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EDITORIAL

Neoadjuvant chemo(radio)therapy in upfront resectable pancreatic cancer – can we stratify patients better in the future?

Pancreatic ductal adenocarcinoma is associated with one of the lowest survival rates among cancers and recently a 5-year survival still below 5% was reported [1]. Despite that pancreatic cancer is fairly infrequent, the lack of substantial breakthroughs results in the prognosis that pancreatic cancer will be the second cause of death in cancer within a few years [2]. This lack of improvements includes both absence of novel tools for early diagnosis that will render more patients suitable for treatment with curative intent (surgery and chemotherapy) and lack of more effective and goal directed therapy options. Marginal improvements have been reached in pancreatic cancer patients receiving palliative chemotherapy with Folfirinox (oxaliplatin, irinotecan, leucovorin, fluorouracil) and the combination of gemcitabine and nab-Paclitaxel [3,4]. Adjuvant chemotherapy following pancreatic resection has been reported beneficial with increased survival, recently mostly employing Folfirinox or the combination nab-Paclitaxel and gemcitabine [5,6].

In patients with borderline resectable pancreatic cancers, neoadjuvant treatment has resulted in 60–90% resectability rates through tumor regression and treatment of micrometastatic disease, thereby rendering radical (R0) resections possible to a higher extent and longer survival reported as compared with upfront surgery, especially in groups with poorly differentiated and higher stages of pancreatic cancers [7]. Many consider pancreatic cancer to represent a systemic disease already at diagnosis. For this reason, systemic therapy from the very beginning should potentially have its benefits. There are both potential advantages and disadvantages to consider with neoadjuvant therapy also in patients with resectable pancreatic cancer. By this approach, all patients are guaranteed a chemotherapy option and when receiving neoadjuvant therapy, patients may also be allowed time to improve their clinical and biological performance. At least theoretically, micrometastatic disease could be dealt with earlier, as well as achieving an improved rate of R0 resections and less positive lymph nodes. By effects on the pancreatic parenchyma by chemoradiotherapy (fibrosis), less postoperative pancreatic fistulas could be expected. One other potential advantage listed would also be that progression during neoadjuvant chemotherapy allows a selection of those patients who never will reach surgical resection. Existing results are though still quite limited and the use of neoadjuvant therapy in upfront resectable pancreatic cancer patients should not be performed outside randomized clinical studies [8], where a few are ongoing and results are eagerly awaited. Information up to now, however, state that up to 40% may have disease progression during neoadjuvant treatment due to a more aggressive underlying tumor biology [9]. These patients with progressive disease will be found unoperable and also have declining performance status. Ongoing analysis of prospective randomized studies on neoadjuvant therapy in upfront resectable pancreatic cancer will also show to what extent treatment had to be modified or even withdrawn and to what extent this has a relation with unresectability. Distant metastases during treatment are also frequent, in similarity to the fairly frequent development of early distant metastases following upfront surgical resection, in which category also up to 30% of patients never reach adjuvant chemotherapy due to complications or early disease recurrence [10]. In patients subjected to neoadjuvant therapy in resectable pancreatic cancer, serum CA 19-9 levels with normalization or strong decline have been reported associated with a longer median overall survival [11,12]. It is also to be mentioned that biochemical markers might preceed radiological evidence of recurrence by a few months, allowing a shorter interval to salvage treatment [13,14].

In summary, neoadjuvant therapy in upfront resectable patients may provide a tool for patient selection avoiding futile surgery. What can be discussed is the (marginal?) value these patients have through a quite aggressive therapy with frequent side effects and not at least associated costs. A plea for tools based on improved knowledge on underlying tumor biology and biomarkers in order to stratify patients better as comes both prognosis and prediction of response to therapy is warranted. Endoscopic ultrasound with core biopsies may be a methodological platform that allows improvements in precision oncology in pancreatic cancer [15]. Hopefully, the wait and see approach will be outperformed by tumor biology staging in the future, directing the choice of treatment strategy. This should then be done prior to initiation of any therapy.

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