Editorial

Liver metastasis of pancreatic cancer: the new choice at the crossroads

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Keywords: Pancreatic cancer with liver metastasis (PCLM); systemic chemotherapy; surgery; liver oligometastasis

Submitted Oct 14, 2022. Accepted for publication Dec 20, 2022. Published online Jan 16, 2023.
doi: 10.21037/hbsn-22-489
View this article at: https://dx.doi.org/10.21037/hbsn-22-489

In recent years, the incidence of pancreatic cancer has increased markedly both in China and internationally. For patients with pancreatic cancer, surgical resection remains the only effective method of obtaining a cure and long-term survival, although only few patients can expect this benefit. Most pancreatic cancers have a hidden onset, and the early symptoms are atypical, resulting in most patients being in the middle to late stage of disease at the time of clinical consultation. Moreover, more than half of the patients have distant metastasis at the time of diagnosis, with the liver being the most common site of pancreatic cancer metastasis. Indeed, liver metastatic pancreatic cancer accounts for more than half of all pancreatic cancers.

The liver metastasis of pancreatic cancer is a multistage and multistep process. The primary tumor is highly similar to the liver metastasis: the primary tumor is highly invasive and the metastasis is highly proliferative. The adaptation and interaction between tumor cells and tumor microenvironment promote the colonization and growth of pancreatic cancer cells in the liver (1). Genomic data have shown that the tumor mutation spectrum is very similar between pancreatic cancer *in situ* and liver metastases, with the mutations of pancreatic cancer driver genes (including *KRAS*, *TP53*, *SMAD4*, etc.) being almost identical (2). In the early stages, mutations in the KRAS gene and activation of epithelial-mesenchymal transition (EMT) in pancreatic cancer cells facilitate the spread of tumor cells from the primary site. After colonization of the liver, the disseminated tumor cells regain their epithelial phenotype, while their energy metabolism is remodeled to achieve stronger oxidative phosphorylation and aerobic glycolysis, all of which provide the necessary infrastructure for tumor cell colonization and growth. However, in contrast to genome sequencing, comparison of transcriptomic data from primary and metastatic tumors containing microenvironmental tissues suggests significant differences between pancreatic cancer *in situ* and liver metastases, with significant differences in the expression of genes related to the tumor microenvironment (3). This undoubtedly shows that liver metastasis of pancreatic cancer is not only related to pancreatic tumor cells but is also affected by tumor microenvironment. Pancreatic ductal adenocarcinoma (PDAC) is nonimmunogenic and characterized by a profibroproliferative tumor microenvironment with a large number of fibroblasts and extracellular matrix (ECM) deposits (4). A similar desmoplastic stroma has been found in liver metastases. Cancer-associated fibroblasts (CAF) not only supports cancer cell growth and egress from the primary tumor, but also escort cancer cells to distant organs in order to be able to establish micrometastases (5). Xie *et al.* found that PDAC-derived exosomes (Pex) can promote the formation of the hepatic fibrosis microenvironment by reconstructing liver ECM, which in turn may indicate liver-specific metastasis (6). Pancreatic cancer cells and hepatocytes communicate with each other over long distances via Pex, which is essential for the formation and metastasis of the prometastatic microenvironment (7). The Pex-derived CD44v6/C1QBP complex mediates the positive effects of Pex on liver fibrosis and PDAC liver metastasis, and their expression in tissues-derived

extracellular vesicles (EVs) and circulating exosomes predicts prognosis and liver metastasis in patients with PDAC (6). The metastatic tumor microenvironment is relatively rich in immune cell infiltration (8), so the immunosuppressive microenvironment formed during pancreatic cancer with liver metastasis (PCLM) is crucial for tumor cells to evade immune destruction. Analysis via spatial metabolomics indicates that different metabolites in pancreatic cancer, mesenchymal, and paraneoplastic tissues may contribute to pancreatic cancer micrometastasis and the immunosuppressive microenvironment.

Patients with PCLM have a worse prognosis compared to those with lung metastases or bone metastases. After liver metastasis, most patients lose the opportunity of surgical resection. For patients with PCLM, a combination of systemic chemotherapy and local treatment remains the first choice. Chemotherapy regimens mainly include the FOLFIRINOX regimen (calcium folinate, fluorouracil, irinotecan and oxaliplatin) and gemcitabine combination regimen (Gemcitabine plus albumin-bound paclitaxel) (9). However, the effect of chemotherapy was very limited, with a median overall survival (OS) of 11.1 months for FOLFIRINOX and 6.8 months for nab-paclitaxel plus gemcitabine (10,11).

In the era of targeted immunotherapy, the exploration of targeted and immunotherapy for pancreatic cancer is far behind that of other solid tumors, mainly because the detection rate of related mutated genes in patients with pancreatic cancer is extremely low. However, developing targeted and immunotherapy with fewer side effects is clearly critical for treating advanced pancreatic cancer. In 2019, olaparib became the first targeted drug for advanced pancreatic cancer, nearly doubling median progression-free survival in patients with advanced pancreatic cancer. Current National Comprehensive Cancer Network (NCCN) guidelines recommend olaparib maintenance therapy after first-line platinum-based chemotherapy for patients with BRCA germline mutations (12). Fortunately, the number of viable molecular targets for PDAC is increasing significantly, providing promising potential therapeutic approaches. In terms of immunotherapy, pancreatic cancer has been considered to be a "cold tumor" in immunotherapy, mainly because of the weak immunogenicity of pancreatic cancer cells, the lack of effector lymphocytes in tumor tissues, and the massive infiltration of immunosuppressive cells, that is, the low immunogenicity and noninflamed phenotype of PDAC in pancreatic cancer cells. Therefore, immunotherapy alone cannot improve the prognosis of patients with pancreatic cancer. Yang *et al.* reported that M2-type macrophage-derived classical complement C1q, which was significantly expressed in the primary and metastatic mesenchyme, was also confirmed to promote the invasion and metastasis of pancreatic cancer cells in vitro. Metastases are richer in CD8-positive T cells than in primary lesions, suggesting the possibility of immunotherapy for hepatic metastatic pancreatic cancer (1). Forkhead box protein 3 (FOXP3), a key factor in regulatory T cells (Treg cells), is highly expressed in PDAC and is involved in the remodeling process of infiltrating immune cells in pancreatic cancer. Its function is to recruit FOXP3 + Treg cells by upregulating CCL5 to mediate immune evasion, which provides a brand new perspective for the immunotherapy of pancreatic cancer. With the continuous development of new drugs and clinical trials (e.g., gemcitabine combined with tumor vaccine, PD-1 antibody combined with CTLA-4 antibody, TNF-α and dendritic cell vaccine), immunotherapy will eventually be more widely used in pancreatic cancer (13).

For patients with PCLM to be operated on, the primary pancreas and liver metastases need to be resectable and not accompanied by metastasis of other organs. Moreover, if the liver diverges more in the metastatic lesion, this indicates that the tumor is highly malignant and has entered a very late stage. Patients with PCLM with 3 or fewer liver metastases are referred to as pancreatic cancer patients with hepatic oligometastasis. The liver metastases in these patients are between isolated metastases and extensive multiple metastases, and they are also regarded as potential radical surgical targets. Finally, the responsiveness of patients with PCLM to systemic chemotherapy is also an important factor in the efficacy of surgery. Serum tumor markers are widely used as objective indicators to evaluate the efficacy of systemic therapy. Reni *et al.* reported that patients with CA19-9 decreased by ≥50% after induction chemotherapy for pancreatic cancer were more likely to receive survival benefit after surgery (14). In addition, the evaluation of heterogeneous phenotypic profiling of circulating tumor cells (CTCs) can also help to establish promising diagnostic and prognostic markers for PDAC patients (15). It should be noted that all patients with PCLM should receive adjuvant chemotherapy after surgical resection.

Currently, international and Chinese guidelines, including the NCCN guidelines, do not recommend surgical treatment for patients with PCLM. However, a research team from Shanghai Jiao Tong University

School of Medicine has shown that for highly select patients with hepatic oligometrically metastatic pancreatic cancer whose primary tumor is located in the body and tail of the pancreas, simultaneous surgery on the primary and metastatic lesions can provide significant survival benefits, with a median survival time of 16.8 months being reported (16), Tachezy *et al.* also found a significant improvement in median OS in patients who underwent combined pancreatic and hepatic resection compared with those who did not (14.5 versus 7.5 months, P<0.001) (17). In addition, Shrikhande *et al.* and Ouyang *et al.* showed that surgical treatment brought a significant increase in median OS in PCLM patients in their respective studies (18,19). But in their paper, Dünschede *et al.* (20) did not recommend simultaneous resection of pancreatic cancer and liver metastases, as the median survival of patients who received simultaneous resection was not better than that of those who received chemotherapy. Takada *et al.* (21) also reported that simultaneous resection of pancreatic tumors with liver metastases is not recommended because it does not provide a survival benefit to patients. Despite this, retrospective studies do show that simultaneous resection of primary lesions and liver metastases provides a survival benefit. However, due to the limitations of retrospective studies and the possible large selection bias involved, the cases included are highly limited and heterogeneous. We believe that radical surgery can only bring survival benefits to a few select PCLM patients, and combined resection of primary tumors and metastases is not recommended and should thus not be extended to all patients with PCLM. Only carefully selected patients with PCLM may benefit from surgical resection.

In conclusion, patients with PDAC and oligometastases to the liver should receive primary chemotherapy (9). For the select patients who have long-term chemotherapy response to primary chemotherapy, surgical resection can be considered because these patients may benefit from the subsequent resection. Prospective and multicenter studies are needed to confirm this trend and better define criteria for appropriate patient selection for this innovative treatment, which should still not be considered as common clinical practice.

Acknowledgments

Funding: This study was supported by a grant from the Liaoning Provincial Department of Education Science Research Project (No. LJKZ0743).

Footnote

Provenance and Peer Review: This article was a standard submission to the journal. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-489/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editor: J. Gray)

Cite this article as: Liu Z, Gou A, Wu X. Liver metastasis of pancreatic cancer: the new choice at the crossroads. HepatoBiliary Surg Nutr 2023;12(1):88-91. doi: 10.21037/hbsn-22-489