

## BP SY 1-2

# Role Of Surgery In The Treatment Of Oligometastatic / Recurrent Pancreas Cancer

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**Lecture :** One major challenge for the surgical treatment of PDAC shows that only approximately 15% of patients are resectable upon diagnosis, whereas 40% show distant metastasis and 45% present with locally advanced unresectable disease. Although progress has been made in the multimodal treatment of patients with resectable and locally advanced PDAC, one principle of therapy still prevails: surgical resection of the primary tumor and metastases in PDAC M1 patients, regardless of individual tumor and patient characteristics, is explicitly not recommended in clinical guidelines. PDAC M1 patients are referred to palliative chemotherapy or best supportive care independent of the number and localization of metastases or other individual patient characteristics. In this situation, the most effective palliative chemotherapeutic regimens can improve median overall survival from 6.7 to 8.5 months (gemcitabine plus nab-paclitaxel) and 6.8 to 11.1 months (FOLFIRINOX), respectively. But now, considering the above mentioned modern combination chemotherapies and safer pancreatic surgery, a new approach to metastatic disease in PDAC comes into focus in current research. Johns Hopkins group conducted matched survival analysis between 1995 and 2005, 1563 patients underwent surgical resection for periampullary carcinoma (n = 608 patients) or pancreatic adenocarcinoma (head, n = 905 patients; tail, n = 50 patients). Patients who underwent simultaneous resection for primary adenocarcinoma and for liver metastasis had a similar overall survival (median, 5.9 months) compared with patients who underwent palliative bypass alone (5.6 months; P = .46). They concluded even in well selected patients with low-volume metastatic liver disease, simultaneous resection of periampullary or pancreatic carcinoma with synchronous liver metastases did not result in long-term survival in the overwhelming majority of patients. More promising results were reported from Heidelberg. There, 29 patients with metastatic PDAC who underwent synchronous metastasectomy were analyzed. 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. So they

concluded that simultaneous liver resection for metastatic disease can be performed with acceptable safety in highly selected patients. Many published data also 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. In 1995, Hellman et al. proposed the idea of oligometastasis (OM) of advanced malignancies, which is defined as a state of limited metastasis. The basis of this concept is that a particular group of patients with metastasis may achieve long-term survival through surgical resection after precise imaging and appropriate multimodal treatment. For instance, hepatic resection of limited colorectal liver metastases led to 5-year overall survival (OS) of 28-58%. Local therapy was also reported to improve the OS of the patients with OM non-small cell lung cancer. Furthermore, Ozawa et al. reported that the 5-year OS rate of the patients treated with curative resection of limited peritoneal metastases was significantly higher than that of patients with diffuse peritoneal metastases. But, regarding OM in PDAC, there are no established criteria or consensus on diagnosis and treatment strategy. Damanakis et al. reviewed Data of 128 PDAC M1 patients treated at the University of Cologne between 2008 and 2018. Patients with a single organ metastasis (SOG) pattern independent of the metastatic site showed a significantly longer median overall survival of 12.2 months compared to 4.5 months for multiorgan metastasis (MOG) patients (95% CI 5.7-9.8;  $p = < 0.001$ ). Compared to the remaining collective, median overall patient survival of liver-only (12.0 vs 6.7 months; 95% CI 5.7-9.8;  $p = 0.148$ ), peritoneum-only (8.7 vs 7.7 months; 95% CI 5.7-9.8;  $p = 0.439$ ) and lung-only (19.5 vs 7.2 months; 95% CI 5.7-9.75;  $p = 0.072$ ) involvement showed no statistically significant difference. A concept of oligometastatic disease has been substantiated in recent years by various studies of gastrointestinal tumor diseases. Thus, Damanakis et al hypothesize the existence of OMD in pancreatic cancer that identifies patients with better tumor biology. They further hypothesize that OMD patients benefit from surgery in the sense that they live substantially longer. To approach oligometastatic disease(OMD) using a biological marker, they further categorized the limited disease group with up to 4 metastases into those with a baseline CA 19-9 below 1000 U/mL and above 1000 U/ ml. There, survival analysis revealed a significantly longer median overall survival of 16.0 months vs 6.9 months in favor of the low CA 19-9 group (95% CI 5.7- 9.8;  $p = 0.021$ ). Finally, to define the OMD, they added stable disease or response to first-line chemotherapy as another criterion representing greater benign. So, Damanakis et al. proposed a definition of OM in PDAC as cases with single-organ metastasis, the presence of no more than four metastases in the liver or lung and baseline serum cancer antigen 19-9 (CA19-9) level of  $<1,000$  U/ml. And they showed patients with OM survived significantly longer than those with other types of metastatic unresectable PDAC. Nagoya group attempted to identify cases in line with this OM concept. They reviewed A total of 130 cases with unresectable metastatic pancreatic cancer underwent non-curative surgery from April 2001 to December 2019. Peritoneal metastases. Information on peritoneal metastases was also collected from preoperative computed tomographic images and surgical records. Peritoneal metastases were also classified into four categories following the criteria of JSCCR : P0: No peritoneal metastasis, P1: metastasis localized to adjacent peritoneum, P2: limited metastasis to distant peritoneum, P3: diffuse metastases to distant peritoneum. No significant difference was found between P1 and P2-3 groups,

whereas P1-2 cases tended to have more favorable OS than P3 [median OS=14.9 months, 95% confidence interval (CI)=8.4-23.4 months for P1-2 vs. 9.7 months, 95% CI=8.4-15.8 months for P3,  $p=0.140$ ]. They chose to use the 20-month survival-specific receiver operating characteristics curve because it had the most significant area under the curve (0.661) compared with others (0.576 for 5-month survival, 0.523 for 10-month survival). The optimal cut-off value for predicting survival of  $\geq 20$  months was 2,000 U/ml. They divided 130 patients with single-organ metastasis into OM ( $n=54$ ) and non-OM ( $n=76$ ). The survival of OM cases was significantly longer than non-OM cases (median=13.0 vs. 8.4 months,  $p=0.003$ ). So, Nagoya group propose single-organ metastasis of limited tumor volume (H1 or P1/2 by the Japanese Society of Cancer of the Colon and Rectum classification) and low serum cancer antigen 19-9 level ( $<2,000$  U/ml) as new criteria for defining OM pancreatic cancer. Some studies including a larger number of patients were published recently. Tachezy et al did a retrospective analysis of 6 European pancreas centers. They identified 69 patients with pancreatic ductal adenocarcinoma and synchronous liver metastasis who underwent simultaneous pancreas and liver metastasis resections. Patients receiving exploration without tumor resection served as the control group. The median OS of patients after resection of the primary PDAC and synchronous liver metastases tended to be greater compared with patients in the non-resection group (14.5 months, 95% confidence interval [CI] 10.8–18.2 months and median 7.5 months, 95% CI 4.9–10.2 months,  $P < .001$ ). Body/tail pancreatic ductal adenocarcinomas showed no benefit of resection (median OS 14 vs 15 months,  $P = .312$ ). In the multivariate analysis, tumor resection was the only independent prognosticator for OS. Sakaguchi et al conducted a comprehensive literature search and they concluded Encouraging OS was indicated in patients with synchronous mPDAC of liver and peritoneum who underwent conversion surgery. Metastasectomy for metachronous lung and liver oligometastases could be considered a practical treatment option. As a result, 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. Local recurrence of pancreatic cancer occurs in 80 % of patients within 2 years after potentially curative resections. Among them around 30 % of patients have isolated local recurrence (ILR) without evidence of metastases. Here, an isolated local recurrence (ILR) is usually defined as a tumoral recurrence localized to the posterior resection margin, the pancreatic remnant, or the locoregional lymph nodes As is oligometastatic pancreas cancer, in spite of localized disease these patients usually only receive palliative chemotherapy and have a short survival. But, little is known about the role of surgery for recurrent PDAC. Only anecdotal experiences and small case series have been previously published, and these series reported outcomes of patients diagnosed with a variety of periampullary neoplasms or those with recurrence limited to certain anatomic sites. Some authors have recently reported encouraging results of surgical management of pancreatic cancer recurrence in selected patients, but results are inconsistent. Kleeff et al reviewed 30 patients for recurrent pancreatic cancer between October 2001 and April 2005. There was a tendency of increased median survival in the group of patients undergoing resection (17.0

months) compared with the bypass/ exploration group (9.4 months), although this difference was not significant ( $P=0.084$ ). In addition, patients with a prolonged interval (9 months) from resection to recurrence were more likely to benefit from re-resection compared with patients with recurrence within 9 months (median survival 17.0 vs. 7.4 months;  $P=0.004$ ). MD Anderson Cancer Center retrospectively evaluated the outcomes of all patients diagnosed at their institution with recurrent PDAC who underwent reoperation with curative intent over an 18-year period. The median disease-free interval after initial resection among reoperative patients was longer for those with lung or local-regional (DFI) recurrence (52.4 and 41.1 months, respectively) than for those with liver recurrence (7.6 months,  $p=0.006$ ). Re-operative patients with an initial disease-free interval  $>20$  months also had a longer median survival than those who did not (92.3 versus 31.3 months, respectively;  $p=0.033$ ). They conclude that patients who develop a solitary recurrence of PDAC in the lung after a prolonged DFI should be considered for reoperation. China group undertook a systematic review of the literature and pooled individually data to examine the outcomes of second pancreatectomy for the treatment of recurrent pancreatic ductal adenocarcinoma (PDAC) in the remnant pancreas. A total of 19 articles involving 55 patients were eligible for inclusion. The median disease-free interval after initial resection was 33 (range 7 to 143) months. Including 15 patients who developed recurrences more than 5 years after the initial operation. The 1-, 3- and 5-year overall survival rate after the second pancreatectomy was 82.2%, 49.2% and 40.6% respectively. So they concluded second pancreatectomy for recurrent PDAC can be performed safely with long-term survival in selected patients. Kim et al. reported on a cohort of 1610 consecutive patients with pancreatic cancer who underwent initial pancreatectomy with curative intent between January 2000 and December 2014 at Asan Medical Centre, Seoul, Korea. The authors performed a survival analysis according to the recurrence pattern. Survival after recurrence was better in patients who underwent resection of isolated recurrence in the remnant pancreas (median 28 vs. 12 months) and lung (median 36.5 vs. 9.5 months) than in those who did not undergo resection. Groot et al reviewed systematically treatment options for isolated local recurrence (ILR). After screening 1152 studies, 18 studies reporting on 313 patients undergoing treatment for ILR, they concluded in selected patients, treatment of ILR following pancreatic resection for pancreatic cancer seems safe, feasible and associated with relatively good survival. Another result of a systematic review and meta-analysis for isolated local recurrence of pancreatic cancer from University of Padua, Italy showed that overall survival and post-recurrence survival were significantly longer in the re-resected group) with a median overall survival benefit of 28.7 months ( $p < 0.001$ ) and median survival benefit of 15.2 months after re-resection ( $p = 0.048$ ). In conclusion, in selected patients with recurrent pancreatic cancer, resection is safe and feasible, and may offer a survival advantage. So, surgery should be considered as part of the multimodality management of relapsing pancreatic cancer. But, an accurate patient selection, considering the site and time of recurrence, and a multidisciplinary approach are essential to choose the best appropriate treatment.