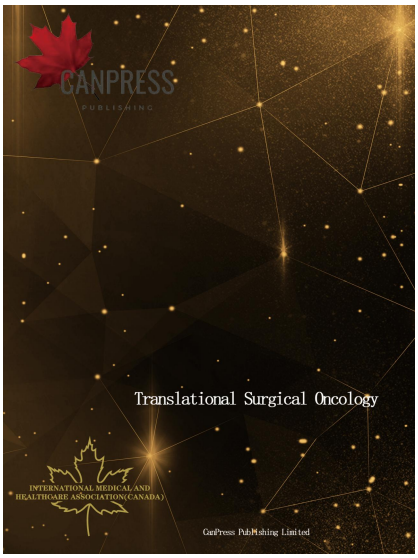
Laparoscopic intraoperative restaging for pancreatic cancer



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Abstract

Early recurrence of pancreatic cancer after resection is common, which may be due to the existence of occult metastasis in abdominal cavity or the liver which is difficult to be detected by preoperative imaging. Intraoperative restaging, including detection of occult metastases, peritoneal cytology, exclusion of liver metastasis and paraaortic lymph node sampling by using staging laparoscopy, can identify the patients with occult metastasis, avoid unnecessary radical resection, and initiate systemic treatment as early as possible, so as to prolong the survival of these patients.

Keywords: Pancreatic neoplasms; Intraoperative restaging; Recurrence; Metastasis; Laparoscopy

Introduction

With the development of systemic therapy, the overall prognosis of patients with pancreatic cancer has improved, with a 5-year survival rate of approximately 9.3%. Although surgical resection is expected to cure early-stage pancreatic cancer, the proportion of patients suitable for surgical resection is less than 20%, and early tumor recurrence commonly occurs after surgery[1-2]. Surgical procedures usually focus on R0 resection of the tumor, resulting in a series of concepts related to resectability (resectable, borderline resectable, and unresectable) and the corresponding standard[3-6]. Although it is clearly defined that distant organ metastases are unresectable, systematic diagnosis or exclusion of distant metastases remains unclear[3-6]. Currently, preoperative imaging is usually used to determine whether the tumor can be clinically resectable. However, given the frequent resection of pancreatic cancer and distant metastases in early life, clinicians should suspect the presence of microscopic metastases that are not detected by routine preoperative imaging. Therefore, in this review we propose the importance of intraoperative restaging of pancreatic cancer.

Recurrence patterns of pancreatic cancer

Johns Hopkins Hospital reported that tumor recurrence occurred in 692 patients who underwent surgical resection of pancreatic cancer, with a median follow-up time of 25.3 months. Of the 692 patients, 531 developed tumor recurrence, with a recurrence rate of 76.7% (n=531) and a median time to recurrence of 11.7 months. Among the 531 patients with tumor recurrence, distant metastasis was the most common, with an incidence of 57.8% (n=307), followed by simple local recurrence of 23.7% (n=126). For the site and time of tumor recurrence, simple liver metastasis was the most common. The recurrence rate was 25.2% (n=134), and the median follow-up time was only 6.9 months. For simple local recurrence, the rate was 23.7% (n=126), with a median follow-up time of 14.6 months, followed by simple pulmonary metastasis, which was relatively rare, with a recurrence rate of 14.7% (n=78) and a median recurrence of 18.6 months[7].

Recently, Groot et al summarized the distribution of tumor recurrence time after pancreatic cancer, reporting a median follow-up of 957 patients of 24.2 months, with tumor recurrence in 78.7% (n=753) of patients and tumor recurrence rates at 3, 6, 12, and 18 months of 11.3% (n=85), 24.2% (n=182), 51.5% (n=388), and 69.9% (n=526), respectively[2].

According to the *P*-value distribution of the survival curve, this study defined tumor recurrence as early recurrence within 12 months, which was significantly associated with poor patient prognosis[2]. A study by Honselmann et al. showed that lymph node status was closely related to postoperative recurrence time in patients with pancreatic cancer, with shorter recurrence-free survival in N1 than in N0 patients (10 vs. 16 months, *P* <0001). Moreover, patients who received neoadjuvant therapy had a longer recurrence-free survival time than those who did not receive neoadjuvant therapy (21 vs. 11 months, P <0001)[8]. However, neoadjuvant therapy and lymph node status did not affect the postoperative tumor recurrence pattern of pancreatic cancer, and distant metastasis was the most frequent in patients with tumor recurrence, followed by local recurrence, whereas distant metastasis combined with local recurrence was rare[8].

Tummers et al. showed that the surgical margin status of pancreatic cancer patients was significantly associated with patient prognosis but did not affect the tumor recurrence pattern. For patients with surgical resection margins of R0 or R1, the most common sites of tumor recurrence were the liver (63%-69%), followed by local recurrence or lung metastasis (24%), and finally, peritoneal metastasis (17%). Of the 196 patients with tumor recurrence, 55 had early recurrence within 6 months after surgery. The surgical margin of R1 resection correlated with recurrence-free survival time. The overall survival time of patients with R1 resection was significantly shorter than those with R0 resection[9].

Risk factors for postoperative tumor recurrence in pancreatic cancer include a low degree of tumor differentiation, large tumor size, vascular invasion, R1 resection, lymph node metastasis, and a lymph node positive rate (lymph node ratio, LNR> 0.2), while neoadjuvant therapy, postoperative adjuvant chemotherapy, or chemoradiotherapy can reduce the risk of recurrence [7,8]. Studies have shown that R1 resection is an independent risk factor for postoperative local recurrence, whereas lymph node metastasis or high LNR is closely related to distant metastasis, especially early distant metastasis [2,9].

Intraoperative re-staging strategy for pancreatic cancer

We believe that the laparoscopic approach for complete intraoperative restaging of pancreatic cancer should include the following four aspects: (1) exclusion of peritoneal microscopic metastasis; (2) peritoneal cytology (Cy) examination; (3) exclusion of liver metastases; and (4) histopathological examination of abdominal para-aortic lymph nodes. A reasonable operation process still needs to be explored in clinical practice.

Peritoneal microscopic metastasis

At present, it is difficult to detect microscopic metastases (diameter of approximately 1 mm) using imaging. Previous laparoscopic staging surgery has focused on these metastatic[10]. The positive rate of laparoscopic exploration of peritoneal microscopic metastases for pancreatic cancer is 11%-56%, that of laparoscopic exploration for resectable pancreatic cancer is 10%-20%, and the positive rates of laparoscopic exploration of peritoneal microscopic metastases for possible resection and locally advanced pancreatic cancer are 15%-25% and 30%-56%, respectively[11-13]. The local stage of pancreatic cancer is positively correlated with intraperitoneal microscopic metastases. A Cochrane meta-analysis showed that for resectable pancreatic and ampullary cancers, the laparoscopic test rate was approximately 21% [14], which suggests that performing laparoscopic exploration reduces unnecessary laparotomies by approximately 20%.

Peritoneal microscopic metastasis can easily occur in the omentum, mesentery, liver surface, and parietal peritoneum. During routine exploration, surgeons should pay special attention to the surface of the right posterior lobe of the liver, the proximal jejunal mesenteric surface within the omentum capsule, and the retroperitoneal area around the duodenum. Previous studies have shown that implant transfer in the above areas can account for 60% of all patients with peritoneal metastasis; however, the comparison of the detection rate of open abdomen and laparoscopic exploration was not significant[15]. At present, some researchers have tried to use near-infrared imaging (NIR) to detect pancreatic cancer microscopic metastasis, the principle of which is the use of green or other specific imaging agents combined with tumors, which are not easy to remove, using approximately 700 nm near-infrared light excitation and a special image sensor detection to detect abnormal fluorescence area lesions. A prospective study on NIR testing for the imaging diagnosis of non-metastatic pancreatic cancer was reported[16].

Cytology (Cy)

Cy examination is widely performed in gastric and ovarian cancers and is closely related to patient prognosis. Yamada et al. reported the results of Cy examination in patients with pancreatic cancer (n=390); the positive Cy examination rate in patients with pancreatic cancer with routine surgical resection was approximately 13.1%. Even if the Cy test was positive, if patients received adjuvant chemotherapy, the prognosis was significantly better than that of patients without surgical resection or patients with obvious peritoneal metastasis[17]. Therefore, a positive Cy test result is not a contraindication for surgical resection. This view differs significantly from that of scholars in Western countries. Ferrone et al. analyzed the Cy examination data of 462 patients with pancreatic cancer (including 217 patients who underwent surgical resection) at the Memorial Sloan Kettering Cancer Center and showed that the overall positive rate of Cy examination was 17%, among which the positive Cy examination rates of patients with surgical resection, local progression, and metastasis were 5%, 11%, and 37%, respectively18. Even if patients with positive Cy examination underwent surgical resection, the prognosis was not statistically significant compared with that of patients

in other IV stages. Therefore, radical surgery is not recommended for such patients[18]. A meta-analysis of previous literature showed that the positive Cy test rate of resectable pancreatic cancer was approximately 11.8%, and the positive Cy test was associated with peritoneal metastasis (OR = 4.57, 95%CI:3.08 ~ 6.78, P = 0000), overall survival time (HR = 3.18, 95%CI:1.88 ~ 5.39, P = 0000), and disease-free survival time (HR = 2.88, 95%CI:2.39 ~ 3.49, P = 0000)[19].

Whether a positive Cy examination result is equivalent in patients with distant metastasis is controversial. The National Comprehensive Cancer Network (NCCN) guidelines suggest that patients with positive pancreatic cancer are consistent with those with distant metastasis, and surgical resection should be avoided. However, the Japanese pancreatic cancer regulation holds that the prognosis of patients with positive Cy examination is worse than that of patients with negative Cy but better than those with distant metastasis, which can be separately recorded in the case for future analysis. A positive Cy examination is not an absolute contraindication for surgical resection6,[20].

At present, Cy examination still has several problems. First, Cy examination has high requirements for diagnostic physicians. If Cy examination is routinely performed in clinical practice, diagnostic physicians face tremendous pressure on technical and personnel grounds. Second, Cy examination methods are diverse and include HE, Gimsa, and Pap staining, but their accuracy needs to be improved. Moreover, the analysis and detection methods developed in recent years, such as real-time fluorescence quantitative PCR, need further tests to validate their specificities and sensitivities. Finally, in some experienced units, Cy examination shows whether patients with positive intraoperative pathological examination results should continue with pancreatic resection; however, there are no control study results on surgical resection and non-resection in patients with positive Cy examination results and resectable pancreatic cancer. Drawing on the experience of gastric cancer, we believe that if the patients with positive Cy examination results terminate surgical resection, Cy examination response is good, and Cy examination may turn negative. Abdominal exploration can be considered in patients with primary tumors that can be excised. If Cy examination is negative during surgery, surgical resection of the primary tumor can be considered.

Hepatic metastases

The liver is the most common metastatic site of pancreatic cancer and accounts for 70% of patients with distant metastasis, while patients with pancreatic cancer and liver metastasis have poor prognosis[21]. Therefore, detecting liver microscopic metastasis and avoiding unnecessary surgical resection are important to prolong patient survival time. Enhanced MRI examination of liver metastasis is better than CT and should be performed preoperatively. In conditional medical institutions, the liver-specific contrast agent, gadololite, should be used to improve the detection rate of liver metastases. In addition to routine intraoperative examination, clinicians can use ultrasound (with or without contrast sonography) and NIR to further explore and exclude liver metastases.

In recent years, the use of NIR spectroscopy in pancreatic surgery has gradually increased. In addition to the detection of liver metastases, NIR can be used for pancreatic margin determination, lymph node metastasis detection, neuroendocrine tumor localization, and photoimmunotherapy for pancreatic cancer[22-24]. At present, new NIR imaging agents are consistently available; however, indocyanine green is still the most commonly used agent. Yokoyama et al. reported 49 patients with pancreatic cancer who were treated with 25 mg (diluted concentration to 2.5 mg/mL) indocyanine green 1 d before surgery[25]. The intraoperative exploration results showed that 13 patients had abnormal liver fluorescence areas, and pathological examination confirmed that 8 cases were microscopic metastases. The analysis results at 6 months of follow-up showed that 10 out of 13 patients showed liver metastasis, while 36 patients without abnormal fluorescence aggregation and only one case had liver metastasis, and the prediction rates of positive and negative liver microscopic metastasis by indocyanine green was 77% and 97%, respectively[25].

Endoscopic ultrasound (EUS) can further detect liver lesions based on an ordinary intraoperative ultrasound examination. Research reports that even if patients with rectal cancer have undergone MRI before surgery, intraoperative ultrasound contrast examination can still detect more metastases, and the diagnostic accuracy can be improved from 83% to 97%[26]. NIR and intraoperative ultrasound technology can complement each other in the ultrasound-blind area near the liver surface and in the deep liver area where fluorescence cannot penetrate. Recently, the results of laparoscopic NIR and intraoperative ultrasound detection of tiny metastases showed that seven out of 25 patients with resectable pancreatic cancer had suspected metastases, including two liver metastases. In addition, NIR imaging quality was closely related to the time of indocyanine green administration; 2 d before surgery was better than 1 d before surgery, and NIR imaging was valuable to exclude false positive lesions found by ultrasound examination[27].

At present, it is necessary to note the clinical combination of NIR and intraoperative ultrasound exploration of liver metastasis and to include the following considerations about its use: (1) Exclusion of false-positive patients. NIR and intraoperative ultrasonography revealed several abnormal nodules in the liver. Clinicals adjacent to the liver surface are prone to undergo biopsy by surgical resection, whereas those deep in the liver are relatively difficult to biopsy. When there are many technical and diagnostic difficulties in puncture biopsy, it is necessary to accumulate experience and develop new contrast or imaging agents to improve diagnostic

accuracy. The sensitivity, positive predictive value, and accuracy of liver metastasis using ultrasonography can reach 99%, 98%, and 97%, respectively[26]. (2) Selection of the appropriate NIR imaging and ultrasound contrast agents. In addition to the commonly used indocyanine green, many new NIR imaging agents have been used in the diagnosis and treatment of pancreatic cancer; however, whether these imaging agents can be used in the detection of liver metastasis of pancreatic cancer and are better than indocyanine green remains in need of further study. Currently, the most commonly used ultrasound contrast agent is Sonovue, which has the disadvantage of no Kupffer cell stage that quickly subsides in the liver and is, therefore, not conducive to a comprehensive liver scan. The new ultrasound contrast agent, Sonozoid, can compensate for this defect. (3) Reasonable administration time of the NIR imaging agent. Currently, when NIR examines liver metastasis, indocyanine green is administered intravenously, and after a period of time, is completely excreted by the normal liver tissue, with abnormal fluorescence in the remaining lesion. To improve the imaging rate, it is necessary to determine the best time window to minimize the liver background, and the fluorescence at the lesion is significantly higher than that in normal liver tissue. Currently, the time of preoperative administration remains controversial, and the best time still needs to be determined.

Para-aortic (No. 16) lymph node metastasis

No. 16 lymph nodes are those distributed from the diaphragm angle to around the abdominal aorta at the bifurcation of the iliac artery. According to the anatomical site, it can be divided into groups a1, a2, b1, and b2, which are located at the upper edge of the start of the abdominal trunk, lower edge of the left renal vein, and upper edge of the inferior mesenteric artery, respectively. According to the relationship between the lymph nodes and the inferior vena cava and abdominal aorta, it can be divided into the prevena cava, posterior vena cava, preaorta and postaortic, intervena cava, para cava, and para-aortic groups. At present, extended lymph node dissection, including No. 16 lymph nodes, is not recommended in domestic and foreign guidelines; however, lymph node metastasis in No. 16 is closely related to patient prognosis, and there is no reliable means to detect No. 16 lymph node metastasis before surgery[28-29]. Therefore, it is necessary to make a clear diagnosis by lymph node biopsy in No. 16 and to record it as an important prognostic factor. The rate of lymph node metastasis in No. 16 ranges from 10% to 34%[30]. Risk factors for lymph node metastasis in No. 16 include late tumor T stage, arterial and nerve invasion, station 1 (such as groups 13 and 17 for pancreatic head cancer) and station 2 (e.g., group 14 for pancreatic head cancer), and others[31].

The equivalence of No. 16 lymph node metastasis with distant metastasis remains controversial. Experts in Western countries believe that patients with No. 16 lymph node metastasis have a poor prognosis and are no longer suitable for surgical resection[32]. However, a Japanese study showed that No. 16 lymph node metastasis was not an independent risk factor for patient prognosis, and some patients may benefit from pancreatectomy[33]. Other studies have shown that patients with pancreatic head cancer had preoperative CA125 <18.62 U/mL, which may still benefit from radical surgery, even in No. 16 lymph node metastases[34].

Regarding No. 16 lymph node biopsy, factors such as the site of lymph node biopsy in No. 16 and the treatment of lymph node-positive patients in No. 16 should be considered. As previously described, the No. 16 lymph nodes can be divided into multiple regions, wherein groups a2 and b1 lymph nodes are closely associated with pancreatic cancer metastasis. We believe that the tumor site should be considered in the lymph node biopsy site, preoperative imaging examination, and intraoperative exploration site in No. 16. Patients with pancreatic head cancer can undergo biopsy of the IVC interaortic lymph node (No. 16 lymph node a2, b1) by Kocher incision, while those with pancreatic tail cancer, except in the above areas, can have para-aortic lymph nodes explored via the Treitz ligament approach.

In view of the current consensus on the significance of lymph node metastasis in No. 16, we believe that each medical center can choose different treatment methods according to their own experience and record them separately for later analysis. LNR is an important indicator of patient outcome[2,35]. In clinical practice, our team required four examinations of lymph node biopsy in No. 16, expanded patients with positive biopsy and calculated LNR, and abandoned surgical resection if LNR> 025.

The feasibility of laparoscopic restaging

In recent years, minimally invasive surgery has rapidly developed, and laparoscopic technology has covered all fields of pancreatic surgery. Despite a long learning curve, laparoscopic pancreatectomy is safe and feasible[36]. The work of intraoperative restaging recombined the work once performed clinically, which did not increase the difficulty of surgery. Based on our previous experience, the operation time did not affect operation safety. Reasonable arrangement of the process of intraoperative re-staging can be helpful in shortening the operation time. We recommend the following procedure: (1) Laparoscopic (fluorescent laparoscopic) exploration, excluding abdominal microscopic metastasis; (2) cytology; (3) laparoscopic ultrasonography of the liver, after the examination of which the ultrasound contrast agent is injected (the contrast agent containing Kupffer cells is recommended); (4) sampling of lymph nodes in No. 16; and (5) laparoscopic ultrasound to examine the liver in patients with a contrast medium containing Kupffer cells. We expect that after strict intraoperative restaging, the positive rate for resectable pancreatic cancer is ≥10%.

Conclusions

Pancreatic cancer is highly malignant with common distant

metastases, and systemic therapy is the main means to improve prognosis. If unnecessary surgery is performed, patients usually need to wait 6-8 weeks before receiving systemic treatment, which prevents a survival time of only 3-6 months for patients with pancreatic cancer with distant metastases[37,38]. Therefore, we recommend that all patients with pancreatic cancer who have undergone radical surgery be restaged, that potential patients with distant metastasis be identified, that unnecessary surgical resection be avoided, and that patients undergo systemic treatment as soon as possible to prolong their survival time. Further studies are required to confirm the effectiveness of these strategies.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgement

This study was supported by Beijing Municipal Science & Technology Commission (grant number: Z171100001017077); Beijing Municipal Science and Technology Commission Clinical Diagnosis and Treatment Technology Research and Demonstration Application Project (grant number: Z191100006619038); Capital Medical Development and Research Special Project (grant number: 2020-1-2012); Construction Project of Clinical Advanced subjects of Capital Medical University (grant number: 1192070312); Capital Medical Development and Research Special Project (grant number: Z201100005520090).

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