Editorial Commentary

Surgical resection for pancreatic ductal adenocarcinoma with liver metastasis: is this the beginning of a new era?

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Stage IV pancreatic ductal adenocarcinoma (PDAC) is considered unresectable by the European Society for Medical Oncology (ESMO)-European Society of Digestive Oncology (ESDO) Clinical Practice Guidelines, and treatment for these patients, remains mostly palliative (1). In non-metastatic PDAC, and whenever feasible, surgery remains a crucial component, playing a key role in improving survival rates. While the general trend has been to prepare as many patients as possible for surgical intervention, the necessity for proper patient selection has become increasingly evident (2).

On the one hand, it is clear that we need to move beyond the surgical indications defined by guidelines, allowing more aggressive surgeries even in selected cases of both advanced locoregional growth and metastatic disease (1). On the other, it is essential to identify patients who would benefit the most from surgical treatment. For example, a small tumor with unfavorable biology may represent a contraindication for surgery, even if the procedure is technically feasible (3).

The focus of the scientific community has shifted from anatomical resectability to biological resectability, emphasizing the intrinsic characteristics of tumor growth and response to chemotherapy. These factors now play a critical role in determining whether a patient should undergo surgery or receive chemotherapy as the primary treatment (4).

We read with great interest the paper by Kaslow *et al.*, which focuses on identifying potential prognostic factors in the context of stage IV PDAC (5). The authors conducted a single-center retrospective analysis of a cohort of 712 patients with PDAC from 2010 to 2016. Among these patients, 245 (34%) presented with synchronous stage IV at diagnosis, and 241 were included in the final analysis. Overall, 140 patients (58%) received systemic chemotherapy, while 29% did not. Notably, in 13% of cases, it was unclear whether the patient received chemotherapy.

The authors found no statistically significant association between the primary cancer's locoregional status and overall survival (OS). However, they did report significantly better OS in a subgroup of 90 patients who achieved a landmark survival of 12 months, of which nine patients had undergone chemotherapy and had resectable synchronous liver metastases and a resectable or borderline primary tumor. These nine patients had a median OS of 39 months. Interestingly, this subgroup did not include patients with

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locally advanced PDAC, although they did not report survival outcomes for locally advanced PDAC patients. Unexpectedly, the metastatic load to the liver did not appear to play a major role in prognosis, nor did the presence of extrahepatic disease. This finding is in contradiction with previous studies which suggested that a lung metastatic pattern is associated with a favorable prognosis, while peritoneal spread is typically linked to worse outcomes (6,7).

The effort by Kaslow *et al.* to create a hypothetical cohort aligns with emerging practices at certain centers, where surgery is being performed even on metastatic patients, particularly those with liver metastases (1,6,8). For instance, Liu *et al.* reported a significant difference in survival of operated cases with liver metastasis *vs.* non-operated (6).

Pausch *et al.* demonstrated a significant improvement in the median OS for patients with PDAC and liver metastasis receiving cancer-directed surgery (CDS) compared to those who did not undergo surgery (8–12 *vs.* 4–7 months) (9).

Surgery for oligometastatic PDAC should be performed only in selected cases after a careful multidisciplinary diagnosis and treatment (9). This approach is critical, especially considering the potential impact of postoperative recovery on the quality of life, as noted by Wright *et al.*, where non-operative management might be more beneficial in certain cases (10). They also reported that up to 30.4% of patients with stage IV PDAC experienced early recurrence (within 6 months) following surgery, despite responding to neoadjuvant chemotherapy. This data could underline that response to systemic treatment is not the only factor to be considered. Therefore, optimal patient selection is crucial.

Voss *et al.* also highlight the importance of proper patient selection, though clear criteria for selection are still lacking. This includes the absence of established cut-off levels for tumor markers, as well as definitive biomarkers or guidelines regarding the size and number of liver metastases (8).

Other factors like differentiation, tumor burden, general physical status, and age should also be considered when selecting candidates for metastasectomy (6).

Older age and poor differentiation are associated with worse survival outcomes and can be considered to appropriately select candidates for CDS (10). Shi *et al.* also report age (greater than 62 years) as a prognostic factor (11). In addition to being under 70 years old, patients should also have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (8).

In the article, patient status was not used as a selection criterion; however, it was noted that 42% of the patients did not receive treatment, suggesting that many had a poor baseline functional status.

In this study, not all patients had complete data on carbohydrate antigen 19-9 (CA19-9) levels. Consequently, CA19-9 was not included as a criterion for selection. Nonetheless, the authors acknowledged CA19-9 as a potential tool for decision-making. According to Crippa *et al.*, a reduction in CA19-9 by less than 50% following chemotherapy was indeed associated with a worse prognosis, as patients with this level of reduction faced a higher risk of mortality. Patients selected for surgery were those who exhibited a significant biochemical response, defined as a CA19-9 reduction of at least 90%. Patients who underwent surgery experienced a significantly improved median survival of 39 months, compared to 11 months for those who did not have surgery (12). According to Frigerio *et al.*, patients with PDAC and synchronous liver metastases who were CA19-9 secretors and demonstrated a reduction of 50% or more in CA19-9 levels from baseline were considered suitable candidates for surgical resection. However, no independent correlation was found between improved survival and either the degree of CA19-9 reduction or post-treatment normalization (13).

While decrease of CA19-9 level may be an important factor as a candidate for surgery (3), it may be insufficient to be used as a predictor of long-term survival after surgery. Shi *et al.* attempt to identify prognostic factors for OS in patients with synchronous liver metastasis (11).

When patients are carefully selected, the extensive surgery does not appear to confer an increased risk of morbidity. Hackert *et al.* did not find a decreased quality of life due to post-operative morbidity after resection of liver metastases (14). Moreover, Shi *et al.* showed that there was not a statistical increase in complications related to the liver-specific surgery with respect to a standard pancreatectomy alone (11).

Systemic chemotherapy might be helpful in selecting patients, as only those that respond to it might benefit from aggressive surgery (14). Crippa and colleagues hypothesize that chemotherapy might not only help in identifying patients that have a progressive disease and that thus would not benefit from surgery, but it might also select patients with a favorable tumor biology (12).

In this study, patients received systemic treatment, which was predominantly multiagent chemotherapy, but specific details are lacking. The literature indicates that variations in chemotherapy regimens exist, highlighting the importance of considering the type of chemotherapy as a

significant factor. Nichetti *et al.* emphasizes the importance of multiagent neoadjuvant chemotherapy for achieving optimal tumor effect while managing toxic effects. The tolerable toxicity profile and high response rate make regimens like NALIRIFOX and FOLFIRINOX promising options in settings such as neoadjuvant therapy (15).

The duration of chemotherapy beyond 12 months as the sole selection criterion, underscores the importance of effective chemotherapy (5). From this standpoint, optimal treatment should be chosen based on the individual patient's condition.

In conclusion, this study by Kaslow *et al.* provides valuable data and insights that can enhance clinical decision-making and guide future research. The findings highlight the evolving role of curative-intent surgery for stage IV PDAC patients with synchronous liver metastases, offering hope for improved survival in carefully selected cases. However, a multidisciplinary approach involving surgeons, oncologists, radiologists, and palliative care specialists is essential in making these complex treatment decisions.

Future research should focus on identifying specific patient characteristics, biomarkers, and the optimal type and duration of chemotherapy to predict which patients with stage IV disease are most likely to benefit from surgical resection. Randomized controlled trials involving multiple centers are warranted to refine treatment strategies and establish clear selection criteria. While surgery may offer a survival advantage for some patients, the risks and impact on quality of life must continue to be balanced in the clinical practice.

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