

# Neoadjuvant therapy for pancreatic ductal adenocarcinoma—real effects or patient selection?

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Surgery is the only treatment with curative potential for patients with pancreatic ductal adenocarcinoma (PDAC). Unfortunately, the majority of patients do not qualify for curative resection due to locally advanced or metastatic disease at presentation. Historically, these patients received palliative therapy, while patients with resectable and non-metastatic PDAC underwent surgery. However, recurrence rates approximated 100% and overall survival was limited. The most likely explanation for these dismal results is the presumed early tumor spread of pancreatic cancer: micrometastatic spread is estimated to occur already in a third of tumors smaller than 1 cm and in more than 90% of tumors up to 3 cm at diagnosis (1).

Due to refined surgical techniques and establishment of effective chemotherapy protocols, resectability and recurrence rates as well as overall survival have significantly improved over time. Moreover, the understanding of the disease has grown, and different subgroups of pancreatic cancer have been suggested in the literature. First, several expert associations differentiate resectable and borderline resectable from locally unresectable disease (2). However, the treatment of patients with borderline resectable disease varies according to the surgical expertise: e.g., while some surgeons consider tumors infiltrating the superior mesenteric vein as unresectable, experienced pancreatic surgeons would proceed to surgery including vascular reconstruction. The cohort of borderline resectable patients is therefore heterogenous, and the reading of the literature

concerning this cohort of patients is extremely difficult. Moreover, amongst metastatic disease with poor prognosis in general, a subgroup with “oligo metastatic disease” has been created, which has a better survival and presumably benefits from local therapies. However, a clear definition of this subgroup is lacking. In general, multimodality protocols are tested increasingly to achieve resectability for all these subgroups with advanced disease.

Neoadjuvant therapy is increasingly used in all gastrointestinal cancers, since it is better tolerated than adjuvant therapy, and down-sizing the tumor results in higher R0-resection rates. Additional advantages of neoadjuvant therapy are treatment of micrometastases and better tolerability of the treatment (2). Many series report excellent secondary resectability rates of PDAC patients with borderline or locally advanced, unresectable but non-metastatic disease after neoadjuvant chemo or chemoradiation therapy. Moreover, retrospective analyses suggest even lower surgical complication rates as well as a better outcome for patients who develop complications from surgery after neoadjuvant therapy compared to those who undergo upfront surgery (2). Also, a recent analysis of Crippa *et al.* suggested that some patients with synchronous hepatic metastases from pancreatic cancer may benefit from resection of the pancreatic primary tumor as well as liver metastases, if they responded to neoadjuvant chemotherapy (3). In that series, completely resected patients with metastatic PDAC revealed a median survival

of 46 months. Following this trend of extending the indications for local therapies in advanced disease, also patients with metachronous liver metastases and local recurrences have been reported to benefit from repeat surgery or local ablative treatments. Also, neoadjuvant therapy is often used in these patients to decrease the tumor load or to increase the probability of an R0 resection.

In their paper, Lu *et al.* report on their institutional experience with 50 patients who underwent a successful pancreas resection for pancreatic cancer between 1995 and 2013 after an initial exploration had failed (4). In order to assess a potential benefit of neoadjuvant therapy patients who had an R2-resection served as control group. The study group of re-explored patients revealed significantly lower T- and N-stages as well as a smaller proportion of perineural invasion in the resected specimen compared to R2-resected patients. These histological parameters are established prognostic factors for PDAC, and the study group consequently revealed a significantly better overall survival compared to patients after R2-resections. Interestingly, only 6% of these patients required vascular resections after neoadjuvant therapy, although the majority of patients did not undergo primary pancreas resection due to suspected vascular infiltration.

In accordance with the literature, this analysis confirms that secondary pancreas resection after neoadjuvant therapy can be performed with acceptable morbidity and mortality rates in experienced hands. Moreover, it supports the concept of secondary re-assessment of resectability after neoadjuvant therapy for locally advanced PDAC. Also, the study by Lu *et al.* confirms the importance of patient referrals to obtain a second opinion, if a tumor is considered unresectable at one institution. The majority of initial explorations (86%) had been performed at other institutions, and the reasons for unresectability were presumed vascular infiltration in 72.5% and celiac or portal lymphadenopathy in 20% of the cases. Upon evaluation of resectability in the authors center, a significant proportion of patients (26%) underwent upfront successful resection.

As in this paper, large database as well as meta-analyses revealed lower T- and N-stages as well as lower smaller proportions of patients with perineural or lymphovascular tumor invasion and higher R0-resection rates after neoadjuvant therapy (5,6). Although these findings may be attributed to the effect of neoadjuvant therapy, they might also reflect patient selection for re-exploration in the absence of randomized trials. Sohn *et al.* also reported high resectability rates by re-exploration without neoadjuvant

therapy before: 67% of re-explored patients, who had previously been judged unresectable at outside hospitals, underwent direct successful resection. These patients were also younger and had smaller tumors with a smaller proportion of positive lymph nodes compared to the general population at this center (7).

Moreover, the study group represents a highly selected cohort of patients: during the same period, more than 2,000 successful pancreatic resections had been performed at the same institution, of which the study group is only about 2%, and the median age of these 50 patients was only 66 years (59.8–75.3 years). The number and outcome of patients with locally advanced disease who did not adequately respond to neoadjuvant therapy to undergo re-exploration as well as the number of patients who underwent unsuccessful re-exploration remain unknown.

These data, however, suggest that pancreatic resections should not be attempted, if an R2-resection is likely to happen during exploration, since an R0-resection with better outcome may be achieved by an effective neoadjuvant therapy. Whether chemoradiation therapy or multidrug chemotherapy (e.g., FOLFIRINOX) are more effective in downsizing the primary tumor remains unclear at the moment, although FOLFIRINOX achieved a local resectability rate of 25% in initially unresectable disease (8).

Considering the potential benefits of neoadjuvant therapy for patients with PDAC, neoadjuvant therapy also appears attractive for primarily resectable PDAC since response to neoadjuvant therapy seems to increase R0 resectability and resection margins, which are prognostic according to recent analyses (9). Although venous resections can be safely performed with low complication rates in experienced hands, prognosis is impaired in case of deep vascular infiltration (10). Neoadjuvant therapy may also improve the outcome of this cohort of patients.

In conclusion, this paper by Lu *et al.* supports the current literature on the efficacy of multimodality treatment for locally advanced PDAC. The paper demonstrates the necessity of uniform definitions of resectability, which should stratify patient management and referral strategies. The main conclusion of this paper is that patients in good general condition who respond to a neoadjuvant therapy appear to have a better outcome than patients who undergo incomplete (R2) resection. Whether the better outcome is related to the multimodality treatment or a better patient selection remains unclear. Accordingly, analyses like this emphasize the importance of randomized trials in order to exclude selection bias of retrospective studies, and to proof

the real effects of neoadjuvant therapy for PDAC.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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