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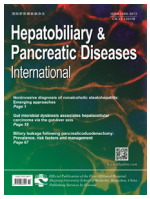

Editorial

# Pathological tumor response to neoadjuvant therapy in borderline resectable pancreatic cancer

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Surgery is the standard therapy for pancreatic ductal adenocarcinoma (PDAC). After the dramatic decline of operative mortality over the past decades, the indications for pancreas resections have been continuously extended: currently resections of the portal/superior mesenteric vein are considered standard by many centers, and even arterial resections are under debate. Following these changes, different expert groups have defined resectability criteria containing a grey zone ("borderline resectable disease") of tumors, which may be technically resectable with appropriate surgical expertise, but resection inherits an increased risk of an R1-resection [1].

In addition to the technical and perioperative improvements, the understanding of PDAC is currently evolving: the majority of PDAC has already (micro-) metastasized at the time of diagnosis and contains high-risk stigmata for an aggressive tumor biology such as perineural or lymphvascular invasion. Moreover, recent reports [2,3] demonstrate a significantly better survival for PDAC patients, if the width of the circumferential resection margin is more than 1 mm [1,4]. Following these analyses, the majority of pancreas resections should be considered R1 resections, which is an established negative prognostic factor in PDAC [4].

Neoadjuvant and perioperative therapies have been established for many cancer types with the aim of increasing resection margins and treatment of micrometastases. After systemic chemotherapy has proven effective in unresectable, metastatic and resected PDAC, multimodality therapies are also increasingly offered to patients with PDAC respecting the above mentioned tumor biology of the disease [5,6]. Considering the morbidity of pancreas surgery, neoadjuvant offers the additional advantages over adjuvant therapies that all patients receive the combination therapy, and that it is generally better tolerated than an adjuvant therapy [1].

The paper by Peng et al. [7] reports the experience of the Cleveland Clinic with multimodality therapy of borderline resectable PDAC: 71 patients received neoadjuvant therapy, which was a gemcitabine-based chemoradiotherapy in the majority of the patients, and the authors reported four complete and 12 marked histological responses. In addition, 69% of the patients received an adjuvant chemotherapy with gemcitabine. Despite the initial tumor extent, only one third of patients required a venous resection due to the intraoperative suspect of a tumor infiltration, and only 28% of the resections were R1, although the definition of R0-resections required at least a 1 mm tumor-free margin. Furthermore, the proportion of node positive disease as well as T-stages decreased with the degree of histological response of the primary tumor. Also, less patients had lymphovascular or perineural invasion in case of tumor response to neoadjuvant therapy. Finally, although not statistically significant, these effects translated into longer disease-free and overall survival rates in patients with more intense tumor response. These factors as well as the low rate of local recurrences (11%) suggest the local effectiveness of the neoadjuvant therapy. On the other hand, the three times higher rate of distant recurrences is presumably due to the limited systemic effect of chemoradiotherapy. Unfortunately, information about the proportion of patients who had been excluded due to (systemic) tumor progression under neoadjuvant therapy as well as the surgical morbidity and mortality have not been reported in this paper. For these reasons, data must be interpreted with caution.

Despite these limitations, the results of this analysis fit well to the literature, which generally suggests lower T- and N-stages in the resected specimen of pretreated patients as well as higher R0 resection rates. General concerns against neoadjuvant therapy are a disease progression under therapy and a higher surgical morbidity. The rate of disease progression under therapy depends on the patient cohort and the applied therapy, and is generally a rare event. Interestingly, the surgical morbidity seems to be even lower after neoadjuvant therapy. Whether this is due to an improvement in the nutritional status of the patients or whether it is due to an increasing fibrosis of the pancreas in response to the treatment remains unclear [8].

As for other cancer types, there is little doubt that the future of PDAC management will be a multimodal therapy. Unfortunately, such protocols have been introduced on a pragmatic basis rather than on scientific data. Probably according to the oncological attitude of the center, the type of multimodality therapy is based on systemic chemotherapy or chemoradiotherapy. Both options have been reported to be effective even in converting unresectable to resectable PDAC, with systemic chemotherapy being even more effective. In this light, the excellent local and the limited systemic effects of the applied neoadjuvant protocol in the Peng et al. paper also fit well the current literature. In order to confirm the efficacy

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of neoadjuvant therapy and to define the optimal type, timing and duration of therapy, all centers should include their patients into prospective (randomized) clinical trials.

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