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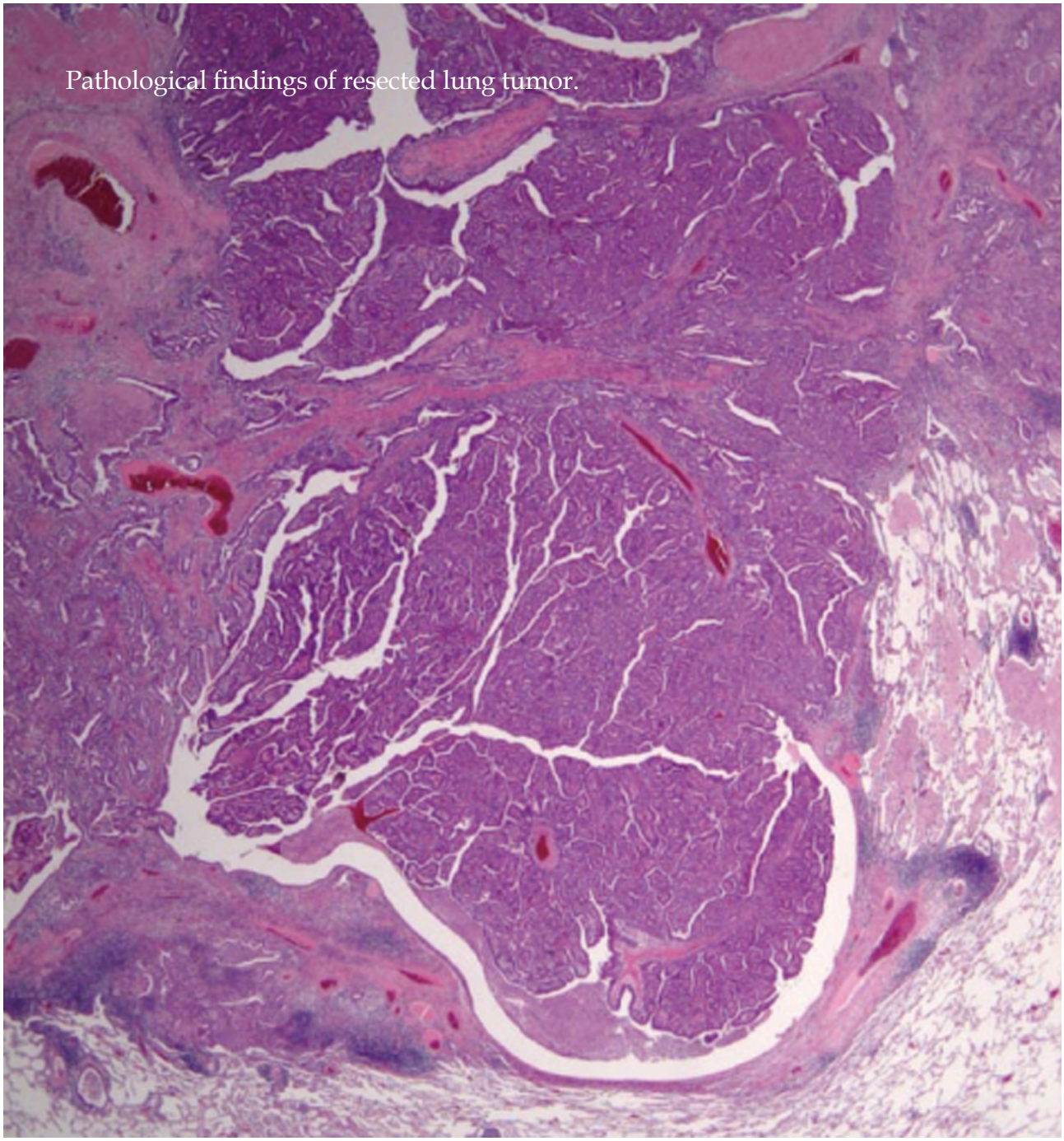

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Beijing 100025, China
Telephone: 0086-10-8538-1892
Fax: 0086-10-8538-1893
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No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: 0086-10-8538-1891
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EDITORIAL

Pancreatic metastases: An increasing clinical entity

Alessandro Zerbi, Nicolò Pecorelli

Alessandro Zerbi, Pancreatic Surgery Section, Third Department of Surgery, IRCCS Istituto Clinico Humanitas, Rozzano, 20089 Milan, Italy
Nicolò Pecorelli, Pancreas Unit, Department of Surgery, IRCCS San Raffaele Hospital, 20127 Milan, Italy
Author contributions: Zerbi A and Pecorelli N equally contributed to the conception and drafting of the article.
Correspondence to: Alessandro Zerbi, MD, Pancreatic Surgery Section, Third Department of Surgery, IRCCS Istituto Clinico Humanitas, via Manzoni 56, Rozzano, Milan 20089, Italy. alessandro.zerbi@humanitas.it
Telephone: +39-2-82245941 Fax: +39-2-82244590
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Abstract

Pancreatic metastases, although uncommon, have been observed with increasing frequency recently, especially by high-volume pancreatic surgery centers. They are often asymptomatic and detected incidentally or during follow-up investigations even several years after the removal of the primary tumor. Renal cell cancer represents the most common primary tumor by far, followed by colorectal cancer, melanoma, sarcoma and lung cancer. Pancreatic metastasectomy is indicated for an isolated and resectable metastasis in a patient fit to tolerate pancreatectomy. Both standard and atypical pancreatic resection can be performed: a resection strategy providing adequate resection margins and maximal tissue preservation of the pancreas should be pursued. The effectiveness of resection for pancreatic metastases is mainly dependent on the tumor biology of the primary cancer; renal cell cancer is associated with the best outcome with a 5-year survival rate greater than 70%.

Key words: Pancreas; Pancreatic cancer; Secondary tumor; Pancreatic resection; Renal cell cancer

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INTRODUCTION

Metastatic lesions in the pancreas are rare and account for about 2% of all pancreatic malignancies[1-3]. Most patients have widespread systemic diseases at the time of diagnosis and the detection of a solitary, resectable pancreatic metastasis is uncommon. However, reports of surgically resected pancreatic metastases have recently dramatically increased and in 2008, 15 papers in the English language were published on Pub-Med indexed journals on this topic[4-18].

High-volume pancreatic surgery centers are now seeing an increasing number of patients affected by pancreatic metastases amenable to resection. Several reasons may explain this phenomenon: the introduction of standardized oncologic follow-up programs for all patients with malignant diseases; the improved sensitivity of diagnostic examinations; the better awareness of this oncological entity; the more aggressive therapeutic attitude developed by many oncologists and surgeons; and the progressive centralization of patients with surgically resectable pancreatic diseases in high-volume centers.

DIAGNOSIS

Pancreatic metastases are asymptomatic in more than 50% of cases[4,5,19]: they are often detected during follow-up investigations after surgery for a primary lesion or as an incidental finding on imaging studies performed for an unrelated indication. Symptoms, when present, are often nonspecific and subtle such as abdominal pain, weight loss or nausea; only occasionally jaundice or gastrointestinal bleeding have been reported[4,5].

When a pancreatic mass is detected by imaging, the suspicion of a metastatic disease should arise from clinical history, tumor markers assessment and computed tomography (CT) appearance. For example, metastases from renal-cell cancer (RCC) present as contrast-enhanced, hypervascular lesions[17]. A CT-guided fine-needle biopsy to confirm the clinical suspicion is seldom necessary. It is mandatory to rule out the presence of other metastatic lesions by a whole body CT and/or a PET scan.

Pancreatic metastases typically occur a long time after the removal of the primary tumor. This is particularly true for metastases from RCC where an interval of over 10 years after nephrectomy is almost the rule. In a different way, metachronous lesions from other primary malignancies tend to arise earlier although cases of solitary metastasis from colorectal cancer presenting with an interval of more than 10 years have been reported[20]. This indicates the need for long follow-up periods and a high index of suspicion to promptly detect a pancreatic metastasis.

INDICATIONS FOR SURGERY

The role of pancreatic metastasectomy is not well defined and not every pancreatic metastasis represents an indication for its removal. There is a need to balance the potential morbidity following a pancreatic resection with the oncological benefit of the removal. However, the marked decrease in mortality and major morbidity of pancreatic surgery recently observed in many high-volume centers[21] makes pancreatic metastasectomy not radically different from liver and lung metastasectomy which is now considered the standard treatment for several neoplasms. Despite the fact that the superiority of resection versus other therapeutic options has never been clearly demonstrated, surgical removal of lung and liver metastases is now routinely performed in metastatic colorectal cancer and soft-tissue sarcomas with an apparent benefit in long-term survival[22,23]. It then seems reasonable that pancreatic metastasectomy is indicated for an isolated and resectable metastasis in a patient fit to tolerate pancreatectomy. It is necessary to carefully consider the primary cancer type, its biological behavior, its outcome, the presence of synchronous or metachronous disease and the disease-free interval; however, no single cancer-type seems to be a contraindication in appropriately selected patients. It is important to evaluate each single case on an individual basis; ideally this should be done by a multidisciplinary medical team, including an experienced pancreatic surgeon and a medical oncologist. The availability and effectiveness of systemic therapies should always be considered and eventually a combined approach with pancreatic resection could be planned.

TYPE OF SURGERY

The type of surgical procedure is an important and controversial aspect in the treatment of pancreatic metastases. Some authors advocate standard radical pancreatic resection because of the risk of recurrence[24-27]. For example, Bassi, adopting a policy of atypical resections in cases of metastases from RCC, observed a 29% rate of pancreatic recurrences[24]. Other series did not confirm this finding[5]. Considering the high frequency of multiple metastases[19,28], the occurrence of a pancreatic recurrence is more likely to be the expression of an undetected multifocality than the result of an inadequate surgical procedure. The choice of a standard or an atypical surgical procedure is then probably less important than an accurate investigation for multiple pancreatic lesions. When intraoperatively facing a case of pancreatic metastasis, an attitude similar to that adopted for small endocrine tumors should be chosen: complete mobilization of the whole pancreas, careful manual palpation and intraoperative ultrasonography to search for multiple lesions. Intraoperative ultrasound plays a key role: it not only increases the accuracy in detecting all pancreatic nodules but also precisely defines the relationship between the nodule and the main pancreatic duct, allowing the most appropriate surgical procedure to be chosen. When each pancreatic metastasis is detected, the decision to perform either a standard or an atypical resection is probably not important assuming that the margins of resection are cancer-free. In fact, incomplete resection (R1 or R2) results in poor survival rates, supporting the idea that pancreatectomy should only be undertaken if complete resection is anticipated[29]. Furthermore, the main advantage of a standard resection should be an easier removal of peripancreatic lymph nodes. However, the usefulness of lymphadenectomy in this setting is actually quite controversial as several reviews reported no lymph node involvement[5,28,30] whereas in other reports a lymph node involvement was observed in about 30% of cases[4,26]. Therefore an individual surgical approach should probably be chosen with an optimal resection strategy providing adequate resection margins and maximal tissue preservation of the pancreas.

OUTCOME OF METASTASECTOMY

The effectiveness of resection for pancreatic metastasis is mainly dependent on the tumor biology of the primary cancer. According to a recent literature review[27] which included 243 patients subjected to pancreatic resection for isolated metastases to the pancreas, RCC, colorectal cancer, melanoma and sarcoma represent the primary cancer site in about 80% of all cases. In addition, data from other clinical series also indicate lung cancer as one of the most common primary malignancies metastasizing to the pancreas.

RCC is associated with the best outcome whereas lung cancer predicts the worst outcome.

Renal cell cancer

RCC represents by far the most common primary tumor in case of isolated, resectable pancreatic metastasis. In a recent review of 421 patients undergoing resection of pancreatic RCC metastases, the actuarial 5 years survival rate, calculated on 321 patients for which data were available, was 72.6% with a 5 years disease-free survival rate of

57.0%[19]. In the largest single-center experience published, an 88% 5 years survival rate was reported[5]. These figures compare favorably with those reported after lung resection of metastatic RCC where 5 years survival rates ranging from 31% to 44% are observed[31,32].

The behavior of metastatic RCC is difficult to predict and quite heterogeneous: in some cases a rapid progression of disease is observed whereas in other cases a very slow growth pattern and even spontaneous regression are reported[33]. Pancreatic metastases from RCC seem to represent a less aggressive variant of RCC recurrence although there are no studies to support such a supposition.

The contribution of surgery to the outcome of patients with pancreatic metastasis from RCC is difficult to assess. In a recent review, the survival of 321 patients undergoing surgery was compared to that of 73 non-surgically treated patients: 2 and 5 years overall survival rates were 80% and 72% in the operated group and respectively 41% and 14% in the non-operated group[19]. Similarly, in a single-center experience, 23 patients undergoing pancreatic metastasectomy were compared to 13 non-operated patients: 5 years survival rates were respectively 88% and 47%[5]. Despite the potential strong selection bias, the remarkably higher survival rate observed after surgery justifies the concept of pancreatic resection for RCC metastasis.

Single prognostic factors after pancreatic metastasectomy for RCC have not been clearly identified. From single series, tumor grade of the primary RCC[34], lymph node involvement and vascular invasion[4] have been reported as significant predictors of survival. A disease-free interval after nephrectomy less than 2 years was related to a poorer outcome in the wide review by Tanis *et al*[19]. Interestingly, neither the number of lesions nor their size showed a significant correlation with survival in any report; considering the high rate of multiple metastases currently reported (39% in the review by Sellner *et al*[28]), it is important to stress that multifocality should not represent a contraindication to surgery. Also, the previous removal of another metastatic lesion in a different organ does not represent a negative prognostic factor[5,19]: previous disease recurrence, regardless of site, should then not dissuade the surgeon from considering resection of pancreatic metastasis.

In selected cases, for example, in patients belonging to a favorable risk group (according to the Memorial Sloan-Kettering prognostic factors model[35,36]), pancreatic resection should be proposed even with another metastatic site[5].

In addition to immunoreactive cytokines, the mainstay of treatment of metastatic RCC for the last 15 years, several anti angiogenetic agents such as bevacizumab, sunitinib, sorafenib have recently showed promising results[37]. Therefore, surgical resection should not be considered the only therapeutic tool against pancreatic metastases from RCC: a combination of various treatment approaches in the different periods of the natural history of metastatic RCC might produce synergistic antitumor activity. The correct way to combine surgery with medical treatment in metastatic RCC will be an important field of investigation in the future.

Colorectal cancer

The treatment of metastatic colorectal cancer is based on a multidisciplinary approach by surgeons and medical and radiation oncologists with recent advances in the systemic therapy of this malignancy in both the adjuvant and palliative settings. Most frequently this type of disease metastasizes to the liver and lung while pancreas represents an uncommon location. Few cases of pancreatic metastasectomy for colon or rectal cancer localization are reported in the literature; a recent review by Reddy *et al*[27] collected a total of 19 reported cases, a few more derive from other single case reports[20]. However, it is well documented that resection of isolated hepatic or lung metastases from colorectal cancer in selected patients combined with effective systemic therapy results in greater survival rates[38,39]. This appears to be true despite the few data available as well as for patients undergoing pancreatectomy. In their pooled analysis, Reddy *et al*[27] found that these patients seem to benefit from surgery resulting in a 5 year survival rate approaching 30%, similar to that for hepatic metastasectomy. Moreover, it is important to stress the fundamental role that, in addition to surgery, chemotherapy and biological therapy have in the treatment of this particular disease, allowing a better long-term outcome.

Melanoma

In a different way, metastatic melanoma always correlates with a poor prognosis with modest results from systemic therapy. Both chemotherapy and biological drugs, even when combined, did not significantly improve survival rates despite carrying high toxicity. Considering patients with AJCC stage IV disease, gastrointestinal visceral metastases bear the worst prognosis[40], usually presenting at a later time; this most likely includes the rare cases of isolated pancreatic metastases. A recent review by Olilla *et al*[41] investigated the role of surgery in metastatic melanoma showing that the effectiveness of metastasectomy is dependent on the site of metastasis. Although no studies have directly addressed the prognosis and outcomes for patients undergoing pancreatic metastasectomy, the few reported data show that pancreatic resection is associated with poor outcome (pooled median survival time: 14 mo)[27]. Despite these results, as mentioned above, no other effective therapeutic weapon is available and pancreatic resection seems to be a reasonable option as long as a complete margin free resection can be achieved. Palliative surgery should only be undertaken for symptomatic patients since it is ineffective but carries the numerous risks of pancreatic surgery.

Sarcoma

In metastatic sarcomas, only gastrointestinal stromal tumors show a sustained response to systemic therapy with the recently introduced molecular targeted therapy even in unresectable disease while non-GIST systemic sarcomas are usually unresponsive to chemotherapy. In addition, reports from different groups show encouraging results from surgery in the treatment of sarcoma metastatic to lung and liver suggesting a potential role for surgery even

in the rare case of solitary pancreatic involvement[42,43]. Once again, literature data is scanty and patients undergoing pancreatic resection for isolated metastasis constitute a small sample. The reported cases, however, resulted in lower survival rates compared to results after lung or liver metastasectomy with pooled analysis showing a 5-year survival rate of 14%[27].

Lung cancer

Lung cancer metastasizes to many sites but most frequently to the bone, the liver and the adrenal glands[44] while rarely involving the pancreas. The few reports available in the literature show that small cell lung cancer (SCLC) represents the most typical histological subtype[45] metastasizing to the pancreas, usually presenting as a metachronous lesion identified at follow-up investigations. Metastatic lung cancer has a very poor prognosis, especially SCLC, and is usually treated with best supportive care or systemic therapy; nonetheless, several reports in the literature suggest that a survival benefit may be achieved by surgical treatment of solitary extracranial spread of non small cell lung cancer[46,47]. This is confirmed by a recent case report regarding a patient presenting with jaundice subsequently diagnosed with a lung adenocarcinoma with a synchronous single metastatic lesion to the pancreatic head[48]. The patient was subjected first to a pancreaticoduodenectomy and then to the removal of the pulmonary lesion; 18 mo after surgery, the patient is asymptomatic and disease-free. However, this case represents an exception since a few other reports of resected lung metastasis to the pancreatic gland resulted in frequent disease relapse and poor survival rates[27].

CONCLUSION

Pancreatic metastases represent a new clinical entity and both gastrointestinal oncologists and pancreatic surgeons should be aware of their presence. It is likely that in the near future an increasing number of patients affected by pancreatic metastases will be observed. Pancreatic metastasectomy has shown favorable outcomes so far and it should always be considered among the therapeutical options, especially in cases of RCC. A more detailed definition for the criteria for the selection of patients for pancreatic metastasectomy is needed, representing the main goal of investigations in the near future.

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BRIEF ARTICLE

A standardized technique for safe pancreaticojejunostomy: Pair-Watch suturing technique

Yoshinori Azumi, Shuji Isaji, Hiroyuki Kato, Yuu Nobuoka, Naohisa Kuriyama, Masashi Kishiwada, Takashi Hamada, Shugo Mizuno, Masanobu Usui, Hiroyuki Sakurai, Masami Tabata

Yoshinori Azumi, Shuji Isaji, Hiroyuki Kato, Yuu Nobuoka, Naohisa Kuriyama, Masashi Kishiwada, Takashi Hamada, Shugo Mizuno, Masanobu Usui, Hiroyuki Sakurai, Masami Tabata, Department of Hepatobiliary Pancreatic and Transplant Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan

Author contributions: Azumi Y performed the majority of the clinical data analysis and performed the operation; Isaji S developed this new technique and directed entire study; Kato H, Nobuoka Y, Kuriyama N, Kishiwada M, Hamada T, Mizuno S, Usui M, Sakurai H and Tabata M participated in the operation as surgeon or assistant.

Correspondence to: Yoshinori Azumi, MD, Department of Hepatobiliary Pancreatic and Transplant Surgery, Mie University Graduate School of Medicine, 2-174 Edobashi, Tsu, Mie 514-8507, Japan. azu1121@clin.medic.mie-u.ac.jp

Telephone: +81-59-2321111 Fax: +81-59-2328095

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Abstract

AIM: To prevent pancreatic leakage after pancreaticojejunostomy, we designed a new standardized technique that we term the "Pair-Watch suturing technique".

METHODS: Before anastomosis, we imagine the faces of a pair of watches on the jejunal hole and pancreatic duct. The first stitch was put between 9 o'clock of the pancreatic side and 3 o'clock of the jejunal side, and a total of 7 stitches were put on the posterior wall, followed by the 5 stitches on the anterior wall. Using this technique, twelve stitches can be sutured on the first layer anastomosis regardless of the caliber of the pancreatic duct. In all cases the amylase activity of the drain were measured. A postoperative pancreatic fistula was diagnosed using postoperative pancreatic fistula grading.

RESULTS: From March 2007 to July 2008, 29 consecutive cases underwent pancreaticojejunostomy using this technique. Pathologic examination results showed pancreatic carcinoma (n = 14), intraductal papillary-mucinous neoplasm (n = 10), intraductal papillary-mucinous carcinoma (n = 1), carcinoma of ampulla of Vater (n=1), carcinoma of extrahepatic bile duct (n = 1), metastasis of renal cell carcinoma (n = 1), and duodenal carcinoma (n = 1). Pancreaticojejunal anastomoses using this technique were all watertight during the surgical procedure. The mean diameter of main pancreatic duct was 3.4 mm (range 2-7 mm). Three patients were recognized as having an amylase level greater than 3 times the serum amylase level, but all of them were diagnosed as grade A postoperative pancreatic fistula grading and required no treatment. None of the cases developed complications such as hemorrhage, abdominal abscess, and pulmonary infection. There was no postoperative mortality.

CONCLUSION: Our technique is less complicated than other methods and very secure, providing reliable anastomosis for any size of pancreatic duct.

Key words: Pancreaticoduodenectomy; Pancreaticojejunostomy; Suturing technique

Peer reviewer: Alessandro Zerbi, MD, Department of Surgery, San Raffaele Hospital, Via Olgettina 60, Milano 20132, Italy

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INTRODUCTION

Pancreaticoduodenectomy has become a standard proce-

dure, and the critical step is no longer the resection itself but the reconstruction of the pancreaticoenteric anastomosis. This is underscored by the fact that, despite significantly reduced mortality in recent years, morbidity remains as high as 30% to 50%, even in large series[1]. Complications related to pancreaticoenteric anastomosis are pancreatic fistula, anastomotic dehiscence, abscess formation, and septic hemorrhage. The pancreatic anastomosis is still the Achilles heel of pancreatic surgery because it has the highest rate of surgical complications among all abdominal anastomoses. Many risk factors previously shown to predispose to pancreatic leakage after pancreaticoduodenectomy include advanced age, prolonged operation time, major blood loss, jaundice, soft pancreatic parenchyma, small pancreatic duct, and number of patients per surgeon[2,3].

More than 80 different methods of pancreaticoenteric reconstruction have been proposed, illustrating the complexity of surgical techniques as well as the absence of a gold standard. Pancreatic anastomosis using a jejunal loop is the most commonly used method of surgical reconstruction after pancreatic head resection. There are two main types of anastomosis: pancreatojejunostomy, so-called invagination anastomosis, and pancreaticojejunostomy, so-called duct-to-mucosa anastomosis. It has been found that duct-to-mucosa anastomosis is more effective than invagination anastomosis for the prevention of postoperative pancreatic duct dilatation and atrophy of the remnant pancreas[4,5]. However, prospective randomized trials have found no differences between the two methods regarding fistula rates, morbidity, or mortality[2,6]. Irrespective of the method adopted, it is the technique of anastomosis that is more important than other factors that are known to influence the formation of pancreatic fistulae. It should be therefore emphasized that a standardized approach to pancreatic anastomosis and the consistent practice of a single technique can help to reduce the incidence of complications[7]. For effective prevention of the development of pancreatic leakage, we designed a new standardized technique that we term the "Pair-Watch suturing technique", which is a duct-to-mucosa pancreaticojejunostomy technique.

MATERIALS AND METHODS

Operative technique

Here we describe our technique of end-to-side pancreaticojejunostomy in a typical case in which the caliber of the main pancreatic duct is around 3 mm with normal and soft pancreatic parenchyma. After proximal or medial pancreatectomy, the cut end of the distal pancreas is mobilized for approximately 2 cm to allow the placement of interrupted sutures to the posterior surface of the pancreas. Stay sutures at the superior and inferior border of the cut remnant allow partial reflection of the gland and easier access to the posterior surface. Our procedure consists of two-layer anastomosis; duct-to-mucosa anastomosis and pancreatic parenchymal to jejunal seromuscular anastomosis. We always use a surgical scope with magnification of 1.5 to 2.5, which is very helpful for performing a safe and secure anastomosis.

A pancreatic duct tube (4/6 or 5 Fr, Sumitomo Bakelite, Tokyo, Japan) is inserted as a splint tube into the main pancreatic duct of the pancreatic remnant from the cut-end and tied to pancreatic parenchyma with 6-0 PDS Ⅱ (Ethicon, Inc, Somerville, NJ), as shown in the Figure 1A.

After cutting a very small part (usually 2-3 mm in diameter) of the jejunal serosa using an electric cautery as shown in the Figure 1B, the metallic needle of the pancreatic duct tube is introduced into the jejunum through the site of the serosal cut and then taken out of the distal end of the jejunum (Figure 1C). While interring the stitches on the posterior wall duct-to-mucosa anastomosis of pancreaticojejunostomy, the distance between the induced jejunal hole and the cut end of the main pancreatic duct should be kept at 5 cm or more, making the tube loop-shaped (Figure 1D).

Before starting the duct-to-mucosa anastomosis, we imagine the faces of a pair of watches, the jejunal hole corresponding to the left-side watch and the pancreatic duct hole to the right-side one (Figure 2). The posterior wall of pancreatic duct consists of the latter half of the clock cycle, from 6 o'clock to 12 o'clock, and the posterior wall of jejunal hole consists of the first half of the clock cycle, from 12 o'clock to 6 o'clock.

Using a 6-0 PDS Ⅱ, the first stitch is put in the center of posterior wall, that is, between 9 o'clock of the pancreatic side and 3 o'clock of the jejunal side. The stitch should be made so that a suture knot is placed outside the anastomosis, and the pancreatic duct stitch should be placed at the pancreatic parenchyma from the edge of the duct. The second stitch is put on the caudal side of the first stitch, that is, between 8 o'clock of the pancreatic side and 4 o'clock of the jejunal side. In the same way, the third and fourth stitches are put between 7 o'clock and 5 o'clock, and between 6 o'clock and 6 o'clock, respectively. In the cranial side of the posterior wall anastomosis, the fifth, sixth, and seventh stitches are sequentially put between 10 o'clock and 2 o'clock, between 11 o'clock and 1 o'clock, and between 12 o'clock and 12 o'clock, respectively. After these seven sutures on the posterior wall have been completed, we usually put the remaining 5 stitches from 1 to 5 o'clock on the anterior wall of the pancreatic duct in advance (Figures 2 and 3A). To prevent these twelve sutures from being mixed up, we grasp them with twelve mosquito clamps that are numbered from one to twelve, corresponding to the site from one to twelve o'clock of the pancreatic duct side watch (right side watch) (Figure 2). The jejunum is carefully approximated to the pancreas with simultaneous pulling of the stent tube to make it straight, and the seven knots on the posterior wall are gently tied in order, from the first to seventh stitch.

Thereafter we move to the anterior wall anastomosis. The pancreatic side has been already sutured, and thus the sutured strings are used. Each stitch from 1 to 5 o'clock is placed on the corresponding site on the jejunum from 11 to 7 o'clock. The duct-to-mucosa anastomosis is complete once these 5 stitches have been gently tied. The stent tube

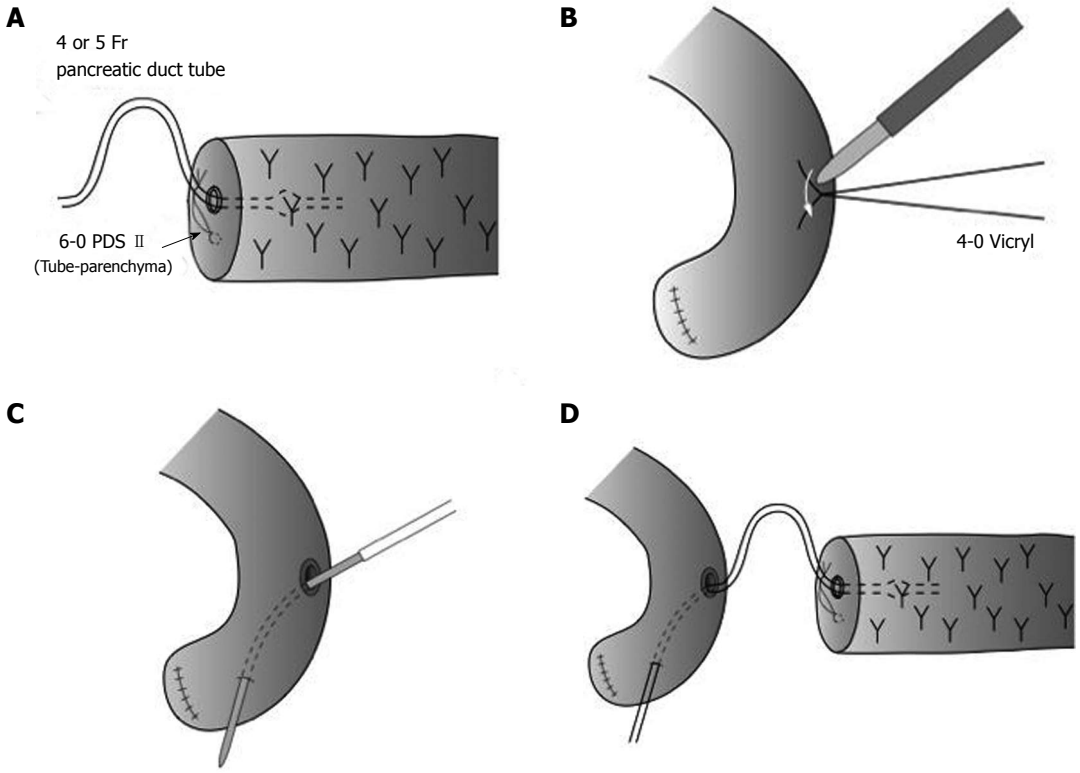

Figure 1 Preparation of pancreaticojejunostomy using pancreatic duct tube. A: A pancreatic duct tube is inserted as a stent tube into the main pancreatic duct of the pancreatic remnant from the cut-end; B: A very small part (usually 2-3 mm in diameter) of the jejunal serosa is cut by an electric cautery; C: The metallic needle of the pancreatic duct tube is introduced into the jejunum through the site of serosal cut and then taken out of the distal end of the jejunum (Roux-en-Y jejunal limb); D: The distance between the induced jejunal hole and the cut end of the main pancreatic duct should be kept 5 cm away or more, putting the pancreatic duct tube like a long loop during pancreaticojejunostomy.

is then fixed to the jejunal wall with Witzel's method using 4-0 Vicryl (Ethicon, Inc, Somerville, NJ) interrupted sutures.

The second layer anastomosis is a pancreatic parenchymal-jejunal seromuscular anastomosis by interrupted sutures with 4-0 Vicryl. Usually, 5-7 stitches each are sutured on the anterior and posterior side (Figure 3B). After completion of the reconstruction, a closed vacuum-drainage system (J-VAC drainage system; Ethicon, Inc, Somerville, NJ) is placed near the site of pancreaticojejunostomy, and the postoperative secretion is routinely monitored with respect to the volume and amylase activity.

Postoperative care

In all cases the amylase activity of abdominal drain and serum amylase activity are measured on postoperative day 3. A postoperative pancreatic fistula was diagnosed using the report by Bassi *et al*[8].

RESULTS

From March 2007 to July 2008, 29 consecutive cases underwent pancreaticojejunostomy using this technique. Pathologic examination results showed pancreatic carcinoma (n = 14), intraductal papillary-mucinous neoplasm (n = 10), intraductal papillary-mucinous carcinoma (n=1), carcinoma of ampulla of Vater (n = 1), carcinoma of extrahepatic bile duct (n = 1), metastasis of renal cell carcinoma (n = 1), and duodenal carcinoma (n = 1). Pancreaticojejunal anastomoses using this technique were all watertight during the surgical procedure. The mean diameter of main pancreatic duct was 3.4 mm (range 2-7 mm). Three patients were identified as having an amylase level greater than 3 times the serum amylase level, but all of them were diagnosed as grade A postoperative pancreatic fistula grading[8] and required no treatment. None of the cases developed complications such as hemorrhage, abdominal abscess, and pulmonary infection.

The splint tube was usually removed 6 wk after operation, because the stent tube was fixed to the jejunal wall with Witzel's method using 4-0 Vicryl interrupted sutures. In all patients, the stent tube had been active in draining pancreatic juice of 50-200 mL/d for 7 to 14 d. Thereafter in half of patients we clamped the stent tube as it had become inactive in draining pancreatic. There was no postoperative mortality. All of the patients recovered well in the 8- to 26-mo follow-up period at the time of writing.

DISCUSSION

Mortality after pancreaticoduodenectomy has decreased in recent years. However, it has been shown that pancreatic leakage is still the most important determinant of morbidity, carrying a mortality of 28%[9]. Several methods have

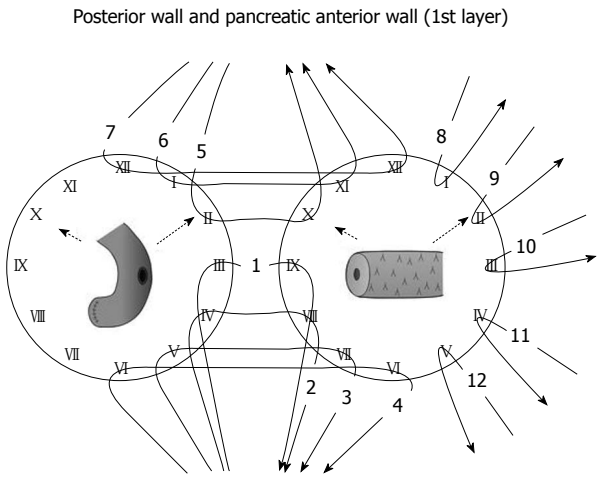

Figure 2 A pattern diagram of first step of Pair-Watch suturing technique. After the seven sutures on the posterior wall have been finished, the following 5 stitches on the anterior wall of the pancreatic duct are usually placed in advance.

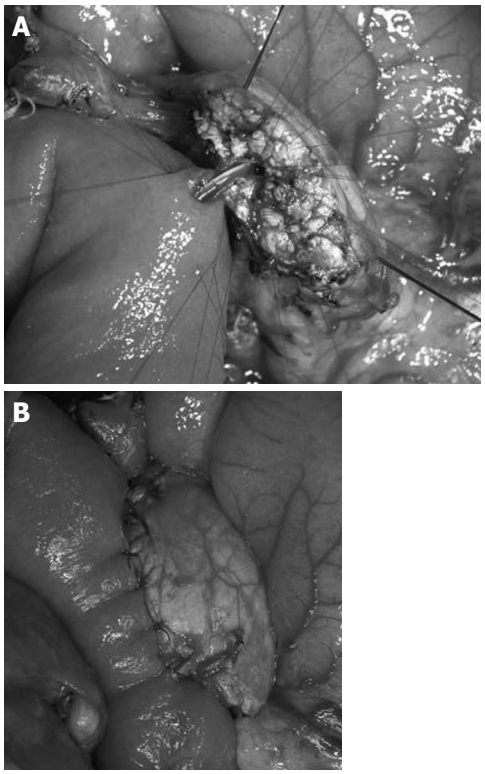

Figure 3 An intraoperative photograph of Pair-Watch suturing technique. A: All of twelve stitches are already put on between pancreatic duct and jejunal mucosa. B: Second layer anastomosis is finished.

been advocated to prevent pancreatic leakage, but a standardized method has not been established. Several steps, such as duct-to-mucosa adaptation and temporary ductal stenting, are thought to be important factors in achieving safe pancreaticojejunostomy. The anastomotic technique, pancreatic duct size, and texture of the remnant pancreas are all identified as significant intraoperative parameters affecting pancreaticojejunostomy leakage and related mortality[9]. Where the pancreas is relatively soft and/or the duct is relatively narrow, the possibility of pancreatic leak is increased[10,11].

We have developed a watertight and standardized pancreaticojejunostomy technique, the pair-watch suturing technique, that is not influenced by the caliber of pancreatic duct. Before introduction of this technique in our institution, the number of stitches used for duct-to-mucosa pancreaticojejunostomy had been 5 to 7 if the diameter of pancreatic duct is less than 5 mm. In our pair-watch suturing technique, however, the number of stitches is not influenced by the diameter of the duct. This is the most important point of this technique. Twelve stitches on duct-to-mucosa anastomosis are always inserted using a surgical scope, even if the pancreatic duct is 2 mm. By imagining the pancreatic duct and jejunal hole as the faces of a pair of watches, surgeons who are experienced in pancreaticoduodenectomy are able to be aware of every stitch during the procedure and to suture twelve stitches exactly by using the surgical scope. In other words, the technical variations between experienced surgeons can be eliminated by introduction of this technique, resulting in standardization of duct-to-mucosa pancreaticojejunostomy. Pancreaticoduodenectomy is a high-risk, technically demanding operation and the morbidity remains high, even in high-volume centers. Therefore, the adoption of our technique of pancreaticojejunostomy should under the guidance of highly experienced surgeons when less-experienced surgeons are operating.

Many surgeons usually increase the number of stitches when the caliber of pancreatic duct becomes wider. In contrast, they are obliged to decrease the number of stitches, when the duct is narrower. With the narrowing of duct size, the risk of pancreatic fistula significantly increases. Although there is no strong evidence that the functioning of duct-to-mucosa anastomosis depends on the absolute number of stitches used, we believe that increasing the number of stitches for narrow pancreatic ducts makes the anastomosis watertight, resulting in the risk of pancreatic fistula, because a pancreas with a narrow pancreatic duct usually also has soft parenchyma.

In our technique, we always insert the pancreatic duct tube during anastomosis. The insertion of a pancreatic tube has two purposes: one is partial pancreatic juice drainage, and the other is as a probe for secure suturing of the pancreatic duct. For partial drainage, the caliber size of stent tube should be small enough relative to that of the pancreatic duct. If the stent tube is as wide as the pancreatic duct for complete pancreatic juice drainage, the pancreatic duct pressure increases if there is accidental obstruction of the tube, resulting pancreatic leakage. For the anastomosis probe function, putting the stent tube into the site of a duct-to-mucosa anastomosis helps the surgeon make a secure suture because the tube becomes a landmark for the orifice of the anastomosis and prevents accidental suturing of both anterior and posterior walls.

Our technique is not totally original and is similar to the method reported by Z'graggen *et al*[12]. Their technique used 4-8 sutures for anastomosis, depending on duct size, and they did not use the pancreatic duct tube during duct-

to-mucosa anastomosis, resulting in very low pancreatic fistula rate of 2%. In contrast, to standardize the technique we use 12 stitches irrespective of the anatomical characteristics of the pancreatic stump and we keep the stent tube for partial drainage. Given the excellent results of reported by Z'graggen *et al*[12], it may be thought that we don't need stent tube insertion because we use twelve stitches even in narrow ducts. To evaluate the necessity of stent tube insertion, now we are now run a prospective study to determine whether the stent tube insertion or the suture technique which is the most significant factor for success.

In conclusion, the results obtained with the described technique of pancreaticojejunostomy indicate that pair-watch suturing technique is less complicated than other methods and very secure, providing reliable anastomosis for any size of pancreatic duct. Although the number of enrolled patients is small, our results are very encouraging and we hope that this method will be used more widely in the future.

COMMENTS

Background

The pancreatic anastomosis is still the Achilles heel of pancreatic surgery because it has the highest rate of surgical complications among all abdominal anastomosis.

Research frontiers

More than 80 different methods of pancreaticoenteric reconstruction have been proposed, illustrating the complexity of surgical technique as well as the absence of a gold standard. It should be therefore emphasized that a standardized approach to pancreatic anastomosis and the consistent practice of a single technique can help to reduce the incidence of complications.

Innovations and breakthroughs

Many surgeons usually increase the number of stitches when the caliber of pancreatic duct becomes wider. In contrast, they are obliged to decrease the number of stitches, when the duct size becomes narrow. As the duct size narrows, the risk of pancreatic fistula significantly increases. The authors have developed a watertight and standardized pancreaticojejunostomy technique, the Pair-Watch suturing technique, that makes us possible to put 12 stitches even if the duct size is 2 mm.

Applications

Since pancreaticodudenectomy is a high-risk, technically demanding operation and the morbidity is still high, even in high-volume centers, this technique of pancreaticojejunostomy should be adopted under the guidance of highly experienced surgeons when less-experienced surgeons are operating.

Terminology

The Pair-Watch suturing technique for pancreaticojejunostomy is described as the following procedure. Before starting the duct-to-mucosa anastomosis, we imagine the faces of a pair of watches, corresponding the jejunal hole for the left-side watch and the pancreatic duct hole for the right-side one. The posterior wall of the pancreatic duct consists of the latter half of the clock cycle, from 6 o'clock to 12 o'clock, and the posterior wall of jejunal hole consists of the first half of the clock cycle, from 12 o'clock to 6 o'clock.

Peer review

This paper reports a personal technique of pancreaticoenteric reconstruction developed by the authors. The argument is of great interest and deals with the most controversial topic in pancreatic surgery. The technique is clearly described; the figures add useful details and make the procedure easy to understand.

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CASE REPORT

Peritoneal seeding from appendiceal carcinoma: A case report and review of the literature

Valentina R Bertuzzo, Federico Coccolini, Antonio D Pinna

Valentina R Bertuzzo, Federico Coccolini, Antonio D Pinna, Department of General, Emergency and Transplant Surgery, Sant'Orsola-Malpighi University Hospital, Via Massarenti 9, 40138 Bologna, Italy

Author contributions: Bertuzzo VR was responsible for the conception and design of the study, acquiring, analyzing and interpreting the data, drafting the manuscript and for critical revision; Coccolini F was responsible for analyzing and interpreting the data and for critical revision; Pinna AD was responsible for critical revision of the paper

Correspondence to: Valentina R Bertuzzo, MD, Department of General, Emergency and Transplant Surgery, Sant'Orsola-Malpighi University Hospital, Via Massarenti 9, 40138 Bologna, Italy. valentinabertuzzo@hotmail.com
Telephone: +39-051-6363597 Fax: + 39-051-6363719

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Abstract

Non-carcinoid appendiceal malignancies are rare entities, representing less than 0.5% of all gastrointestinal malignancies. Because of their rarity and particular biological behavior, a substantial number of patients affected by these neoplasms do not receive appropriate surgical resection. In this report, we describe a rare case of primary signet-ring cell carcinoma of the appendix with peritoneal seeding which occurred in a 40-year old man admitted at the Emergency Surgery Department with the clinical suspicion of acute appendicitis. After a surgical debulking and right hemicolectomy, the patient had systemic chemotherapy according to FOLFOX protocol. After completion of the latter, the patient underwent cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. This report offers a brief review of the literature and suggests an algorithm for the management of non-carcinoid appendiceal tumors with peritoneal dissemination.

Key words: Appendiceal neoplasms; Signet-ring cell carcinoma; Peritoneal carcinomatosis; Hyperthermic intraperitoneal chemotherapy; Therapeutic algorithm

Peer reviewers: Theodoros E Pavlidis, MD, PhD, Professor, Department of Surgery, University of Thessaloniki, Hippocration Hospital, A Samothraki 23, Thessaloniki 54248, Greece; Giulio A Santoro, Professor, Pelvic Floor Unit and Colorectal Unit, Department of Surgery, Regional Hospital, Treviso 31000, Italy

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INTRODUCTION

Appendiceal cancers represent less than 0.5% of all gastrointestinal tumors. In one series, the age-adjusted incidence of cancer of the appendix was 0.12 cases per 1 000 000 people per year[1].

While the most common histopathologic type of appendiceal tumor is carcinoid, adenocarcinoma including the histological variants of mucinous adenocarcinoma, signet-ring cell carcinoma (SRCC) and goblet cell carcinoma[2-4] follow in the incidence rate. Benign histology includes leiomyomas, neuromas, lipomas and angiomas.

Primary SRCC of colon and rectum, described for the first time by Laufman and Shapir in 1951[5], is a rare histological finding in colorectal carcinomas (CRC); in western countries it accounts for 0.01% to 2.6% of all CRC[6-9]. SRCC of the appendix (A-SRCC) is an exceedingly rare entity, diagnosed in just 4% of appendiceal malignancies[9]; in fact, only a few cases are reported in the literature[1,9-16] (Table 1).

CASE REPORT

A 40-year old man reported to the Emergency Department with sudden onset of acute abdominal pain localized

Table 1 Literature review of appendiceal signet-ring cell carcinoma

	No. of cases	Manifestations	Treatment	Survival
McCusker *at al*[1]	70	-	Hemicolectomy or more (72%) less than hemicolectomy (26%)	5-yr survival 20%
McGory *at al*[9]	113	-	-	5-yr survival 18%
Ko *at al*[10]	1	Abdominal distension	Appendectomy, bilateral salpingo-oophorectomy	Alive after 12 mo
No authors[11]	1	Adnexal mass	Appendectomy and bilateral salpingo-oophorectomy	-
Suzuki *at al*[12]	1	Intestinal obstruction	Hartmann's operation, ileocecal resection, total hysterectomy, bilateral salpingo-oophorectomy	-
Niesel *at al*[13]	1	Scrotal metastasis	Ileocecal resection, omentectomy, right testis, right testicular cord and right hemiscrotum resection	-
Glehen *at al*[14]	36	-	Cytoreductive surgery plus perioperative intraperitoneal chemotherapy	3-yr survival -25%
Özakyol *at al*[15]	1	Crampy abdominal pain and weight loss	Total hysterectomy, bilateral salpingo-oophorectomy, appendectomy, pelvic and para aortic lymphadenectomy	-
Uharcek *at al*[16]	1	Lower abdominal mass	Total hysterectomy, bilateral salpingo-oophorectomy, appendectomy, omentectomy, pelvic and para aortic lymphadenectomy	Died after 18 mo

in his right lower quadrant; on examination, the patient was found to be feverish (body temperature 37.6℃/99.68°F), pulse was 96 beats/min and blood pressure 100/60 mmHg. Abdominal examination showed guarding and tenderness in the lower abdomen with positive rebound tenderness. Blood tests showed neutrophil leucocytosis (WBC 17.830/mm^3, neutrophils 78.9%) and an elevation of C-reactive protein (CRP 12.6 mg/dL). The patient's significant medical history was bilateral inguinal hernioplasty.

Abdominal radiography showed intestinal distension with some air-fluid levels in the central abdomen. The ultrasound scan revealed a swollen hypoechoic appendix with a 10-mm diameter; the lumen was occupied by a thin liquid layer and coprolites. All other abdominal organs were found to be within normal limits.

The surgical intervention took place on the same day as arrival. At laparoscopy, we found a bulky abscess at the appendiceal site involving the cecum and terminal ileum. As this surrounded the appendix making a direct intervention impossible, we decided to do a laparotomic McBurney incision.

The appendix was completely replaced by a purulent and lardaceous material; the extemporaneous histological exam revealed a signet-ring cell carcinoma diffusely infiltrating the vermiform appendix and extending to the appendix mesentery and surrounding adipose tissue. The immunohistochemical research was negative for chromogranin, serotonin, somatostatin and pancreatic polypeptide, which excluded a mixed carcinoid and adenocarcinoma of the appendix[17].

Then, following most current guidelines[9], we undertook a midline incision from the xyphoid bone to the pubic bone. Due to the presence of peritoneal seeding on the ileal mesentery and the parietal peritoneum, we performed a right hemicolectomy enlarged to 35 cm of the ileum and the abdominal wall. With the intention of staging the disease, we also removed some other peritoneal nodules in the Douglas pouch and on the jejunal mesentery.

Definitive histological examination showed cecum neoplastic infiltration of SRCC with neoplastic mucosal ulceration and massive nodal metastases in 9 of 29 analyzed lymph nodes. All the nodules removed from the peritoneal surface were metastatic localizations of SRCC.

Table 2 Variables associated with increased chances of having a complete cytoreduction (modified from Esquivel *et al*[18])

First international symposium on regional cancer therapies rules
1 Eastern cooperative oncology group performance status two or less[9]
2 No evidence of extra-abdominal disease
3 Up to three small, resectable parenchymal hepatic metastases
4 No evidence of biliary obstruction
5 No evidence of ureteral obstruction
6 No evidence of intestinal obstruction at more than one site
7 Small bowel involvement: no evidence of gross disease in the mesentery with several segmental sites of partial obstruction
8 Small volume disease in the gastro-hepatic ligament

The patient recovered uneventfully and was released from hospital 7 d after the operation.

A complete staging with total body-CT revealed no distant metastases but the presence of three peritoneal nodules suggested neoplastic nodules so our patient had systemic chemotherapy with 8 cycles of FOLFOX protocol (5-fluorouracil, folinic acid plus oxaliplatin).

After completion of the latter, a second complete staging was done which demonstrated an increase in the number and dimensions of the peritoneal nodules and numerous enlarged lymph nodes in the retroperitoneum and along the aorto-mesenteric trunk.

Since the patient fulfilled the necessary criteria (Table 2)[18-20], he was again admitted to our Institution and, after a prophylactic ureteral stent placement as previously reported[21], he underwent surgical intervention. Peritoneal cavity exploration revealed peritoneal nodules along the transverse and descending colon, greater and lesser omentum, Glisson's capsule, gallbladder, hepatic hilum, spleen, bilateral diaphragmatic peritoneum, pelvic and paracaval peritoneum. The calculated peritoneal cancer index was 22[22]. We performed total colectomy, splenectomy, cholecystectomy and complete peritonectomy followed by a 90-min long hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin and mytomicin C. The intervention was completed by an ileorectal anastomosis with protective ileostomy. On the first post-operative day, the patient underwent an explorative laparotomy due to an acute he-

morrhage. Diaphragmatic bleeding was found and brought under control by means of local hemostatic agents. The remaining post-operative course was regular and the patient was discharged 22 d after surgery.

Five months later, the patient is well and has a good quality of life. He completed systemic chemotherapy and follow-up imaging revealed no peritoneal recurrence or metastatic lesions.

DISCUSSION

Appendiceal malignancies represent less than 0.5% of all gastrointestinal tumors with an age-adjusted incidence of 0.12 cases per 1 000 000 people per year[1]. The international classification of diseases for oncology divides tumors of the appendix into malignant carcinoid, goblet cell carcinoma, colonic type adenocarcinoma, mucinous adenocarcinoma and signet-ring cell carcinoma[4].

Because adenocarcinoma of the appendix is so rare, its clinical presentation and natural history are still not well described. The clinical presentation of the majority of patients reported in the literature is acute appendicitis or an abdominal mass but preoperative diagnosis is rarely evident and most patients are not identified until the disease is advanced[1,9-16]. Moreover, up to 70% of cases are not diagnosed intraoperatively[2,23].

The anatomic peculiarities of the appendix allow for several considerations in regard to appendiceal neoplasms to be made. The narrow appendiceal diameter predisposes to occlusion of the lumen by the neoplasm early in its course. This creates the potential for superimposed appendicitis and a marked tendency to rupture and, in fact, appendiceal adenocarcinoma represents the gastrointestinal malignancy most commonly linked to perforation[23]. Furthermore, the appendix often has deficiencies of both longitudinal and circular muscle fibres which predisposes to perforation but also leads to the potential for early peritoneal dissemination.

Primary SRCC of the appendix is an exceedingly rare entity with an incidence rate of 0.15 for 1 000 000 people[9]; just 4% of all appendiceal malignancies are SRCC[9]. In fact, there are only few cases reported in the literature[1,9-16] (Table 1).

Due to the intrinsic characteristics of SRCC and to the particular anatomy of the appendix, in patients with primary A-SRCC the possibility that the tumor extends beyond the colon and/or metastases at the time of diagnosis is higher than in other histological types. In particular, McCusker *et al*[1] reported that 76% of people with A-SRCC have distant localization compared to 37% with colonic type adenocarcinoma. According to the same report, lymph node involvement was present in 64% of people with A-SRCC but only in 31% with colonic type adenocarcinoma.

Similarly to SRCC of stomach and colon, SRCC of the appendix causes survival chances to be lower compared to other histological cases. Using multivariate analysis, the presence of signet-ring cells has to be considered as an independent prognostic indicator of poor survival[14]. In fact, the overall 5-year survival for A-SRCC is 18%, ranging from 42%, 46%, 76% and 83% for adenocarcinoma, mucinous carcinoma, goblet-cell carcinoma and carcinoid respectively[9].

The stage-adjusted survival for A-SRCC ranges from 55% in localized disease to 7% in cases of a distant involvement[9]. Moreover, the risk of dying is higher for patients with tumor spread beyond colon and/or metastases in cases of SRCC compared to colonic type adenocarcinoma (HR = 1.82, 95% CI: 1.09-3.04) and with goblet cell carcinoma (HR = 1.66, 95% CI: 1.13-2.44)[1].

According to most current guidelines, a right hemicolectomy should be performed for all non-carcinoid invasive tumors of the appendix: this is also recommended in cases of a secondary procedure[9,23-25]. The 5 year survival rate of patients who underwent a right hemicolectomy was 68% *vs* 20% for those who only underwent appendectomy[23].

However, the optimal therapeutic approach for appendiceal tumors with peritoneal seeding is the object of discussion in the current scientific literature[9,10,14,23-29]. Although complete cytoreductive surgery and HIPEC have recently become the treatment of choice for peritoneal disseminated disease[24-27] and were shown to ensure a 3-year overall survival of 86% for HIPEC patients compared to 29% for unresectable patients[28], it remains unclear which is the best surgical approach when a non-carcinoid appendiceal neoplasm associated with peritoneal carcinomatosis is incidentally found during surgery. While Murphy *et al*[24] have recently suggested that, for an optimal outcome, any neoplasm greater than 2 cm and any other neoplasm involving the base of the appendix or appendix mesentery should undergo an immediate right hemicolectomy, González-Moreno *et al*[27] demonstrated that a right hemicolectomy does not ensure any survival advantage in patients with mucinous appendiceal tumors with peritoneal seeding without peritonectomy and perioperative hyperthermic intraperitoneal chemotherapy. An explanation may be that adhesions induced by prior operations can entrap tumor cells and allow them to progress[27,30]. In addition, Ortega-Perez *et al*[31] studied four patients with a paracaval tissue invasion by an appendiceal mucinous tumor previously removed by right hemicolectomy and argued that open tissue planes at the site of a right hemicolectomy result in deep invasion of the tumor.

For these reasons, some authors have suggested that a right hemicolectomy should be performed only if it is necessary to clear the primary tumor, when lymph node involvement is histologically demonstrated and/or when a non-mucinous histological type is identified[27].

In conclusion, non-carcinoid appendiceal malignancy is a rare entity. Because of its incidental finding in clinical practice and as a general postoperative diagnosis, the correct approach is often not known. Reviewing the literature, we suggest that the therapeutic algorithm for these histological types should be (Figure 1): (1) tumor size less than 2 cm, without appendix mesentery infiltration, lymph node involvement and peritoneal seeding - appendectomy;

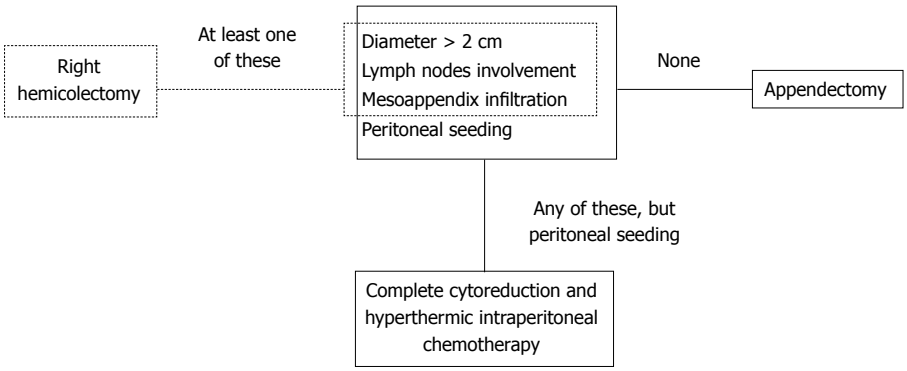

Figure 1 Therapeutic algorithm for non-carcinoid appendiceal tumors.

(2) tumor size more than 2 cm, appendix mesentery infiltration and/or histologically demonstrated lymph node involvement without peritoneal seeding - right hemicolectomy; and (3) any tumor size, lymph node involvement, appendix mesentery infiltration with peritoneal seeding - complete cytoreduction and HIPEC as treatment of choice; if not feasible, appendectomy and refer the patient to an appropriate specialist center.

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CASE REPORT

Endobronchial metastasis from adenocarcinoma of gastric cardia 7 years after potentially curable resection

Takaaki Hanyu, Tatsuo Kanda, Atsushi Matsuki, Go Hasegawa, Kazuhito Yajima, Masanori Tsuchida, Shin-ichi Kosugi, Makoto Naito, Katsuyoshi Hatakeyama

Takaaki Hanyu, Tatsuo Kanda, Atsushi Matsuki, Kazuhito Yajima, Shin-ichi Kosugi, Katsuyoshi Hatakeyama, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori 1-757, Niigata 951-8510, Japan
Go Hasegawa, Makoto Naito, Division of Cellular and Molecular Pathology, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori 1-757, Niigata 951-8510, Japan
Masanori Tsuchida, Division of Thoracic and Cardiovascular Surgery, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori 1-757, Niigata 951-8510, Japan
Author contributions: Hanyu T and Kanda T drafted the manuscript; Kanda T, Matsuki A, Yajima K and Kosugi S were responsible for the patient management; Kanda T and Matsuki A were involved in follow-up of the patient; Tsuchida M played a central role in surgery of the lung tumor; Hasegawa G and Naito M made a great contribution to pathological diagnosis; Hatakeyama K coordinated the research group and supervised this study.
Correspondence to: Tatsuo Kanda, MD, PhD, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Asahimachi-dori 1-757, Niigata 951-8510, Japan. kandat@med.niigata-u.ac.jp
Telephone: +81-25-2272228 Fax: +81-25-2270779
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Abstract

Endobronchial metastasis (EBM) is a rare form of metastasis from extrapulmonary malignant tumors, although there are few reports of EBM from gastric cancer specifically. We report the case of a 51-year-old woman who had undergone gastrectomy for advanced gastric cancer seven years previously but was diagnosed with a solitary lung tumor by follow-up computed tomography. On diagnosis of primary lung cancer, she underwent pulmonary lobectomy, but immunohistochemical examination confirmed the resected tumor to be an EBM from the gastric cancer. Six months later, she was diagnosed with peritoneal metastases and underwent chemotherapy with gastric cancer regimen. She is still alive at 33 mo after the lobectomy. Generally, the prognosis for EBM is poor although multidisciplinary treatment can lead to long-term survival. Precise diagnosis on the basis of detailed pathological and immunohistochemical evaluation can contribute to deciding the most effective treatment and improving prognosis.

Key words: Endobronchial metastasis; Immunohistochemistry; Gastric cancer

Peer reviewers: Iberto Zaniboni, MD, UO di Oncologia, Fondazione Poliambulanza, Via Bissolati 57, Brescia 25124, Italy; Giulio Melloni, MD, Department of Thoracic Surgery, San Raffaele Scientific Institute, Via Olgettina, 60, Milan 20132, Italy

Hanyu T, Kanda T, Matsuki A, Hasegawa G, Yajima K, Tsuchida M, Kosugi S, Naito M, Hatakeyama K. Endobronchial metastasis from adenocarcinoma of gastric cardia 7 years after potentially curable resection. *World J Gastrointest Surg* 2010; 2(8): 270-274 Available from: URL: http://www.wjgnet.com/1948-9366/full/v2/i8/270.htm DOI: http://dx.doi.org/10.4240/wjgs.v2.i8.270

INTRODUCTION

Endobronchial metastasis (EBM) is a rare form of metastasis from extrapulmonary malignant tumors of the lungs. Although EBM can be histologically discriminated from ordinary lung metastasis, EBM is frequently overlooked because it is rare and not widely known by clinicians. We report a case of EBM from an adenocarcinoma of the gastric cardia. In the present case, the tumor was clinically diagnosed as a primary lung carcinoma because the tumor

was solitary and the disease-free interval from the prior gastrectomy was as long as seven years. The lung tumor was surgically excised and histological examination including immunohistochemical analysis revealed it to be an EBM from the adenocarcinoma of the gastric cardia. We present herein the results of immunohistochemical analysis and discuss the clinicopathological features of EBM based on previous literature.

CASE REPORT

A 51-year-old woman was diagnosed with a solitary lung tumor during follow-up after surgery for adenocarcinoma of the gastric cardia (Siewert type Ⅲ)[1]. Eighty-five months earlier, the patient underwent radical surgery for gastric carcinoma. The tumor was highly advanced, invading the esophagus and the pancreas, but was completely excised by transhiatal esophagectomy, total gastrectomy, caudal pancreatectomy, and splenectomy. Histological examination revealed that the gastric tumor was a moderately differentiated adenocarcinoma, and the final stage of the disease was T4(pancreas)N2H0P0CY0M0, stage Ⅳ according to the Japanese classification of gastric carcinoma, 2nd English edition[2]. Thereafter, the patient underwent adjuvant chemotherapy with 16 cycles of weekly administration of methotrexate and 5-fluorouracil and had shown no evidence of disease recurrence in the 85 mo prior to this episode.

Computed tomography (CT) of the chest depicted an irregular nodular mass measuring 2.6 cm × 1.6 cm in size, which was associated with frosted-glass-like finding of the medial segment (S5) in the right lung (Figure 1). Serum carcinoembryonic antigen level was 3.3 ng/mL (normal range: 5.0 ng/mL or less). Other serum tumor markers, including squamous cell carcinoma related antigen, cytokeratin 19 fragment, sialyl Lewis X-I antigen, neuron-specific enolase, and progastrin-releasing peptide, also showed normal levels. The patient underwent Saccomanno's sputum cytology, which revealed adenocarcinoma cells. The patient was diagnosed with primary lung adenocarcinoma and underwent right middle lobectomy. The resected specimen indicated that the tumor measured 3.0 cm in diameter, outgrew as a polypoid in the bronchial lumen, and invaded the surrounding lung parenchyma. Histological findings revealed that the tumor was composed of well-differentiated papillary and tubular adenocarcinoma, displacing the bronchial epithelium. Therefore, the adenocarcinoma was postulated to be a primary bronchial-lung carcinoma (Figure 2).

To distinguish whether the tumor was a primary lung carcinoma or a gastric cancer metastasis, further immunohistochemical examination was performed using an antibody to human thyroid transcriptional factor (TTF)-1, a marker for lung carcinoma, and markers for gastrointestinal carcinoma, an antibody to human caudal type homeobox transcription factor (CDX)2 and an antibody against hepatocyte nuclear factor-4α (HNF4α). Unexpectedly, the lung tumor cells were negative for TTF-1 and positive for both CDX2 and HNF4α, and the same result

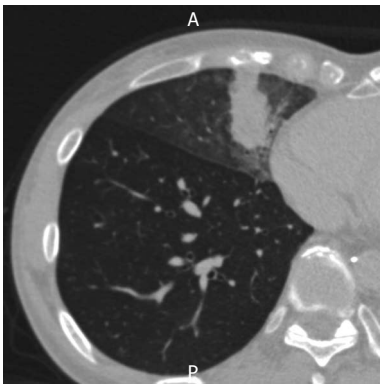

Figure 1 Chest computed tomography showing nodular shadow measuring 26 mm × 16 mm in size with frosted-glass-like shadow in right lung S5.

was obtained for the primary gastric cancer (Figure 3). In addition, the excised lung tumor was negative for CK7 expression, a conventional immunochemical marker for lung-originated tumors (data not shown). Consequently, the lung tumor in the present case was diagnosed as an EBM from the adenocarcinoma of the gastric cardia.

Follow-up CT performed 5 mo after the pulmonary lobectomy revealed massive ascites accompanied by an enlargement of the left ovary. Paracentesis revealed adenocarcinoma cells in the ascites. The patient was diagnosed with peritoneal and ovarian metastases and underwent chemotherapy with paclitaxel (100 mg/body administered weekly for 3 wk per 4-wk cycle). After 8 cycles, the ascites disappeared and ovary size became normal. The patient is continuing this regimen and complete clinical response has been achieved for 19 mo so far.

DISCUSSION

The lungs are often involved in extrapulmonary malignancies, although EBM is uncommon. EBM is clinically characterized by obstructive bronchial symptoms and chest X-ray findings, such as atelectasis. To date, there have been cases where secondary bronchial involvement from mediastinal lymph node, hilar lymph node, or parenchymal metastases has been included in EBM. Currently, EBM is defined as a metastasis developing on the tracheobronchial wall, occupying the mucosal epithelium, growing into a polypoid mass in the bronchial lumen, and invading pulmonary parenchyma. EBM is clearly discriminated from ordinary pulmonary metastases that occur in alveolar parenchyma, and its frequency is estimated to be from 2% to 13% of pulmonary metastases, based on data from cancer autopsy series or bronchoscopic bronchial biopsy series[3-5].

The most common primary tumors associated with EBM are breast, renal, and colorectal carcinomas. Others include tumors of the bladder, skin, thyroid, pancreas, ovary, testis, uterus, melanoma, and various sarcomas[3,5-9]. Many of the pulmonary involvements from gastric cancer appear as carcinomatous lymphangitis or pleuritis. Moreover, solitary pulmonary metastasis was found in only 0.1% to 0.5% of patients who underwent surgery for

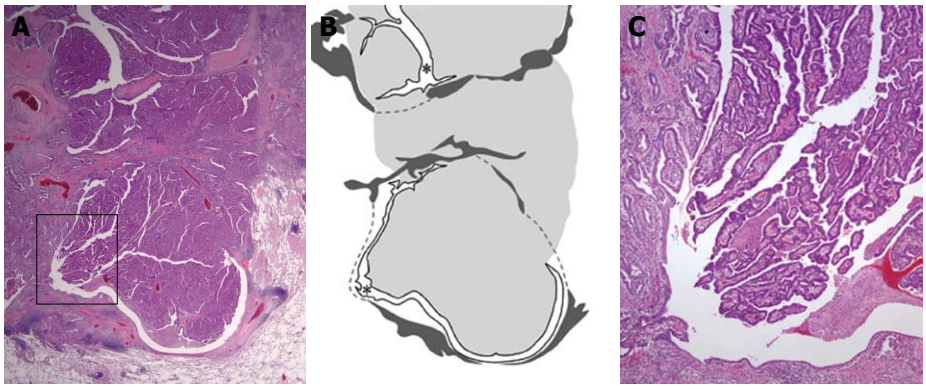

Figure 2 Pathological findings of resected lung tumor (HE staining). The illustration (B) depicts the location and growth pattern of the tumor. A tumor arose from the bronchial wall and grew endoluminally. The tumor, forming a polypoid mass, almost completely obstructed the middle lobe bronchus. The tumor measured approximately 3 cm in diameter. The extent of the tumor is illustrated in light gray. Dark gray areas indicate smooth muscle layers of the bronchial wall. Asterisks indicate the remaining original bronchial lumen. Histologically, the tumor was a well-differentiated papillary and tubular adenocarcinoma. Figure 2C is a magnification of the part enclosed by a grid in Figure 2A. The tumor cells displaced the bronchial mucosal epithelium. Original magnification: ×10 (A), ×40 (C).

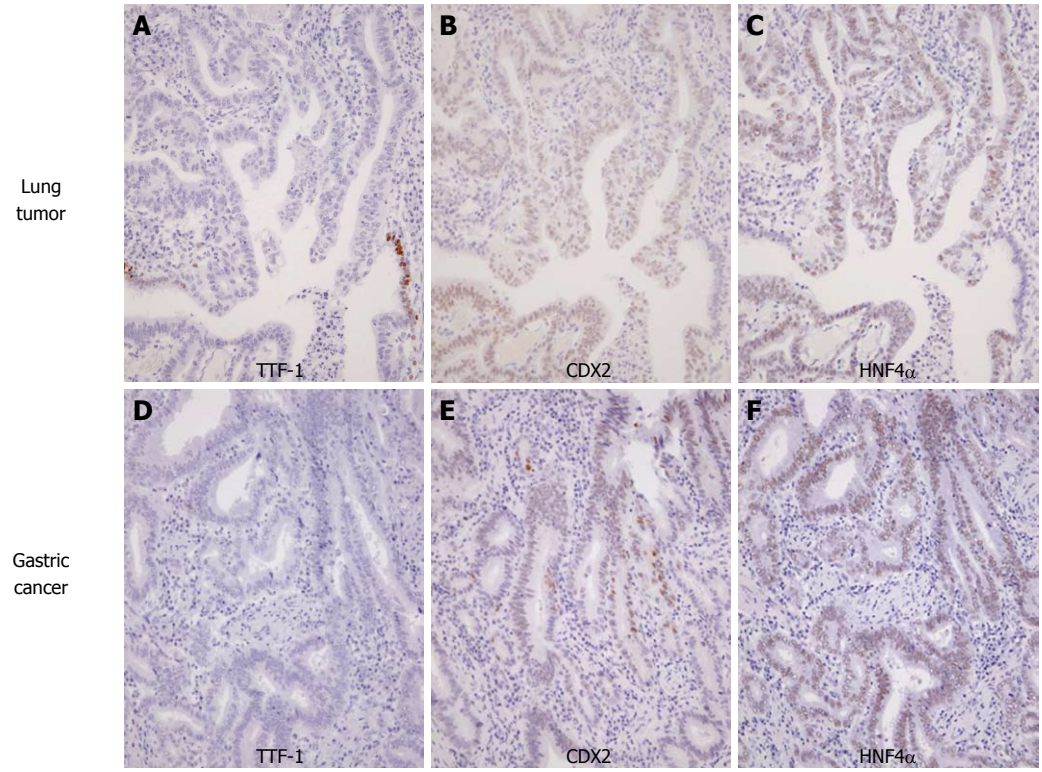

Figure 3 Lung tumor was immunohistologically negative for thyroid transcription factor-1 (A) and positive for caudal type homeobox transcription factor 2 (B) and hepatocyte nuclear factor-4α (C), the primary gastric carcinoma showed the same immunoreactivity (D-F) (Original magnification × 200). Thyroid transcription factor (TTF)-1: NCL-TTF-1 (Novocastra, UK, 1/100 dilution). Caudal type homeobox transcription factor (CDX)2: NCL-CDX2 (Novocastra, UK, 1/100 dilution). Hepatocyte nuclear factor-4α (HNF4α): mouse mAb H1415 (recognizing a wider range of HNF4α isoforms) (Perseus Proteomics, Tokyo, Japan, 1/100 dilution)

gastric cancer[10-12]. Thus, EBM from gastric cancer is very rare from the viewpoint of the primary tumor and the metastatic pattern. To our knowledge, only five cases have been described and detailed information is available only in three[13-15] (Table 1). Of the four EBM patients including ours, two were diagnosed synchronously with the time of diagnosis of the primary tumors and were associated with respiratory symptoms. The two patients died shortly after diagnosis. On the other hand, in the remaining two patients, the tumors were diagnosed as EBM by histological examination of surgically resected specimens. It should be noted that EBM appeared long after gastrectomy and the patients were alive for more than one year after lobectomy for EBM in both cases.

To devise an appropriate treatment strategy, it is vital to differentiate EBM from primary lung cancer although this is usually difficult. In metachronous cases, it was often that EBM occurred after long disease-free intervals; the average intervals were from 3.8 to 5.0 years[5,8,16], indicating that this disease is characterized by relatively slow progres-

Table 1 Reported cases of endobronchial metastasis from gastric cancer

Year	Author	Age/Sex	Primary cancer			Endobronchial metastasis			
			Histological type	Stage (TNM)	Surgery	Opportunity	Interval	Therapy	Outcome
1999	Park *et al*[13]	27/F	por, muc, sig	-	None	Dry cough	Synchronous	Chemotherapy	3 mo dead
2000	Scala *et al*[14]	57/F	por, sig	T4NxMx	TG	Dry cough, dyspnea	Synchronous	No therapy	2 mo dead
2005	Yoshioka *et al*[15]	76/M	tub2	T2N0M1	DG + Hepatectomy	Medical examination	59 mo	Resection	15 mo alive
2009	Present case	51/F	tub2, tub1	T4N1M0	EG + TPS	Follow CT	85 mo	Resection	33 mo alive

por: Poorly differentiated adenocarcinoma; muc; Mucinous carcinoma; sig: Signet-ring cell carcinoma; tub2: Moderately differentiated adenocarcinoma; tub1: Well differentiated adenocarcinoma; TG; Total gastrectomy; DG: Distal gastrectomy; EG: Esophagectomy; TPS: Total gastrectomy with pancreaticosplenectomy; CT: Computed tomography.

sion. Similarly, in our case it took seven years from surgery of the primary tumor to recognize the pulmonary lesion as a malignancy. This was why the tumor in our case was initially diagnosed as a primary lung cancer.

When a metastatic tumor resembles a primary lung cancer histologically, no absolute criteria are available to differentiate primary tumor from metastasis. In such cases, immunohistochemistry should be considered. Park *et al*[17] reported the use of immunohistochemistry in differentiating a primary tumor from a metastatic adenocarcinoma. Su *et al*[18] reported the important role of immunohistochemistry in distinguishing primary lung adenocarcinoma from metastatic lung adenocarcinoma. Cytokeratin (CK)7 and CK20 have been used as markers for this purpose. However, the low specificity of these markers remains problematic. Recently, new organ-specific markers have been reported. The application of these molecular markers is improving the ability of pathological diagnosis. CDX2 expression was found in 93.9% of colorectal cancer cases and 60.9% of gastric cancer cases, but not in any primary lung cancer cases[17]. Tanaka *et al*[19] reported that HNF4α could be a novel diagnostic marker for metastases of unknown primary origin particularly in cases of gastric-origin: HNF4α expression was exclusively found in metastasis from gastric carcinoma[19,20]. Meanwhile, TTF-1 expression was noted in 72.5% to 88.0% of lung adenocarcinoma cases but not in any extrapulmonary adenocarcinoma cases[17,18]. In our case, the lung tumor was immunohistochemically negative for TTF-1 and positive for CDX2 and HNF4α. The immunoreactivity for the three biomarkers was very similar to that of the gastric tumor that was surgically excised seven years earlier and consequently the lung tumor was finally diagnosed as an EBM from the gastric cancer. Furthermore, the disease recurred as a Krukenberg tumor after the lung tumor was excised, supporting the belief that the lung tumor was a metastasis from the gastric cancer despite the long disease-free interval.

Treatments for EBM include surgical resection, local radiotherapy, chemotherapy, and bronchoscopic disobstruction. EBM is essentially a manifestation of the disease at a far advanced stage and has poor prognosis[4,6,16]. Therefore, systemic treatment, i.e. chemotherapy, is recommended in most cases. Distinguishing EBM from primary lung cancer is vital to the selection of the appropriate chemotherapeutic regimen and could be critical for the selection of molecularly targeted drugs. In our case, surgical resection was chosen because the diagnosis could not be made before resection. The patient had peritoneal metastases thereafter and underwent systemic chemotherapy with gastric cancer regimen.

Generally, the survival time from the diagnosis of EBM is short, averaging 9 to 19 mo[4-6,16]. The prognosis for EBM from gastric cancer is unclear because we have data from only a few case reports. In our review of literature, we found that two patients surviving for a long periods were those who underwent lobectomy for metachronous EBM. Although publication bias should be taken into consideration, surgical resection could be the treatment of choice when the target lesion is single and resectable, no extrapulmonary metastasis is found, and the disease-free interval is long. In addition, as patients who underwent resection of EBM face a high risk of recurrence, they should be carefully followed up.

In summary, we have reported a rare case of EBM from gastric cancer, in which immunohistochemical analysis was useful for diagnosis and selection of the appropriate chemotherapeutic regimen. The patient in the present case is alive at 33 mo after the lobectomy. Our findings suggest that precise diagnosis and multidisciplinary treatment of EBM are important, and these could be achieved by detailed pathological analysis, including immunohistochemical evaluation of the tumor.

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Toshifumi Wakai, MD, PhD, Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata City 951-8510, Japan

Shinichi Yachida, MD, PhD, Department of Gastrointestinal Surgery, Kagawa University, 1750-1, Ikenobe, Miki-cho, Kita-gun, Kagawa 761-0793, Japan

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Events Calendar 2010

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The Venetian And Palazzo, 3355 Las Vegas Blvd South, Las Vegas, United States
http://www.gilearn.org/clinical-congress

January 27-31, 2010
Alpine Liver & Pancreatic Surgery Meeting
Carlo Magno Zeledria Hotel, Madonna di Campiglio, Italy
http://www.alpshpbmeeting.soton.ac.uk

February 25, 2010
Multidisciplinary management of acute pancreatitis symptoms
The Royal Society of Medicine, 1 Wimpole Street, London, United Kingdom
http://www.rsm.ac.uk/academ/pancreatitis10.php

March 4-7, 2010
2010 Annual Meeting of the Society of Surgical Oncology
Renaissance® St. Louis Grand Hotel, 800 Washington Avenue, St. Louis, Missouri, United States
http://www.surgonc.org/

March 25-28, 2010
20th Conference of the Asian Pacific Association for the Study of the Liver
Beijing, China
http://www.apasl2010beijing.org/en/index.aspx

April 14-18, 2010
The International Liver Congress™ 2010
Vienna, Austria

May 1-5, 2010
2010 American Transplant Congress
San Diego Convention Center, 111 West Harbor Drive, San Diego, United States
http://www.atcmeeting.org/2010

May 1-5, 2010
Digestive Disease Week 2010
Ernest N Morial Convention Center, 900 Convention Center Blvd, New Orleans, United States
http://www.ddw.org/

May 15-19, 2010
Annual Meeting of the American Society of Colon and Rectal Surgeons
Hilton Minneapolis Hotel & Convention Center, Minneapolis, Minnesota, United States
http://www.fascrs.org/

September 16-18, 2010
Prague Hepatology Meeting 2010
Prague, Czech Republic
http://www.congressprague.cz/en/kongresy/phm2010.html

September 23-25, 2010
2010 Gastrointestinal Oncology Conference
The Sheraton Philadelphia City Center, Philadelphia, United States
http://www.isgio.org/isgio2010/program.htm

October 20-23, 2010
Australian Gastroenterology Week
Melbourne, Australia
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6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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

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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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