplastic stroma. The findings are consistent with intrahepatic cholangiocarcinoma (HE, original magnification × 200).

unremarkable with a negative Murphy's sign. Laboratory tests were performed and reported normal white cell count and hemoglobin. Kidney function and liver function were unremarkable. Tumors markers AFP and CA 19-9 were normal, 1.9 ng/mL and 8.4 U/mL, respectively. Based on the imaging studies, the pre-operative diagnosis was hepatocellular carcinoma. The patient underwent a right hepatic lobectomy and cholecystectomy. At surgery, the uninvolved liver appeared normal and there was no evidence of extrahepatic disease in the lymph nodes or anywhere else in the abdomen.

Pathology: A right liver lobe resection specimen was received and revealed a 6 cm × 5.5 cm × 5 cm white tan well-circumscribed firm mass with scalloped borders (Figure 2A). The tumor was 2 cm from the closest resection margin. Microscopically, the tumor consisted of moderately-differentiated intrahepatic cholangiocarcinoma characterized by anastomosing cords and glands with marked cytological atypical and embedded in dense stroma (Figure 2B). No lymphovascular invasion was noted. The bile duct margin was negative; no lymph nodes were identified from the hilar soft tissue that was entirely submitted. Carcinoma-*in-situ* and dysplastic changes involving adjacent bile ducts were seen. The uninvolved liver showed portal fibrosis but no portal inflammation. Rare ground-glass hepatocytes were idenfied. Immunohisto-

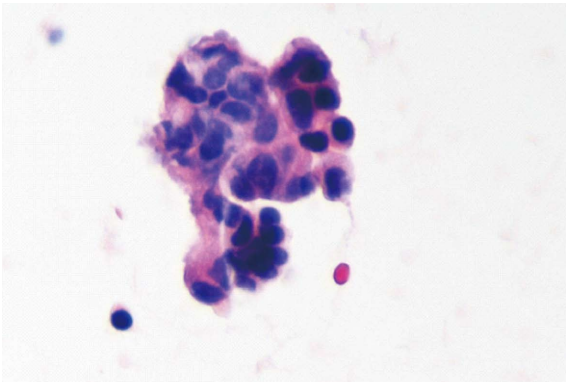

Figure 3 Endoscopic ultrasound-guided fine needle aspiration biopsy of pancreatic tail mass. Cytospin material showing a loose three-dimensional cluster of cells with high nuclear to cytoplasmic ratio, hyperchromasia, and eosinophilic cytoplasm. Several other clusters similar to these were found on the slide. The findings are consistent with adenocarcinoma compatible with metastatic cholangiocarcinoma.

chemical stain for hepatitis B surface antigen showed scattered hepatocytes with positive cytoplasmic staining, whereas hepatitis B core antigen was negative, findings that confirm hepatitis B infection.

The patient recovered with no complication and was discharged 5 d after surgery. She was then routinely followed-up with CT of the chest and abdomen, tumor markers and complete lab tests on an outpatient mode. In January 2012, approximately 2 mo after delivering her baby and almost 4 years after her prior surgery, a CT-scan of the abdomen performed in an outside hospital highlighted a pancreatic ductal dilatation, suspicious to be secondary to a mass in the tail of the pancreas and nine nodules on both sides of the chest; each lesion was then confirmed by a positron emission tomography-computed tomography. In order to determine the nature of the pancreatic lesion, an endoscopic ultrasound (EUS)-Fine needle aspiration (FNA) was performed. In order to clarify the nature of the lung nodules the patient underwent a left video-assisted thoracoscopic surgery wedge resection. The specimen revealed a white firm well-circumscribed lesion measuring 1 cm × 1 cm with free margins. The findings supported metastatic cholangiocarcinoma (Figure 3). Surgery having no role in systemic cholangiocarcinoma, our plan was to introduce chemotherapy with Gemcitabine/Cisplatin for 3 mo followed by restaging.

Currently, the patient is off chemotherapy and remains very well. She is pregnant G2P1, due to have a baby in March 2014.

DISCUSSION

Intrahepatic cholangiocarcinomas are malignant neoplasms arising from the biliary tree, beyond the second order[5]. They represent approximately 10%-20% of all primary liver cancers[2-4]. ICC include different growth types: mass-forming, periductal-infiltrating and intraductal-growth[5]. Furthermore, they display a very malignant potential leading to a high risk of recurrence and a poor prognosis. Surgery, *via* liver transplant and hepatic resection, is considered as the only curative treatment for ICC[15]. Notwithstanding long-term outcomes are still far from reaching the expectancy. Most patients with ICC present recurrence within 2 years after surgery[9,10,12,14]. Not surprisingly survival rates are low. Despite an aggressive approach Konstadoulakis *et al*[13] reported 1-year, 3-year and 5-year survival rates of 80%, 49% and 25%, respectively[13]. Many potential predictor factors have been suggested. Concerning the well-established ones, several studies demonstrated the negative impact of positive margins[8,12,13,16-18]. Lymph nodes metastasis has also been identified as negative predictive factor although the benefit of lymphadenectomy is still debatable[8,10,11,14,16,17]. Intrahepatic cholangiocarcinomas have the potential to invade Glissonean sheath[16] leading to hematogenous, lympatic or direct extension, causing dissemination of the disease. The absence of other lesion or peri-pancreatic adenopathy supports the hypothesis of hematogenous spreading although the dissemination pattern remains unclear in this case.

Concerning the liver lesion, as above mentioned, "carcinoma-in-situ and dysplastic changes involving adjacent bile ducts were seen". This finding supports the diagnosis of primary cholangiocarcinoma, rather than metastatic tumor. This finding, associated with cytological features: (high N/C ratios, pleomorphism and high mitotic rates), permit to confidently rule-out the differential diagnosis of cholangiolocellular carcinoma[19,20].

Considering the pancreatic lesion, its morphology has been compared with the hepatic one; they were considered similar. Unfortunately, no tissue from the pancreatic FNA specimen is available for immunohistochemical studies. If tissue was available we may have add breast cancer markers to rule out metastatic breast cancer that could be considered in a young female patient.

The metastatic lesion in the pancreas could be explained as hematogenous spread from lesions in the lungs.

In term of risk factors the patient was HBV carrier. The role of HBV in ICC needs to be clarified. Although several studies considered it as a risk factor[2-4], a recent study suggested HBV could be a favorable prognostic factor after resection[21]. Liver fluke infestation was not tested. The patient did not present any other major risk factor but her recent history of pregnancy should be addressed although its role remains uncertain. Little is known in this field but clinical courses of ICC worsened by gravid state have been reported[22,23]. Indeed the high concentration of estrogen and the suppression of the immune system arising from pregnancy could potentially promote recurrence of ICC like it can aggravate preexisting liver lesion[24]. Chemotherapy is considered as the standard care for extrahepatic recurrences while surgery is not the gold standard in these cases[15]. Nevertheless data are strongly limited in this field and further studies are needed, especially to assess to role of combining therapies that may play an increasing role in the future.

Considering the absence of reported pancreatic metastases from ICC, achieving an EUS-FNA in order to get a diagnosis was probably the correct strategy. Regarding the lungs nodules we decided to perform a video-assisted thoracoscopic surgery resection although they were highlighted on the PET/CT. Many other causes could explain lung nodules in a young Chinese patient. Therefore we needed a precise diagnosis of the lesion to decide whether the patient could be candidate to surgery or to systemic therapy. Yoon *et al*[25] reported a case of cholangiocarcinoma that metastasized to the pancreas, however they did not reported whether it was an intrahepatic, hilar or extrahepatic one[25].

In conclusion, the present case report describes a recurrence of intrahepatic cholangiocarcinoma in lungs and pancreas in a patient who underwent liver resection approximately 4 years previously. This is the first report of pancreatic metastasis from ICC.

ACKNOWLEDGMENTS

This case report was showed at the Swiss Congress of Surgery (Bern, June 2013) and the French Congress of Surgery (Paris, October 2013).

COMMENTS

Case characteristics

A 24-year-old woman was referred for a liver mass.

Clinical diagnosis

No symptom, no jaundice. Abdominal palpation was unremarkable with a negative Murphy's sign.

Differential diagnosis

Hepatocellular carcinoma.

Laboratory diagnosis

Laboratory tests were perfectly unremarkable.

Imaging diagnosis

A computed tomography scan with nonionic contrast confirmed a mass within segments VI-VII measuring 7.2 cm × 6.0 cm. No lesion was observed in the lungs and her pancreas appeared normal.

Pathological diagnosis

The tumor consisted of moderately-differentiated intrahepatic cholangiocarcinoma.

Treatment

Chemotherapy with Gemcitabine/Cisplatin.

Related reports

Intrahepatic cholangiocarcinomas (ICC) are malignant tumors arising from the intrahepatic bile ducts that frequently recur after resection.

Experiences and lessons

The present case report describes a recurrence of intrahepatic cholangiocarcinoma in lungs and pancreas in a patient who underwent liver resection approximately 4 years previously. This is the first report of pancreatic metastasis from ICC.

Peer review

This article shows the risk for intrahepatic cholangiocarcinoma to metastasize to the pancreas.

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CASE REPORT

Retroperitoneal paragangliomas: Report of 4 cases

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Abstract

We reviewed the data of all patients managed for retroperitoneal paragangliomas (PGLs) between June 2010 and June 2011 to present our experience concerning this uncommon entity to highlight diagnostic and therapeutic challenges of retroperitoneal PGLs. All patients were admitted to the department of general and hepatobiliary surgery in the regional hospital of Jendouba, Tunisia. The size of the tumor was taken at its largest dimension, as determined in a computed tomography (CT) scan and pathological reports. There were 4 patients (all women) with a median age of 48 years (range 46-56 years). Abdominal pain was the commonest presentation. CT showed and localized the tumors which were all retroperitoneal. All patients had successful surgical resection of the tumors under invasive arterial blood pressure monitoring. One patient underwent surgery for a presumed tumor of the pancreatic head. The fresh-mount microscopic study of the peroperative biopsy yielded inflammatory tissue without malignancy and no resection was performed. Final histological examination of the biopsy concluded PGL. A second laparotomy was performed and the tumor was entirely resected. The diagnosis was made after surgery by histology in all patients. The control of the blood pressure was improved after surgery in 3 patients. Paragangliomas are rare tumors. The retroperitoneal localization is uncommon. Complete surgical resection remains the only curative treatment but it is often challenging as these tumors are located near multiple vital blood vessels.

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Key words: Paraganglioma; Extra adrenal pheochromocytoma, Retroperitoneal; Surgery; Histology

Core tip: Retroperitoneal paragangliomas are uncommon tumors causing considerable difficulty in both diagnosis and treatment. Its complete surgical removal is often challenging as these tumors are located near multiple vital blood vessels. Any surgeon could face such a rare tumor.

Kallel H, Hentati H, Baklouti A, Gassara A, Saadaoui A, Halek G, Landolsi S, El Ouaer MA, Chaieb W, Maamouri F, Mannaï S. Retroperitoneal paragangliomas: Report of 4 cases. *World J Gastrointest Surg* 2014; 6(4): 70-73 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i4/70.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i4.70

INTRODUCTION

Paragangliomas (PGLs), or extra-adrenal phaeochromocytomas, are tumors arising from chromaffin tissues. Abdominal localizations are less frequent than head and neck. Retroperitoneal PGLs are more uncommon, causing considerable difficulty in diagnosis and treatment. In this article, we present our experience concerning this uncommon entity to highlight diagnostic and therapeutic

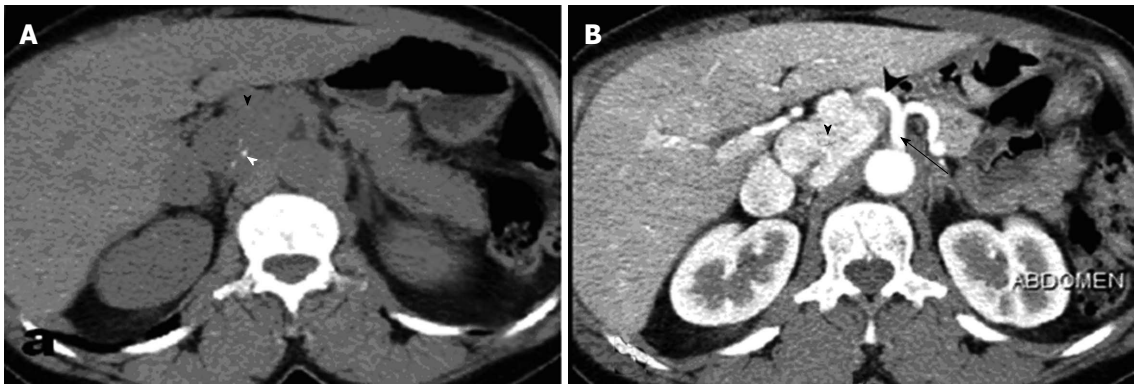

Figure 1 Abdominal computed tomography without (A) and after (B) contrast material administration, showing the tumor (arrowhead) with calcifications (white arrowhead) and precocious enhancement. Note the close tumoral relationship to the celiac trunk (black arrow) and hepatic artery (black arrowhead).

Table 1 Clinical features of the patients with paragangliomas

Patient	Age (yr)/sex	Abdominal pain	Hypertension	Palpitation	Headache	Sweating	Location	Size (cm)
1	54/F	Y	N	Y	N	Y	Celiac region	6
2	46/F	Y	Y	N	Y	N	Right para-aortic	4
3	56/F	Y	Y	Y	N	N	Retrocaval	5
4	48/F	Y	Y	N	Y	N	Near right adrenal Near pancreatic head	5

F: Female; Y: Yes; N: No.

challenges of retroperitoneal PGLs.

CASE REPORT

We reviewed the data of all patients managed for retroperitoneal PGLs between June 2010 and June 2011. All patients were admitted to the department of general and hepatobiliary surgery in the regional hospital of Jendouba, Tunisia. The size of the tumor was taken at its largest dimension, as determined in a computed tomography (CT) scan and pathological reports.

There were 4 patients (all women) with a median age of 48 years (range 46-56 years). The clinical features are shown in Table 1. Abdominal pain was the commonest presentation, followed by hypertension in 3 cases, headache and palpitation in 2 cases and sweating in 1 case. No abdominal mass was detected on palpation in any patient. Abdominal CT showed and localized the tumor in all patients. The tumor measured from 4 to 6 cm in diameter and showed obvious intensification after contrast material administration (Figure 1). All tumors were retroperitoneal. The diagnosis was evoked preoperatively by the CT data for the 3 first patients. Patient 4 underwent surgery for a presumed tumor of the pancreatic head. Surgical exploration revealed a soft mass of the pancreatic head without dilatation of the common bile duct. The fresh-mount microscopic study of the peroperative biopsy yielded inflammatory tissue without malignancy. No resection was performed. Final histological examination of the biopsy concluded PGL. A second laparotomy was performed. The tumor was adherent to the pancreatic parenchyma and the inferior vena cava. It was carefully dissected and entirely resected. Final histological examination of the specimen confirmed the diagnosis of PGL. All patients had successful surgical resection of the tumors under invasive arterial blood pressure monitoring. Complete surgical removal was difficult because the tumors were located near multiple vital blood vessels: celiac region for patient 1 (Figure 2A), right para aortic for patient 2, retrocaval for patient 3 (Figure 2B) and near the pancreatic head for patient 4. There was no evidence of malignancy, as judged by local infiltration or the presence of metastasis. The diagnosis was made after surgery by histology in all cases because of the unavailability of measurements of urinary and plasma adrenaline, noradrenaline and metanephrine concentrations in our hospital. Histology revealed a tumor composed of spindle to polygonal cells with abundant basophilic granular cytoplasm and moderate pleomorphism. The cell architecture was trabecular and nested, pathognomonic of paraganglioma (Figure 3). Low mitotic activity was observed and there was no capsular invasion. The tumor was encapsulated and demarcated from the surrounding effaced pancreatic parenchyma in patient 4. Tumor cells stained positively for synaptophysin, chromogranin and S100 in all cases (Figure 4). The morphological and immunohistochemical profile was consistent with extra-adrenal PGL. The control of the blood pressure was improved after surgery in 3 patients.

DISCUSSION

Retroperitoneal PGL is a rare pathological entity that occurs most often in young adults[1]. PGLs are often unique; multiple tumors are observed in only 10% of the

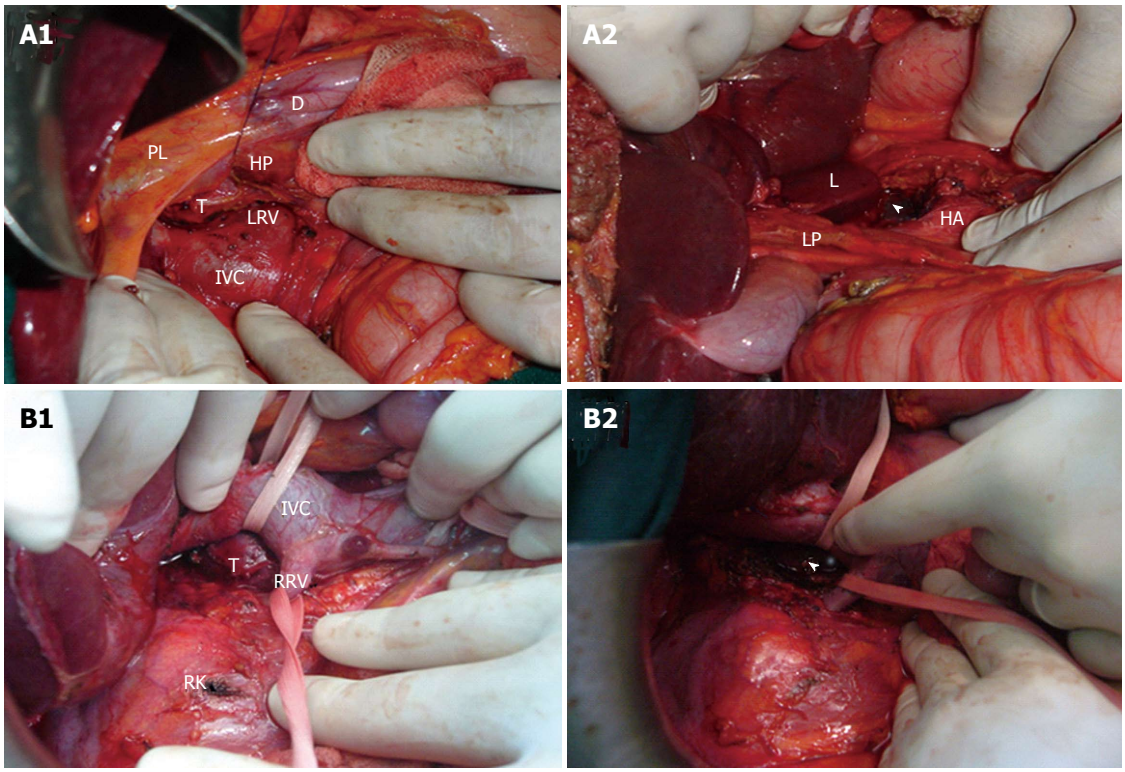

Figure 2 Operative view. A: Patient 1. A1: Separation of the tumor (T) from the anterior aspect of the inferior vena cava (IVC); A2: Surgical site after tumor resection (arrowhead); B: Patient 3. B1: Separation of the tumor (T) from the posterior wall of the IVC; B2: Surgical site after tumor resection (arrowhead). LRV: Left renal vein; D: Duodenum; HP: Head of the pancreas; PL: Liver pedicle; RRV: Right renal vein; RK: Right kidney; HA: Hepatic artery; LP: Liver pedicle; L: Liver (Lobe of Spiegel).

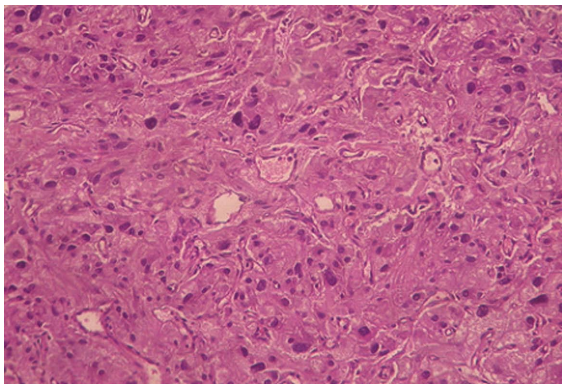

Figure 3 Microscopic view of paraganglioma. Large polygonal cells with granular cytoplasm arranged in nests (hematoxylin and eosin).

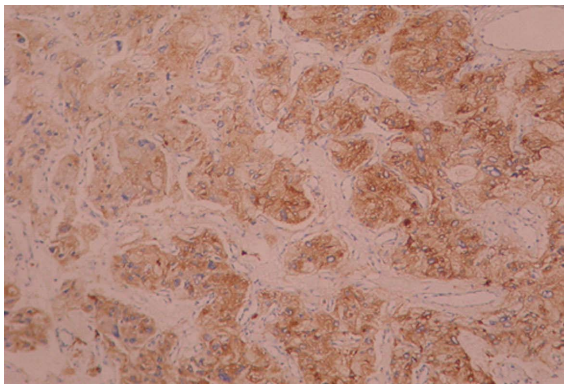

Figure 4 Immunohistochemistry. Tumoral cells strongly express anti-chromogranin antibody.

cases. Signs and symptoms are variable and frequently paroxysmal due to the variable and disorderly release of catecholamines by the tumor. The typical presentation is a combination of variable hypertension with paroxysmal symptoms, either occurring spontaneously or provoked by high abdominal pressure during anteflexion, urination or defecation[2]. The diagnosis of catecholamine-secreting tumors should be based on the determination of plasma or urinary metanephrine concentration[2]. Preoperative imaging tests are used to locate the tumor, to determine whether it is single or multiple, adrenal or ectopic, benign or malignant and isolated or present with other neoplasms in the context of familial syndromes. Magnetic resonance imaging is similar to CT in the diagnosis of PG, but it is preferred in children and pregnant women[2]. Some authors propose ^{123}I-MIBG scintigraphy to diagnose secreting PGLs, with a sensitivity and specificity of 90% and 99% respectively[1]. Complete surgical removal provides a 5 year survival of 75%. It is then considered as the only curative treatment of PGLs[1] but it is often challenging as these highly vascular tumors are located near multiple vital blood vessels. Preoperative pharmacological preparation is necessary. It has an important role in achieving the safest and most successful outcome[3]. Given the hypervascular aspect of the tumor, some authors propose pre-operative embolization. Laparoscopic

resection of PGL has been reported in the literature, with all the known advantages of the mini-invasive surgery. In our patients, we performed open surgery because of the localization of the tumor in contact with important vessels. PGLs also have potential to be malignant. It has been reported in the literature that around 20% of PGLs could be malignant with poor survival[4]. While histopathological findings are not very useful to differentiate between benign and malignant PGLs, extensive local invasion and distant metastasis have been used as indicators for malignancy[5-7]. Recurrences and malignancy are more frequent in cases with large or extra-adrenal tumors. Patients should be followed up indefinitely, particularly if they have inherited or extra-adrenal tumors.

In conclusion, paragangliomas are rare tumors with a limited number of cases reported. The localization in the retroperitoneal region is uncommon and is a challenge for surgical resection. Complete surgical resection remains the only curative treatment. Lifetime follow-up is necessary to detect recurrences.

COMMENTS

Case characteristics

There were 4 patients (all women) with a median age of 48 years (range 46-56 years). Abdominal pain was the commonest presentation. Computed tomography showed and localized the tumors which were all retroperitoneal.

Clinical diagnosis

One patient underwent surgery for a presumed tumor of the pancreatic head. The fresh-mount microscopic study of a preoperative biopsy yielded inflammatory tissue without malignancy and no resection was performed. Final histological examination of the biopsy concluded paragangliomas. A second laparotomy was performed and the tumor was entirely resected.

Differential diagnosis

The diagnosis was made after surgery by histology in all patients.

Experiences and lessons

The retroperitoneal localization is uncommon. Complete surgical resection remains the only curative treatment but it is often challenging as these tumors are located near multiple vital blood vessels.

Peer review

The authors report on a relatively uncommon condition. It would be worth detailing the histopathology and defining how this differs from other retroperitoneal neoplastic lesions.

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CASE REPORT

Recurrence of gastric cancer in the jejunal stump after radical total gastrectomy

Jong Han Yoo, Sang Hyuk Seo, Min Sung An, Tae Kwun Ha, Kwang Hee Kim, Ki Beom Bae, Chang Soo Choi, Sang Hun Oh, Young Kil Choi

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Author contributions: Yoo JH and Kim KH designed the report; Kim KH, Choi CS and Choi YK were the attending doctors for the patient; Kim KH and Choi YK performed the surgical operation; An MS, Ha TK and Bae KB organized the report; and Yoo JH and Seo SH wrote the paper; Oh SH organized the report.

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Key words: Gastric cancer; Recurrence; Jejunal stump

Core tip: In our study, there was a case of recurrence of gastric cancer in the jejunal stump after radical total gastrectomy with Roux-en-Y reconstruction. The patient underwent jejunal pouch resection, distal pancreatectomy and splenectomy. On histopathologic examinations, the patient was diagnosed with gastric cancer.

Yoo JH, Seo SH, An MS, Ha TK, Kim KH, Bae KB, Choi CS, Oh SH, Choi YK. Recurrence of gastric cancer in the jejunal stump after radical total gastrectomy. *World J Gastrointest Surg* 2014; 6(4): 74-76 Available from: URL: http://www.wjgnet.com/1948-9366/full/v6/i4/74.htm DOI: http://dx.doi.org/10.4240/wjgs.v6.i4.74

Abstract

This is a very rare case of the recurrence of gastric cancer in the jejunal stump after radical total gastrectomy with Roux-en-Y reconstruction. In January 2008, a 65-year-old man underwent radical total gastrectomy with Roux-en-Y reconstruction for stage I B gastric cancer of the upper body. At a follow-up in December 2011, the patient had a recurrence of gastric cancer on gastroduodenal fibroscopy. The gastroduodenal fibroscopic biopsy specimens show a well-differentiated tubular adenocarcinoma. Computed tomography showed no lymphadenopathy or hepatic metastases. At laparotomy, there was a tumor in the jejunal stump involving the pancreatic tail and spleen. Therefore, the patient underwent jejunal pouch resection, distal pancreatectomy and splenectomy. The patient was diagnosed with gastric cancer on histopathological examination.

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INTRODUCTION

Gastric cancer is a highly prevalent cancer that occurs the most commonly in Korea. It shows a very good prognosis when detected earlier in a regular medical check-up. In advanced cancer, however, a poor prognosis has been well documented. There are many recurrent cases of gastric cancer despite radical surgery. Its recurrence occurs through hematogenous, peritoneal dissemination or via the lymph nodes. We report a case of recurrence of gastric cancer in the jejunal stump after radical total gastrectomy with Roux-en-Y reconstruction.

CASE REPORT

A 65-year-old man presented with a recurrence on gastroduodenal fibroscopy (Figure 1) at a follow-up after gastric cancer surgery. He underwent radical total gastrectomy with Roux-en-Y reconstruction (end to side esophagojejunostomy with circular stapler), for gastric cancer detected on gastroduodenal fibroscopy in January 2008. The

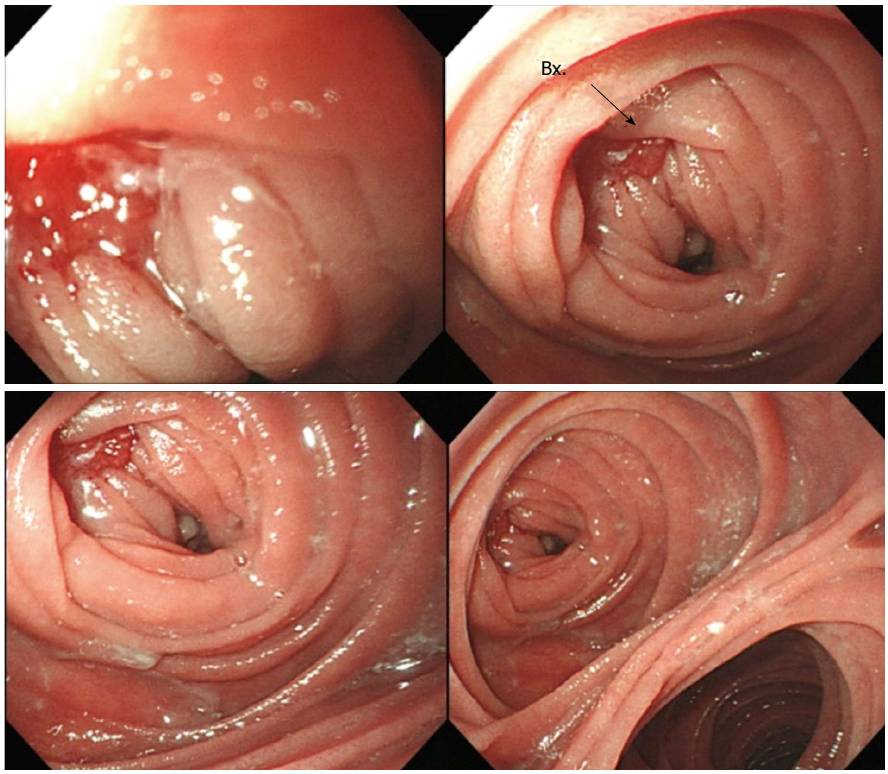

Figure 1 Endoscopic findings. There was a medium-sized single small polypoid infiltrative ill-defined mass, with nodular overlying mucosa without bleeding evidence at jejunal pouch (1.2 cm in diameter). Tubular adenocarcinoma, well differentiated.

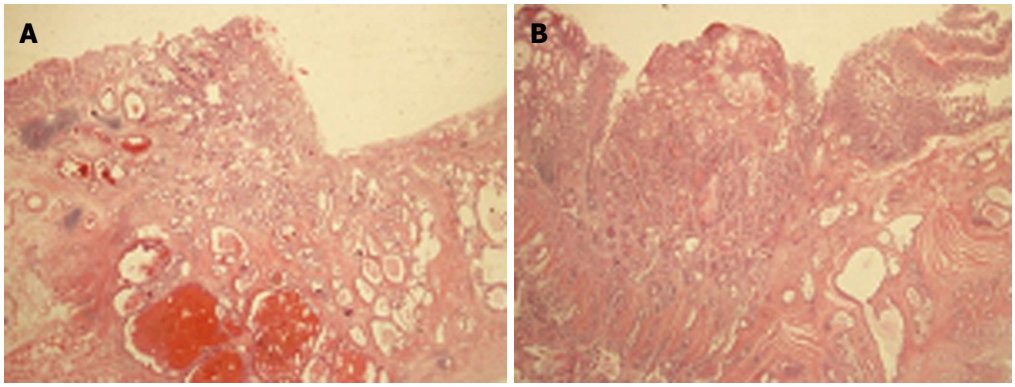

Figure 2 Pathological findings. A: January 2008, slide of gastric cancer lesion (primary lesion); B: December 2011, slide of jejunal stump lesion (recurrent lesion).

gastric cancer had a tumor node metastasis stage of IB (T2N0M0), which had lesions of 2.5 cm × 2.0 cm in size on the posterior wall of the upper part of the gastric fundus. Based on histopathology, findings were suggestive of well-differentiated tubular adenocarcinoma. There was no lymph node metastasis or metastasis to other organs in the abdomen (Figure 2). Postoperatively, the patient underwent an uneventful course without notable episodes and achieved a recovery. The patient had been taking oral chemotherapeutic drugs (5-fluorouracil) during a period ranging from January 2008 to December 2009. Following this, the patient had no recurrence and had an outpatient follow-up. Meanwhile, in December 2011, the patient had a single small polypoid infiltrative ill-defined mass of approximately 1.2 cm in size at the site approximately 3 cm from the distal part of the esophagojejunal junction to the blind loop (the posterior wall of the jejunal stump) on gastroduodenal fibroscopy (Figure 1). The patient therefore underwent histopathological examinations, presenting with findings suggestive of well-differentiated tubular adenocarcinoma. Therefore, the patient was admitted for further evaluation and treatment. At the time of admission, the patient had a good systemic and nutritional status with stable vital signs. On examination, the patient had no palpable left supraclavicular lymph nodes. On abdominal examination, the patient had no tenderness, shifting dullness or palpable abdominal masses. In addition, the patient also had no positive findings on rectal examination. The patient underwent clinical laboratory tests for hemoglobin, white blood cell counts, platelet

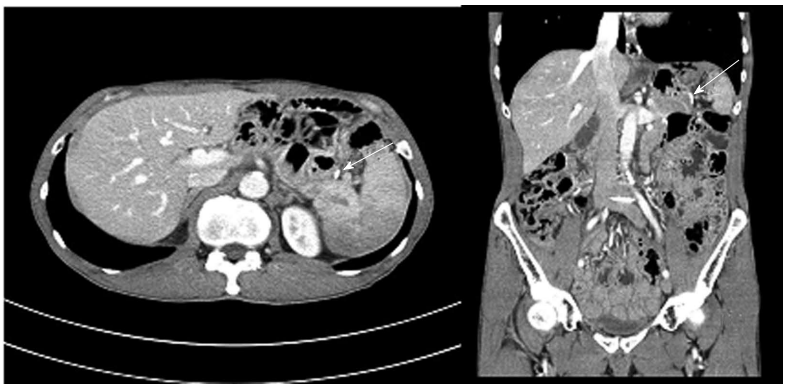

Figure 3 Pre-operation computed tomography findings. No evidence of local tumor recurrence or distant metastasis. Arrow: Distal jejunal stump stapling line (recurrence site).

counts, serum electrolytes, serum biochemistry, urinalysis, serological tests and blood coagulation tests, all of which were normal. Serum levels of carcinoembryonic antigen, a tumor marker, were 4.95 ng/mL. Abdominal computed tomography (CT) showed no recurrence and metastasis, which is also consistent with previous abdominal CT scans (Figure 3). Under general anesthesia, the patient underwent surgery for jejunal stump resection, distal pancreatectomy with splenectomy in January 2012. Intraoperatively, the patient presented with a tumor in the jejunum and invasion to the pancreatic tail and the spleen, with no evidence of hepatic or peritoneal recurrence, for which the patient underwent dissection of the jejunal stump, the pancreatic tail and the spleen. The postoperative course was uneventful. On histopathological examination, there was a recurrence of the gastric cancer in the jejunal pouch, the pancreatic tail and the spleen. Currently, the patient is receiving an injection of chemotherapy regimens (FOLFOX chemotherapy).

DISCUSSION

The local recurrence of gastric cancer after total gastrectomy mostly occurs in the proximal region from the esophagojejunal junction. Anastomotic or suture-line recurrence after gastrectomy is reported to be 3%-10%[1]. Recurrence in the distal jejunal stump is a rare entity. The main theory of the cause and mechanisms of recurrence includes submucosal or subserosal lymphatic spread of cancer, the remainder of the stump and the implantation of exfoliated cancer cells[1-3]. In this case, histological study revealed no lymph node metastasis and no vessel permeation. Both resection margins were also negative for cancer cells. For this reason, the theory of lymphatic spread of cancer and the remainder of the stump can be rejected. The implantation of exfoliated cancer cells may be the reason for recurrence but it is unclear. The recurrence of the anastomosis or suture-line is rare and its mechanism is unclear but local recurrence can be treated by surgery. So, an early diagnosis of local recurrence can improve the prognosis. Gastroduodenal fibroscopy can be useful to detect an intraluminal recurrence. CT or positron emission tomography (PET) can detect gastric bed or regional lymph nodes. We recommend that routine outpatient follow-up includes gastroduodenal fibroscopy, CT and PET.

COMMENTS

Case characteristics

A 65-year-old man presented with gastric cancer recurrence, as shown on gastroduodenal fibroscopy.

Clinical diagnosis

Histopathological examination revealed a diagnosis of gastric cancer.

Imaging diagnosis

Gastroduodenal fibroscopy, computed tomography and positron emission tomography.

Peer review

Yoo JH *et al* described a rare case of recurrence of gastric cancer in the jejunal pouch after radical total gastrectomy with Roux-en-Y reconstruction. This is an interesting case.

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CASE REPORT

Neuroendocrine carcinoma of the stomach: A case report

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Abstract

Neuroendocrine carcinoma (NEC) is a rare tumor, comprising < 1% of stomach cancers. A 55-year-old woman was referred to our hospital with biopsy-proven gastric cancer. A shallow ulcerative lesion was detected in the lesser curvature of the lower body. It was suspected to be early gastric cancer ⅡA + ⅡC type. Thus, endoscopic submucosal dissection was performed. She was subsequently diagnosed with NEC, which is aggressive and carries a poor prognosis. We conducted a radical resection and a laparoscopic-assisted distal gastrectomy. The tumor had infiltrated the subserosal layer and 6/42 lymph nodes were involved. The mitotic index was 16/10 high power fields and the Ki-67 labeling index was 26%-50%. The final diagnosis of NEC was made according to the World Health Organization 2010 criteria. She was suspected of having jumping metastasis to the proximal margin. The patient was treated with an oral anticancer drug (5-flurouracil based drug) for 2 years. The patient has been followed up for 3 years without recurrence.

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Key words: Neuroendocrine carcinoma; Mitosis; Ki-67; Gastrectomy; Prognosis

Core tip: Some studies argue that neuroendocrine carcinoma (NEC) can be removed by endoscopic resection. However, in this case, we found that NEC can have jumping metastasis. Thus, NEC must be removed by radical surgical resection.

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INTRODUCTION

Neuroendocrine carcinoma (NEC) is rare tumor that includes < 1% of stomach cancers. It is aggressive and has a poor prognosis[1-3]. NEC is classified as neuroendocrine carcinoma G3 according to The World Health Organization (WHO) classification of tumors of the digestive system, 2010[4].

In this report, we describe a patient with NEC who underwent endoscopic submucosal dissection (ESD) and laparoscopic assisted distal gastrectomy (LADG) for removal of a tumor.

CASE REPORT

A 55-year-old woman with acid reflux underwent an esophagogastroduodenoscopy (EGD) for a checkup. A shallow ulcerative lesion was detected in the lesser curvature of the lower body (Figure 1). It was suspected to be early gastric

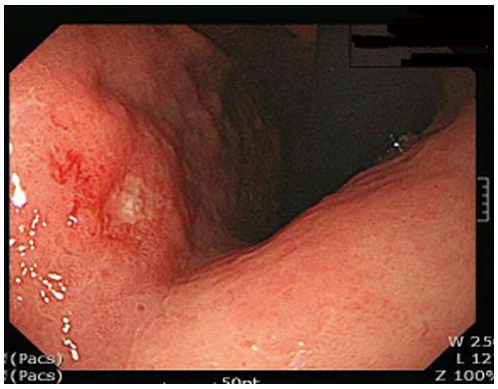

Figure 1 Endoscopic findings. Ulcerative lesion in the lesser curvature of the lower body.

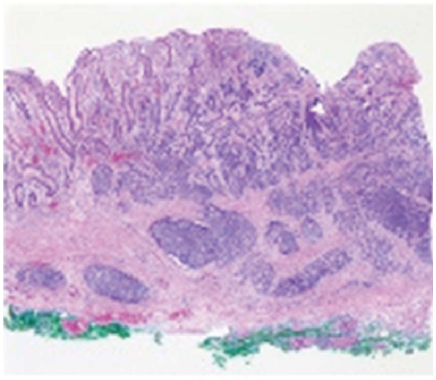

Figure 2 Endoscopic submucosal dissection specimen. A hypercellular lesion was detected in the mucosa and submucosal layers.

cancer ⅡA + ⅡC type. A biopsy was done and it was diagnosed as a well differentiated adenocarcinoma. She was transferred to the digestive department of our hospital.

On July 13, she underwent ESD. The specimen was 6.3 cm × 3.8 cm and a pathological examination revealed a 1.2 cm × 1.4 cm NEC that had invaded the submucosal layer. The tumor cells exhibited mitosis in 16/10 high power fields (HPF). The resection margin was clear (Figure 2) and no lymphatic, vascular or neural invasion was observed. She was advised to undergo an operation due to possible neural invasion by the NEC. On July 24, she vomited blood from an ulcer because of the weakened mucosa after ESD. The bleeding was stopped under emergency EGD. She underwent conservative treatment with a proton-pump inhibitor and no oral intake.

On August 9, she underwent LADG with a D2 lymphadenectomy. A Billroth type I anastomosis was done. A frozen biopsy revealed that the proximal and distal resection margins were clear of lesions. The mass was 2.2 cm × 1.3 cm in size and limited to the subserosa (Figure 3). The proximal resection margin was very close to the lesion but the distal resection margin was clear. Neural and lymphatic invasion was observed with 6 of 42 metastatic lymph nodes harvested. The tumor cells were positive for synaptophysin, chromogranin and CD56. The Ki-67 labeling index was 2+ (26%-50%). These findings led to the diagnosis of NEC, according to the 2010 WHO criteria[4]. The proximal margin was clear but the final pathology showed that some cancer cells were found between the mucosa and submucosa.

Minor bleeding was detected through the drain during the first 3 d. After an antihemorrhagic treatment and a transfusion, the blood tests were stable and the drain color changed to clear. She was discharged after the drain was removed.

She was treated with an oral anticancer drug [5-flurouracil (5-FU) based drug] for 2 years. No recurrence at the anastomosis or other site in the stomach was observed 3 years later.

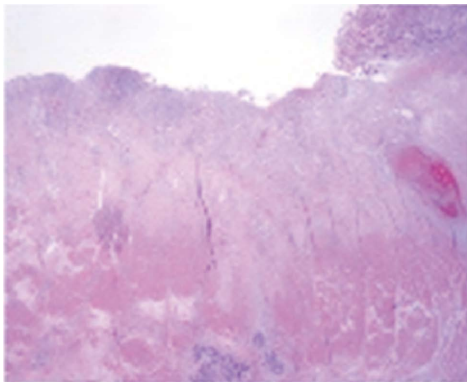

Figure 3 Laparoscopic assisted distal gastrectomy specimen. The ulcerative lesion due to mucosal detachment after endoscopic submucosal dissection is distinguished from normal mucosa (right side). Fibrosis was observed in the submucosal layer and a hypercellular lesion that was the same as the endoscopic submucosal dissection specimen in the muscle and subserosa layers.

DISCUSSION

Neuroendocrine neoplasm (NEN) is an epithelial neoplasm with predominant neuroendocrine differentiation and is an uncommon tumor with multiple sites of occurrence[5].

NENs are commonly divided by origin as located in the foregut (lung, bronchus, stomach or duodenum), midgut (jejunum, ileum, appendix or proximal colon) and hindgut (distal colon or rectum). The percentage of foregut cases is 34%, midgut 30% and hindgut 36%[6].

Gastric NEN is classified into neuroendocrine tumor (NET), neuroendocrine carcinoma (NEC), mixed adenoneuroendocrine carcinoma, enterochromaffin cells, serotonin-producing NETs and gastrin-producing NETs. NETs include NET G1 (carcinoid) and NET G2 (well-differentiated neuroendocrine tumor/carcinoma). NECs include NEC G3 (poorly differentiated neuroendocrine carcinoma small cell type/large cell type)[4]. NEN is positive for synaptophysin and chromogranin A[7].

NEN is classified based on the level of cellular proliferation, including the mitotic and Ki-67 indices[4]. In our case, the mitotic index was 16/10 HPF and the Ki-67 labeling index was 26%-50%. Thus, she was diagnosed with NEC. We suspected jumping metastasis from the main lesion to the proximal margin.

Gastric NEN has different prognoses and treatments depending on type. The prognosis of NET G1 is good and the 5 year survival rate is high. NET G2 has a favorable prognosis but is aggressive. NEC has the highest malignant potential but the 5 year survival rate is 75%-80%; however, the prognosis is poor. NET can be removed by endoscopic resection, whereas NEC requires surgical resection and lymph node dissection[8]. The best choice adjuvant chemotherapy for NEC is cisplatinum-based chemotherapy[9]. However, in this case we used a 5-FU oral agent because of the patient's financial status and compliance.

In conclusion, a neuroendocrine tumor can be removed by endoscopic resection but it must be a radical surgical resection in accordance with a malignant tumor, due to its aggressive tendency and high malignant potential.

COMMENTS

Case characteristics

This case reports a neuroendocrine carcinoma with jumping metastasis.

Pathological diagnosis

Neuroendocrine neoplasm can be diagnosed using a mitotic count and the Ki-67 index.

Treatment

Neuroendocrine tumors can be removed by endoscopic resection but a neuroendocrine carcinoma must be excised by radical surgical resection.

Peer review

In this case, the authors used 5-flurouracil chemotherapy, but a common choice for neuroendocrine carcinoma is cisplatinum-based chemotherapy.

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Acknowledgments

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