



Status and Prospect of Comprehensive Treatment for Pancreatic Cancer with Oligometastatic Disease

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Abstract

Oligometastatic disease indicates a distinct state in cancer patients characterized by a low metastatic burden of the cancer. With recent progress in the concept and strategy of comprehensive treatment of pancreatic cancer, there have been an increasing number of reports on successful conversion therapy for oligometastatic pancreatic cancer. However, there is still a lack of high-quality clinical trials to prove the significance of surgical treatment for metastatic pancreatic cancer, and controversies exist on this topic. In this review, we summarize current status of pancreatic cancer oligometastasis, discuss the significance of conversion therapy strategies and the indications for surgical resection, and propose the future prospects in the field.

Keywords: pancreatic cancer; oligometastasis; chemotherapy; immunotherapy; surgical resection

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Introduction

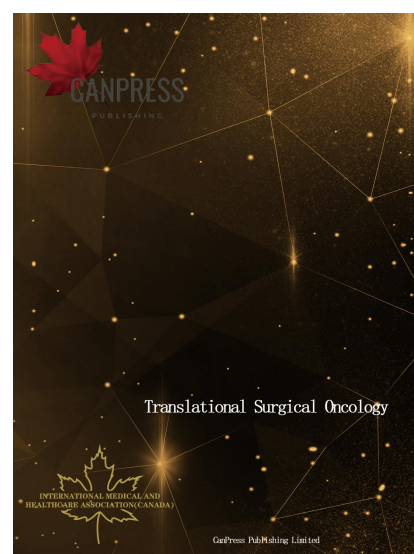
Pancreatic cancer is one of the most dismal malignancies with low rate of early diagnosis and surgical resection, insensitivity to chemoradiotherapy, and lack of effective targeted immunotherapy. The overall prognosis of pancreatic cancer is extremely poor, and the overall 5-year survival rate is only about 10%^[1]. Currently, surgical resection combined with perioperative chemotherapy is the only promising modality to cure pancreatic cancer. However, only about 20% of pancreatic cancer patients are suitable candidates for radical resection. With active adjuvant chemotherapy, the median postoperative survival for patients with resected pancreatic cancer is expected to reach 25.5~54.4 months, with a 5-year survival rate about 20%~28%^[2,3]. More than 50% of patients with pancreatic cancer have distant metastases at the first diagnosis, and the median overall survival of such patients is only 6-9 months^[4].

In recent years, great improvement in the concept and strategy of comprehensive treatment of pancreatic cancer has been made, represented by the progress of chemoradiotherapy and targeted immunotherapy under the guidance of

multidisciplinary team (MDT), which have contributed greatly to the long-term survival of pancreatic cancer patients. For example, the objective response rate of FOLFIRINOX combination chemotherapy was as high as 32%, and the median overall survival reached 11.1 months for patients with unresectable late-stage pancreatic cancer^[5]. Based on these improvements, there have been an increasing number of reports on successful conversion therapy for oligometastatic pancreatic cancer. However, there is still a lack of high-quality clinical trials to prove the significance of surgical treatment for metastatic pancreatic cancer, and controversies exist on this topic. In this review, we summarize current status of pancreatic cancer oligometastasis, discuss the significance of conversion therapy strategies and the indications for surgical resection, and propose the future prospects in the field.

Definition of oligometastatic pancreatic cancer and its effect in prognosis

There are arguments that malignant tumors are systemic diseases. In addition to imaging lesions, there are often a large number of preclinical micrometastases. Therefore, once distant metastasis occurs, even if there is only one visible



metastasis, cancer cells are likely to spread to the whole body and local treatment often has little benefit. In 1995, Hellman first mentioned the concept of "oligometastasis", referring to the distant metastasis lesion number is less than 5 and limited to only one organ (such as the liver, lung, etc.). Hellman hypothesized that such metastasis has not yet made transitions to distant metastasis or multiple metastasis, and could be "cured" if the appropriate local treatment is chosen^[6]. With the progress of systematic chemotherapy, some patients traditionally considered as pancreatic ductal adenocarcinoma (PDAC) in stage IV would benefit from surgical treatment. The definition of oligometastatic is in constant evolution. In addition to considering the number and size of tumor metastasis, primary tumor type, metastasis organ, the biological behavior of tumor should all be factored in comprehensive treatment strategy. In conclusion, the core of the definition of oligometastatic is whether it can bring about patient survival benefit after receiving local treatment.

When distant metastasis of pancreatic cancer occurs, the overall median overall survival (OS) is only 5-9 months. It is generally believed that even if the primary and metastatic lesions can be removed, OS is not improved. Many patients will have new metastases or cancer progression during chemotherapy alone. Distant metastasis is regarded as a surgical contraindication in the past^[7]. In recent years, more retrospective studies have revealed that some highly selected pancreatic cancer patients with concurrent liver oligometastases may benefit from surgery. In 2019, Damanakis et al.^[8] retrospectively reviewed the clinical data of 128 patients with pancreatic cancer complicated with distant metastases. In 63% of these patients, the metastases were confined to a single organ (the liver or lung), and OS was significantly longer than those with multiple organ metastasis (12.2 versus 4 months). It was also found that patients with 4 or fewer lesions limited to only one organ, baseline CA199 <1000 U / mL, and tumors that were stable or in remission after first-line chemotherapy had a better prognosis. Only 7.8% of the total patients (8 cases located in the liver, 2 cases located in the lung) met all criteria. The median OS was 19.4 months, significantly longer than the 7.2 months seen in other remaining patients. It is believed that these patients are expected to benefit from surgical treatment.

The status of surgical treatment of pancreatic cancer with concurrent liver oligometastases

For patients with pancreatic cancer metastatic to the liver, there has been increased interest in exploiting strategies that have successfully been used for the treatment of oligometastases in other tumor types. This suggests that patients with advanced pancreatic cancer do not completely lose the opportunity of local treatment, the results have allowed more patients to undergo surgical resection and the key is how to select the patients who can benefit from surgery.

In 2018, Andreou et al.^[9] analyzed 76 patients undergoing

resection for pancreatic cancer and concomitant hepatectomy for concurrent liver oligometastases. The results showed that R0 resection, preoperative systemic chemotherapy, and postoperative adjuvant chemotherapy represent long-term survival benefits. Increasing the safety of pancreatic surgery has allowed for a combined surgical approach with curative intent for selected patients. The authors believed that pancreatic surgery and liver resection is safe and feasible. Patients had increased survival rate under multimodal treatment strategies including perioperative chemotherapy and liver resection. Crippa et al.^[10] performed a systematic review of the studies that included patients with synchronous liver metastases published in the era of multiagent chemotherapy (after 2011). Six studies with 204 patients were analyzed, 63% patients underwent upfront pancreatic and liver resection, and 35% patients had surgery after primary chemotherapy with strict selection criteria and 2% had an inverse approach (liver surgery first). The perioperative mortality rate was <2%. Median OS ranged from 7.6 to 14.5 months after upfront pancreatic/liver resection and from 34 to 56 months in those undergoing preoperative treatment. It shows that the surgical treatment of pancreatic cancer combined with concurrent hepatic oligometastases is safe and feasible. Careful selection of patients after systematic chemotherapy are more conducive to obtaining long-term survival. Unfortunately, OS of patients with liver metastases of pancreatic cancer is still poor, the preoperative systemic therapy may help evaluate the tumor biological behavior and select the patients with potential benefit from surgical treatment. This evidence lets us speculate that a better knowledge of tumor biology, with a careful evaluation of response to chemotherapy could lead to an increase in conversion surgery rates and a better selection of subjects who can benefit from it.

The Guidelines for the Diagnosis and Treatment of Pancreatic Cancer in China (2021) suggest that systemic treatment is preferred for patients with single liver oligometastases. However, the clinical practice for pancreatic cancer with liver oligometastatic surgery still lacks quantitative standards, such as the specific size, number, the choice of preoperative chemo-chemotherapy regimen, chemotherapy cycle, treatment effectiveness evaluation criteria (based on imaging or tumor markers). Treatment decision is still based on the subjective evaluation and the patient's will. Yu et al.^[11] reported prospective multicenter study on simultaneous surgical treatment of pancreatic cancer with no more than 3 liver metastases, and other enrollment criteria included: tumor reduction or stabilization after FOLFIRINOX, resection of primary and liver metastasis; no new lesions during treatment; a 50% decrease in CA19-9 or an absolute value no more than 500U / mL.

In conclusion, the treatment of pancreatic cancer with liver metastasis should still prioritize systematic treatment. Surgical resection can be attempted on tumor with good biological factors, prudent select potential benefit group, emphasis based on radical expand resection, rather than palliative expansion.

The treatment strategy for pancreatic cancer combined with liver oligometastases

With the development of imaging technology, the presence of distant metastases in pancreatic cancer can be detected by preoperative imaging examination. The traditional workflow of conducting laparotomy before deciding whether to perform radical surgery has been deprecated. If the preoperative imaging diagnosis is not clear, the laparoscopic exploration can still be performed first to detect the occult lesions that cannot be detected before the surgery. However, a small number of patients with pancreatic cancer are combined with distant metastasis, especially for millet-like metastasis which is difficult to identify in the preoperative examination.

In a multicentre retrospective study from Europe, Tachezy et al.^[12] analyzed 69 patients with pancreatic ductal adenocarcinoma and synchronous liver metastasis who underwent simultaneous pancreas and liver metastasis resections. Most of these liver metastases were intraoperative incidental findings. Prognostic analysis found significantly longer median OS of patients in the surgical resection group (14 compared with 8 months, $P < 0.001$). The median OS of the patients with primary tumor located in pancreatic head, which received surgical or nonsurgical treatment was 13.6 and 7 months, respectively ($P < 0.001$), compared to pancreatic tail cancer patients received surgical or nonsurgical treatment (14 versus 15 months, $P = 0.312$). This suggests that patients with pancreatic head cancer with concurrent liver oligometastases may benefit more from surgical treatment than patients with pancreatic tail cancer. In current clinical practice, when the intraoperative liver metastases are evaluated as oligometastatic and R0 resection is possible, most patients may still try concurrent surgical treatment, especially if the tumor is located in the tail of the pancreas. However, even if the radical resection of both primary lesions and metastases is performed, the prognosis improvement is limited, especially for patients with pancreatic tail cancer. Whether such patients should give up surgery to conduct systematic treatment and then radical surgery is to be validated in future prospective trials.

Surgical treatment of liver metastases after radical resection of pancreatic cancer

The surgical resection rate of metachronous liver oligometastasis after radical treatment of pancreatic cancer is low, the patient prognosis is extremely poor, and there is no consensus on therapeutic strategy. Mitsuka et al.^[13] retrospectively analyzed 79 patients with pancreatic cancer who underwent radical resection. In the study, 71 patients were diagnosed with tumor recurrence and metastasis, and 17 patients with only liver metastases. The median OS was significantly better in the liver resection group than the other patients who had a recurrence (55 months versus 17.5 months, $p = 0.016$). Regarding liver-only metastasis, the median survival time after liver recurrence was significantly better in

the liver resection group than in the non-liver resection group (31 months versus 7 months, $p = 0.0008$). The authors found that the disease-free survival (DFS) in the liver resection group was 21 months, significantly longer than the 3 months in the non-resected group. Therefore, the latter metastases appear, the better the prognosis is. The indications criteria for selecting patients with metachronous liver oligometastasis after radical treatment of pancreatic cancer for liver resection are based on: only liver metastasis; no more than three metastases; no new metastases after three months of observation.

For recurrent liver metastases after postoperative liver metastasis resection of pancreatic cancer, the surgical indications are the same as above, but with a requirement of 12 months of recurrence-free time.

Hackert et al.^[14] summarized the experience of surgical treatment of liver metastasis in 23 cases after radical pancreatic cancer. The median interval between the initial and the consecutive operation was 18.4 months, and the median OS after liver resection was 14.8 months, which was significantly better than that of patients in the symptomatic supportive treatment group. Schwarz et al.^[15] reported clinical data of 25 patients, the median interval liver resection between pancreatic resection and liver resection was 17.8 months, 1- and 3-year survival rates of 64% and 12% after liver surgery, respectively, and the median OS was 36.8 months, significantly better than 9.2 months in the non-surgical group. These studies suggest that the time after radical pancreatic cancer to the onset of liver metastasis is an important factor affecting the prognosis. The later the onset of liver metastasis, the greater the possibility of benefit from surgical treatment^[14,16].

In conclusion, current limited data confirm that some patients with liver oligometastases after radical surgery of pancreatic cancer can still perform surgical resection through systemic treatment selection.

Status of surgical treatment of pancreatic cancer combined with pulmonary oligometastases

The lung is the second predominant distant metastatic organ of pancreatic cancer, often presenting with multiple metastases, with little chance of radical resection. Some retrospective clinical studies showed that the prognosis of pancreatic cancer patients with simultaneous or metachronous isolated pulmonary dissemination was significantly better than other patterns of multiple metastasis or multiple organ metastases, and such patients are expected to benefit from radical surgery.

Liu et al.^[14,17] analyzed the data of 11541 patients with pancreatic cancer combined with concurrent distant metastasis in the SEER database between 2010 and 2014. Survival analysis showed that the median OS in patients with single-organ metastases was significantly better than in those with multi-organ metastases. The median survival time of the

patients with pulmonary metastases was significantly better than that of the patients with liver metastases (6.0 ± 0.32 versus 4.0 ± 0.86 months). The survival time of patients with radical resection of primary lesions and pulmonary metastases was significantly better than that for those without surgery (14.0 ± 1.93 versus 6.0 ± 0.32 months, $p < 0.0001$). The indicators for prognosis included TNM stage of primary tumor, time of lung metastasis, interval time and the number of lung metastatic lesions. The authors believe that patients with simultaneous or heterogeneous pulmonary oligometastases pancreatic cancer may have a survival benefit from surgical treatment.

Lovecek et al.^[18] analyzed the characteristics of patients with metachronous pulmonary metastases after radical pancreatic cancer. The study consists of 159 patients with radical surgery pancreatic cancer. Metachronous pulmonary metastases were observed in 20 cases (16.9%). The median DFS and OS of single-organ pulmonary metastasis (including oligometastasis and multiple metastases) were 81.4 and 35.4 months, respectively, while the median DFS and OS in patients with non-pulmonary metastases were only 9.4 and 15.8 months, respectively. The authors considered that the prognosis of patients with pulmonary metastasis after radical pancreatic cancer was better than that of patients with other organ metastases. Patients were divided into three subgroups: isolated pulmonary oligometastases, isolated pulmonary multiple metastases, and pulmonary metastases with other organ metastases. For all patients with isolated pulmonary oligometastases, surgical treatment should be considered while weighing the surgical risks.

Ilmer et al.^[19] reviewed the clinical data of 11 patients with pancreatic cancer and analyzed the risk factors affecting the prognosis. In 2020, Guerra et al.^[20] conducted meta-analysis involving 15 clinical studies data of 11,916 pancreatic cancer patients with simultaneous or metachronous distant metastasis, and confirmed that patients with single organ metastasis have better prognosis than multiple metastasis. Limited to the lung metastasis is associated with better DFS and OS than liver metastasis, local recurrence or peritoneal metastasis.

Conclusion and perspective

In conclusion, with the progress of surgical technology, the surgical treatment of pancreatic cancer with liver and lung oligometastasis is safe and available in clinic (Figure 1). However, the prognosis of patient remains to be confirmed by high-quality clinical trials. The screening of potential patients who can benefit from surgery is also an urgent problem. According to the current limited retrospective clinical studies, the prognosis of patients with oligometastatic pancreatic cancer is better than that of the patients with multiple metastases, especially with multiple organ metastases.

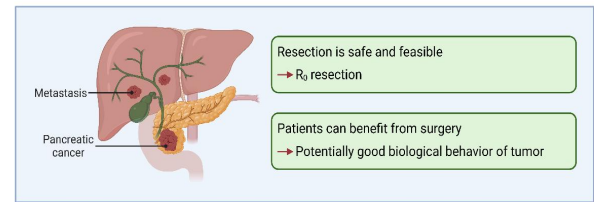


Figure 1. Schematic presentation of the feasibility of surgical resection for pancreatic cancer oligometastasis.

Oligometastatic pancreatic cancer which has potentially good biological behavior may be screened from systemic chemotherapy. We should advocate high-quality clinical trials to promote the selection of surgical benefit group, and evaluate the outcome of simultaneous and metachronous oligometastatic lesion resection. Therefore, we could avoid blind surgery which may increase the burden of patients and offer little advantage or even harm patients. On the other hand, we could avoid missing the opportunity of surgery in other patients, because resection of synchronous and metachronous oligometastatic shows promising results on the safety and survival in highly selected patients.

Conflict of interest

The authors declare no conflict of interest.

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