

Oligometastatic Disease in Pancreatic Cancer – How to Proceed?

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Keywords

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Summary

Background: Pancreatic cancer is a highly aggressive malignancy and will become the second leading cause of cancer-related death in the USA and also in Germany by 2030. Furthermore, the majority of patients with pancreatic ductal adenocarcinoma (PDAC) will present with distant metastases, limiting surgical management in this population as there is little evidence available to support surgical or ablative treatment options for advanced-stage disease. However, highly selected patients suffering from synchronous and metachronous oligometastatic PDAC may potentially benefit from a surgical resection with an acceptable morbidity. **Methods:** This review summarizes and discusses the current literature on the management of oligometastatic disease regarding PDAC, focusing on para-aortic lymph nodes as well as isolated hepatic and pulmonary metastases. **Results and Conclusion:** In order to further investigate the feasibility and efficacy of such an approach, a prospective multicenter trial, in which survival and quality of life after metastatic resection and systemic chemotherapy is evaluated, has to be initiated. Additionally, local and locoregional ablation techniques or stereotactic body radiation therapy as therapeutic options for isolated metastases in PDAC need further research in order to determine their significance and benefit.

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Introduction

Metastatic pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis with a median overall survival of about 6 months and will become the second leading cause of cancer-related death in the USA and also in Germany by 2030 [1, 2]. It is therefore one of the most lethal cancers, as indicated by a very high mortality-to-incidence ratio [3]. In contrast to the steady increase in survival for most cancers, advances have been slow for pancreatic cancer, for which the 5-year relative survival rate is currently 8%. These low rates are explained by the fact that more than 50% of cases are diagnosed at a distant stage discovered by imaging at the time of diagnosis or during attempted pancreatic resection. Furthermore, another 30% present with locally advanced pancreatic cancer [3, 4].

Pancreatic cancer metastasizes primarily to the liver, peritoneum, and lungs [5]. However, distant metastases of PDAC have been reported in almost every organ, including bones and adrenal glands [6–9], the brain and leptomeninges, diaphragm, gallbladder, heart and pericardium, small and large intestines, kidneys, ovaries and uterus, seminal vesicles, skin, stomach, spleen, testis, thyroid gland, urinary bladder, as well as orbit [7, 9–19].

It is widely accepted that surgical resection remains a vital necessity for a potential cure of this cancer entity. Over the past decades, the median overall survival has increased to 25–30 months after surgical resection in combination with adjuvant chemotherapy, and 5-year survival is well over 20% in these patients but still remains poor due to the high propensity of the tumor for locoregional and systemic recurrence [4, 20, 21]. In such palliative settings, therapeutic regimens, such as FOLFIRINOX or gemcitabine and nab-paclitaxel, have been established as the standard of care very recently [22, 23]. Although palliative chemotherapy is the

standard of care for patients with metastatic disease [24], management of the subgroup of patients with oligometastatic disease is not clear. Therefore, unlike in other malignancies, synchronous or metachronous metastasectomy of PDAC is rarely performed in current clinical practice.

Several treatment options, including neoadjuvant therapy with subsequent resection as well as ablative technologies, should be considered. However, there is little evidence available to support treatment options for oligometastatic disease. As valid predictive biomarkers for stratification of therapy are not available today, future trials need to define the role of the different treatment options. This review summarizes the current evidence and discusses available treatment options for oligometastatic PDAC with a specific focus on para-aortic lymph nodes (PALN) as well as on metastases to the liver and lungs.

Para-Aortic Lymph Nodes

PALN (Group 16 according to the Japanese Pancreas Society) [25] are considered as 'extra-regional' lymph nodes and are involved only after the metastatic spread has already reached the peri-pancreatic first-echelon lymph nodes [26]. Although positive nodes in this group are considered as distant metastases (M1 disease), their prognostic value remains controversial [27]. Recently, a systematic review by the Bassi group was performed [26]. Here, 13 studies were included and PALN metastasis appeared to correlate with poor prognosis in patients with PDAC. The largest study was a retrospective multicenter analysis of 882 patients who had undergone pancreatic resection with pathological evaluation of PALN for PDAC [28]. Patients with metastatic PALN in this study had a significantly poorer median survival than those without (17 vs. 23 months; $p = 0.001$). In contrast, Shrikhande et al. [29] compared outcome after resection for M1 pancreatic cancer, including a subgroup with positive PALN. In this study, survival of these patients was significantly better (27 months) than in the subgroup with resected liver (11.4 months) or peritoneal metastases (12.9 months) and was comparable to node-negative patients. In contrast, in a larger study from the University of Heidelberg, a median survival of 12.3 months was reported in $n = 43$ patients with resected positive PALN [30]. Therefore, as the data remains inconsistent, it seems difficult to draw a final conclusion concerning this issue, which is also reflected in a recent consensus statement by the International Study Group on Pancreatic Cancer [25].

Hepatic Metastasis

Role of Surgery

More than 90% of patients who are diagnosed with PDAC die from the disease. Approximately 70% of these patients have extensive metastatic disease at the time of death, with 30% having limited metastatic disease, but many of them have bulky primary tumors [29]. As already mentioned, the liver is the most common site of PDAC metastasis.

For colorectal liver metastases, despite the availability of alternative therapeutic options, hepatectomy remains the treatment of choice. It has been proven to be safe and oncologically beneficial, extending survival and improving quality of life [31, 32]. After curative resection of colorectal liver metastases, 5-year survival rates range from 28 to 60% depending on strategies and preoperative selection criteria [33]. Likewise, resection for hepatic metastases of neuroendocrine tumors, including pancreatic neuroendocrine tumors, is widely accepted with the objective of symptom control and improved long-term outcome [34]. However, in patients undergoing liver resection for non-colorectal, non-neuroendocrine liver metastases, patient selection seems to be even more critical than in colorectal liver metastasis or primary liver tumors [35]; however, the significance of surgery has not been satisfactorily elucidated, especially regarding long-term outcome. Thus, there are still controversies concerning the oncological value of liver surgery in these patients. Therefore, even in high-volume centers synchronous liver and pancreatic resections are performed in very few PDAC cases [30].

Current national and international guidelines [36, 37] do not recommend resection of the primary tumor and synchronous liver metastases; as a result, this particular treatment is only being performed in highly selected patients. It has to be noticed that in most cases the decision for an intentional resection in a patient with PDAC metastasized to the liver is made after subjective considerations of the surgeon. Ideally, this decision is based on a highly individual basis, including the patient's wishes, age, clinical status, local resectability, and the individual risk of complications. However, published data demonstrate that the procedure can be performed safely, but results are inconsistent as to whether complete resection of the PDAC with combined resection of liver metastases will lead to a survival benefit [30, 38–43]. Eight reports including more than 9 patients found median overall survival times between 5.9 and 11.4 months after resection [29, 39, 42, 44–48].

Klein et al. [44] reported a median survival in PDAC patients with hepatic metastases of 7.6 months after resection. Within this small study, 22 PDAC patients who underwent synchronous, liver-directed therapy either with anatomical liver resection (7 patients (32%)) or atypical resection (15 patients (68%)) were analyzed. All patients received adjuvant therapy with gemcitabine. Data to which extent the patients also received neoadjuvant treatment is not mentioned within the publication.

Gleisner et al. [42] reported that even among well-selected patients with low-volume metastatic liver disease, simultaneous resection of pancreatic carcinoma with synchronous liver metastasis did not result in long-term survival in the overwhelming majority of patients. In fact, the median survival of patients who underwent hepatic resection of synchronous metastasis was only 6 months, which was comparable to the survival of matched patients who underwent palliative bypass surgery only.

No benefit in overall survival in patients undergoing pancreatoduodenectomy with synchronous partial liver resection was also reported by Takada et al. [47].

Similar results were obtained by a study from Hanover. Here, a median survival of 8.3 months after synchronous liver and pancre-

atic resection and 5.8 months after metachronous hepatic resection has been reported [40]. Even if the 1-year survival rates were 41% after synchronous resection and 40% after metachronous resection of hepatic metastases of pancreatic (n = 20) or ampullary (n = 2) cancers in this study, hepatic resection could not be recommended based on these data. More promising results were reported from Heidelberg. Here, 29 patients with metastatic PDAC who underwent synchronous metastasectomy were analyzed [29]. Out of these, 11 had hepatic resection for synchronous metastasis. These overall healthy patients (ASA > III) had only one or two isolated hepatic foci and a high probability that histologically negative resection margins could be achieved. Based on the significantly longer median overall survival of 11.4 months in the resected patients compared to 5.9 months in the group who underwent explorative laparotomy only, it was concluded that simultaneous liver resection for metastatic disease can be performed with acceptable safety in highly selected patients.

Most likely owing to a less selective cohort, the group from Mainz argued against simultaneous resection of the primary and liver metastases based on their experience [39]. In contrast, resection of metachronous PDAC liver metastases seems to improve survival in selected patients. The authors reported on 23 patients with metachronous and synchronous hepatic metastases. In 14 cases, liver metastases were found simultaneously, and in 9 cases metachronously. Of these, 13 patients underwent surgery and 10 were treated with gemcitabine only. There was no difference in survival in patients with synchronous liver metastases of PDAC treated by resection of the primary tumor combined with liver resection versus treatment by gemcitabine (8 vs. 11 months). In patients with metachronous liver metastases, the median survival was increased after metastasectomy compared to patients who were treated with gemcitabine only (31 vs. 11 months, respectively) [39].

Two studies including a larger number of patients were published very recently [30, 43]. In a retrospective fashion, six European pancreas centers reported on 69 patients suffering from synchronous hepatic metastasized PDAC who underwent simultaneous pancreas and liver resections [43]. Patients who were explored, but in whom resection was not performed, served as controls. Data from this multicenter trial suggests a significant survival benefit with acceptable morbidity and mortality for patients receiving synchronous hepatic and pancreatic resection compared to patients with liver metastases who did not undergo surgery (14.5 vs. 7.5 months, respectively; $p < 0.001$). 14% of the resected and 1% of the non-resected patients received neoadjuvant therapy ($p = 0.071$). Similar results were reported in the single-center study from Heidelberg [30], in which n = 62 patients underwent synchronous hepatic resection with a median survival of 10.6 months and n = 28 patients had metachronous hepatic resection with a median survival of 14.8 months with acceptable morbidity and mortality. These results have to be compared to exclusive intensified chemotherapy regimen such as FOLFIRINOX with a median overall survival of 11.1 months [22]. It goes without saying that these studies also have many limitations, and general conclusions must be drawn cautiously. Though only PDAC patients were included, the

analyzed groups are heterogeneous, and both PDAC of the head and the body/tail regions are analyzed.

As the FOLFIRINOX regimen is toxic and therefore more grade III and IV toxicities are encountered, this regimen may only be an appropriate option for a subset of patients. Until today we do not know whether patients who are not suitable for an intensified chemotherapy regimen according to their physical strength would do better after standard chemotherapy or synchronous resection regarding the assessment of quality of life.

This further highlights the need for assessments of quality of life when such palliative trials are performed. Given the fact that only a few patients in the study by Tachezy et al. [43] were treated with FOLFIRINOX as first- or second-line treatment due to the time-frame of the study, it is tempting to speculate that metastasectomized patients might benefit from a combination of both treatment approaches.

The question still remains:

- Which patients might benefit from such an individual approach?
- Should only patients with stable disease or also progressive disease that appeared to regress after neoadjuvant therapy be offered aggressive combined resection, or should resection be performed in chemotherapy-naïve patients with a small tumor burden?

Further research is needed to identify biomarkers for stratification of patients with low metastatic burden. In this regard, the predictive value of CA 19-9 was demonstrated in a retrospective cohort study [49]. It was suggested that CA 19-9 predicts resectability, stage of disease, as well as survival in PDAC patients. Highly elevated preoperative or increasing postoperative CA 19-9 levels were associated with low resectability and poor survival rates, and demanded the adjustment of surgical and perioperative therapy.

Role of Ablation Techniques in Liver Metastasis

Nowadays, it is not uncommon to utilize local percutaneous, locoregional transarterial as well as non-invasive local ablation techniques, including thermo-ablative approaches (radiofrequency ablation (RFA), microwave ablation, laser-induced thermal therapy, cryoablation, high-intensity focused ultrasound), chemo-ablative approaches (percutaneous ethanol injection, hepatic arterial infusion chemotherapy, transcatheter arterial chemoembolization and its variants), radio-ablative approaches (stereotactic body radiation therapy (SBRT), selective internal radiation therapy), and electro-ablative approaches (irreversible electroporation (Nanoknife®)) as tools of the multimodal treatment strategies of hepatic metastases from various kinds of tumors. During the last decade, the effectiveness and safety of these techniques have been shown for liver metastases [50–57]. These modalities are currently offered to selected patients with colorectal cancer liver metastasis but results vary due to tumor size, number, volume and location [58]. Accepted applications include inoperable disease due to tumor distribution or inadequate liver reserve. Furthermore, other current indications include concurrent comorbidity, patient choice, and the test-of-time approach. Future applications may include resectable disease, e.g. in patients with limited hepatic disease or with solitary liver metastasis [55, 57, 59–61], but this is of course not an accepted standard yet.

For resectable colorectal cancer liver metastasis, low perioperative morbidity and mortality with long-term survival comparable to hepatic resection in carefully selected patients has been reported [55]. In particular patients with hepatic metastases smaller than 3 cm and no tumors within 1 cm of central biliary structures showed a benefit in this study.

Furthermore, ablation techniques (i.e. RFA) have also been shown to be effective in controlling symptoms and to optimize quality of life in patients suffering from metastatic pancreatic neuroendocrine tumors [62, 63]. Very few studies have specifically analyzed the outcomes of ablation techniques for PDAC liver metastasis [64]. In a retrospective study, RFA of liver metastases was performed on 34 patients with PDAC after pancreatic resection or intraoperatively at the time of resection [65]. Criteria for RFA were liver metastasis up to 3 cm diameter in size, five or fewer lesions, and no other distant metastases. The interval between pancreatic resection and liver metastasis was 3 months (range 0–33 months). The median survival time after liver metastasis ablation was 14 months. Another retrospective series reported the outcome of using SBRT in 27 patients with liver metastasis from unfavorable primaries including 8 pancreatic cancer patients [66]. The authors found 2-year local control and overall survival rates of 85 and 38%, respectively, which suggests that both approaches could be feasible strategies for extending survival in selected PDAC patients with oligometastatic burden of the liver. To further evaluate this approach, future research within controlled prospective clinical trials is urgently needed.

Pulmonary Metastasis

Genetic alterations present in metastatic lesions reflect the mutational landscape in the founder clone and might determine the metastatic pattern of PDAC [67]. Isolated pulmonary metastasis in PDAC is infrequently encountered and might define a biologically distinct subgroup [68]. This observation is supported by data from our pancreatic center where the course of 40 PDAC patients with isolated pulmonary metastasis was analyzed [69]. 22 patients presented with pulmonary metastasis after initial resection of the primary whereas 5 patients had progression of locally advanced and therefore unresectable disease. Median survival after diagnosis of pulmonary metastasis was 25.5 months; however, when patients with less than 10 lung metastases were compared to the remaining patients, a significantly improved median survival of 31.3 versus 18.7 months was reported. The same was true for unilateral localization of lung involvement (31.3 vs. 21.8 months). These patients might therefore indicate distinct clinical and genetic subgroups. Intriguingly, recurrence of metastasis to the lung after initial primary tumor resection is associated with the best long-term survival of at least 5 years for any patient with metastatic PDAC [70]. Although resection of pulmonary metastasis has been shown to provide a survival benefit for colorectal cancer patients [71–75], data

for PDAC on this topic is extremely limited. In a retrospective study from Johns Hopkins University analyzing 31 patients with isolated metastases, a significantly improved median overall survival of 52 versus 22 months ($p = 0.04$) was demonstrated for patients undergoing resection of metastases ($n = 9$) [68].

Additionally, there was a trend in favor of pulmonary resection for post-relapse survival. Patients undergoing resection had a median survival after recurrence of 18.6 months, compared with only 7.5 months for non-surgical patients. It is again important to note that patients in this study were highly selected and had a good biological tumor character identified by a favorable response to systemic therapy. In addition, patients undergoing metastasectomy had a relatively long interval between initial pancreatectomy and pulmonary relapses. Another study from Japan analyzed Japanese case reports of metachronous pulmonary metastases from PDAC [76]. They found 17 case reports published between 1983 and 2014 dealing with pulmonary metastasectomy for PDAC. The median survival after pulmonary resection was 37 months, and the 3- and 5-year survival rates were 50 and 41%, respectively. 14 patients had disease-free intervals after resection of the primary pancreatic tumor of more than 20 months. These patients had a longer median survival after lobectomy (46 vs. 25.5 months; $p = 0.19$). 7 patients had lung metastasis of less than 16 mm. These patients also had a significantly longer overall survival after pulmonary resection (83 vs. 16 months; $p = 0.04$). Even if general considerations need to be drawn with caution, this data implies that patients with at least isolated metachronous pulmonary metastasis might benefit from surgical resection. In the recent decade, SBRT has emerged as an effective alternative resulting in local control rates exceeding 90% in mixed cohorts with very low toxicity [77, 78]. Although data specifically addressing lung metastases from PDAC have not been published, SBRT might serve as an alternative treatment for patients in which surgery is not a suitable option.

Conclusion

Taken together, highly selected patients suffering from synchronous and metachronous oligometastatic PDAC may potentially benefit from surgical resection with an acceptable morbidity. In order to further prove or disprove the feasibility and efficacy of such an approach, a prospective multicenter trial, in which survival and quality of life after metastatic resection and systemic chemotherapy is evaluated, has to be launched. Further research is needed to determine the benefit of local and locoregional ablation techniques or SBRT as therapeutic options for isolated liver metastases in PDAC patients.

Disclosure Statement

The authors declare no competing interests.

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