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FIELD OF VISION

Response evaluation following neoadjuvant treatment of pancreatic cancer patients

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive human neoplastic entities, with a very poor prognosis characterized by a high mortality rate and short survival. This is due both to its aggressive biological behaviour and the high incidence of locally advanced stages at the time of the initial diagnosis. The limits of resectability and the role of neoadjuvant (radio) chemotherapy for PDAC management are still unclear. A recently published article by Kats *et al* compared the radiological, surgical and histopathological results of 129 patients with borderline resectable tumors undergoing neoadjuvant treatment followed by surgery. Although post-neoadjuvant treatment imaging implied a low response rate, a high rate of complete resections was achieved. This seems to confirm that, though radiology has made a significant progress in defining locally advanced PDAC, there is place for further improvement. In particular, the differentiation between radiotherapy-induced scarring/fibrosis and cancer-associated desmoplasia remains a clinical/radiological challenge. Though selection of patients with occult systemic disease is possible with neoadjuvant treatment, downstaging does not seem to occur frequently. Thus, development of novel, more aggressive (radio) chemotherapy regimens is required to improve prognosis of patients with locally unresectable but not systemically micro-metastasized tumors.

Key words: Pancreatic ductal adenocarcinoma; Borderline resectable tumors; Neoadjuvant chemotherapy

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COMMENTARY ON HOT TOPICS

We read with great interest the recent article by Katz *et al*[1] analysing the correlation between clinical and pathological staging following neoadjuvant treatment in patients suffering from pancreatic ductal adenocarcinoma (PDAC). PDAC accounts for more than 85% of all pancreatic tumours, and though it is the 10th most common cancer in Western countries, it is ranked as the 4th most common cause of cancer-related deaths[2,3]. Less than 5% of the patients survive longer than 5 years after the initial diagnosis and the only chance for cure is resection[4]. The main factor contributing to the prognosis of the disease is the stage[5], which also determines resectability. Only 15%-20% of the patients present with a resectable tumor at the time of diagnosis; at least 40% of the tumors are locally advanced and the remaining 45%-50% are metastasized[6]. While treatment of locally confined and of metastasized tumors is not debated, neoadjuvant (radio) chemotherapy in the management of borderline resectable or locally advanced, primarily un-resectable tumours is still a hot topic in clinical research.

Assessment of PDAC resectability

Resectability of the local tumor depends on whether ad-

Table 1 Borderline resectable tumors have been defined according to the most recent national comprehensive cancer network guidelines (version 2.2012)

Tumor-associated deformity of the SMV or PV
Abutment of the SMV or PV > 180°
Short-segment occlusion of the SMV or PV amenable to resection and venous reconstruction
Short-segment involvement of the hepatic artery or its branches amenable to resection and reconstruction
Abutment of the SMA < 180°

SMV: Superior mesenteric artery; PV: Portal vein.

jacent structures (*i.e.*, mostly the vessels) are infiltrated. Multi-detector computed tomography (MDCT) has been widely accepted as the technique of choice for the primary staging of PDAC[7,8]. MDCT and magnetic resonance imaging (MRI) are similarly sensitive and specific[9], but MRI seems to be better in detecting hepatic metastases[10]. Endoscopic ultrasound (EUS) allows EUS-guided fine-needle aspiration, but is technically demanding, and potentially associated with complications. Because preoperative determination of vascular infiltration is important for the assessment of resectability, radiologic criteria have been defined based most importantly on portal/superior mesenteric vein as well as superior mesenteric artery (SMA) and celiac trunk involvement. Borderline resectable tumors have been defined according to the most recent NCCN guidelines (version 2.2012)[11] (Table 1).

Neoadjuvant treatment

Recent studies and meta-analysis have shown that tumor down-staging can be achieved with gemcitabine- or 5-FU-based (radio)chemotherapies in about one third of the patients, with a significantly higher overall survival in resected (compared to non-resected) patients[12-15]. The more aggressive FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) protocol has been shown to be superior to gemcitabine-based regimens in the palliative situation[16] and has also been used in the neoadjuvant setting, demonstrating encouraging results[17].

Comment on the study

In this study Katz *et al*[1] analysed the clinical data of 129 patients with border-line resectable pancreatic cancers who underwent surgery after neoadjuvant therapy. As Katz *et al*[1] point out, there is not yet a general agreement on several topics, such as the definition of resectability and the indication for oncological therapies; the aim of their study was to improve the diagnostic workup and the therapeutic procedure, trying to design simple and sensitive guidelines for the selection of patients who could potentially have an R0 resection.

A review of radiological features (CT) before and after chemotherapy was performed by an experienced gastrointestinal radiologist, according to the MD Anderson and American Hepato-Pancreato-Biliary Association (AHPBA)/Society for Surgical Oncology (SSO)/Society for Surgery of Alimentary Tract (SSAT) criteria in order to determine the clinical response to neoadjuvant treatment. Though only one patient (1%) had a clinical down-staging according both to the AHPBA/SSO/SSAT and MD Anderson criteria, 85 patients (66%) underwent pancreatectomy. The systematic definition of histopathological staging and response to chemotherapy, performed according to the American Joint Committee on Cancer Staging Manual, showed 81 R0 resections (95%) and a histopathologic grade Ⅲ and Ⅳ response in 17% of the resected patients.

Table 2 Some questions towards the aim and the clinical meaning of neoadjuvant treatment in pancreatic cancer

How reliable is traditional imaging assessment of resectability?
Were these tumors resectable even before (radio) chemotherapy administration?
If so, was (radio) chemotherapy useful or did it only delay surgery?
Which exactly is the target of neoadjuvant treatment?

The achievement of R0 resections in a relative high percentage of patients who did not have a significant clinical down-staging reported in this paper raises some questions towards the aim and the clinical meaning of neoadjuvant treatment in pancreatic cancer (Table 2).

Assessment of resectability following neoadjuvant treatment

The most interesting points in the article by Katz *et al*[1] are the use of standard criteria for the indication to resection (AHPBA/SSO/SSAT criteria[11,18] and MD Anderson criteria[19,20]) and the assessment of the clinical and pathological response to chemotherapy (*e.g.*, using RECIST). The authors report a clinical down-staging in only 1% of patients, disease progression in 19% and no change in 80% of the patients according to the AHPBA/SSO/SSAT criteria. Even worse results are reported according to the MD Anderson criteria (1% down staging, 21% progressive disease and 78% no change). Nevertheless, the intraoperative findings showed a much more satisfactory response to chemotherapy: 66% of patients underwent resection and 95% of the resected patients had an R0 resection.

Here, the authors conclude that imaging has a fundamental role in the decision-making phase but still does not seem to be satisfactorily accurate of the actual anatomical situation. Though one imaging modality such as multidector CT is more straight-forward, it seems that additional techniques may be necessary to better judge particularly the presence of vascular infiltration.

Thus, it would be interesting to investigate how to differentiate between chemo- and/or radiotherapy-induced scarring/fibrosis and cancer-associated desmoplasia (following neoadjuvant treatment). Standard descriptive imaging such as CT scans can hardly distinguish between these tissue alterations[21]. Functional imaging modalities such as fluorodeoxyglucose-/fluorothymidine-positron emission tomography-CT may be helpful adjuncts in the

neoadjuvant situation and will have to be analyzed in this particular patient population.

Potential resectability even before administration of neoadjuvant treatment

The radiological results reported by Katz *et al*[1] show no relevant differences between tumor volume and (potential) vascular invasion before and after neoadjuvant treatment. Nevertheless, most of the patients received an R0 resection. The findings may indicate that these tumors could actually have already been resected before administration of chemotherapy. However, because current imaging cannot (easily) distinguish between cancer-associated desmoplasia and (radio) chemotherapy-induced fibrosis or fibrosis due to tumor regression (as described above), it is difficult to retrospectively judge on resectability before neoadjuvant treatment. Refined imaging or rather functional imaging[21,22] seems thus to be necessary to better select patients with truly locally restricted *vs* locally advanced tumors.

Usefulness of neoadjuvant treatment vs delay of surgery

The validity of preoperative (radio) chemotherapy administration in border-line resectable PDAC is still discussed: in fact, neoadjuvant treatment does not induce regression at the same rates in pancreatic cancer as in colo-rectal or esophageal cancers; thus, the relevance of neoadjuvant treatment for downstaging or local control in pancreatic cancer remains unclear. Nevertheless, we agree with the authors that preoperative (radio) chemotherapy is a potentially useful strategy to select patients without occult systemic disease for later surgery. To this end, chemotherapy regimens with better response rates than gemcitabine alone will have to be tested. In this regard, a recent study of advanced and border-line resectable pancreatic cancers[17] reported an R0 resection rate of 44% following treatment with FOLFIRINOX while another study[23] reported resectability in 11 out of 39 patients (15 border-line and 24 primarily unresectable tumors) following neoadjuvant treatment with GEMOX. Survival rates were comparable to patients with resectable tumors in both studies.

Targets of neoadjuvant treatment

The data reported by Katz *et al*[1] suggest that neoadjuvant treatment does not reduce the volume of the tumor, but that it selects tumors with a less aggressive biological behaviour. In fact, only the patients who did not show progression of the disease during neoadjuvant treatment underwent surgery; and these had a survival rate similar to patients with resectable disease at the time of diagnosis. Besides, a good pathological response to neoadjuvant (radio) chemotherapy (in opposite to a disappointing clinical down-staging, as reported in a recent study by Tajima *et al*[24]), seems to confirm the hypothesis that neoadjuvant treatment in PDAC rather acts on the biology of the tumor than on the volume. Thus, the aim of neoadjuvant treatment is not the achievement of a more "permissive" local surgical region, but the selection of patients with less aggressive diseases. However, larger studies using neoadjuvant FOLFIRINOX protocols will be necessary to determinate whether more aggressive chemotherapy results in shrinking of the local tumor.

In conclusion, we support the authors' statement that the development of imaging techniques helps to avoid useless surgery and its associated complications for those patients who would not have any benefit from it (*e.g.*, potential R2 resections)[25]. Though radiology has shown an incredible progression in detection of vessel infiltration, the assessment of resectability is still a delicate, tricky field.

In the absence of an unequivocal definition of the surgical limits, the effort made by Katz *et al*[1] point out the main guidelines in this field is particularly interesting; from these data it seems to emerge that centers with larger clinical volumes have more aggressive surgical standards and potentially also better outcomes, enforcing the conviction that pancreatic surgery should be performed in dedicated centers.

Finally we agree with the authors on the hypothesis that there is a rationale in administrating preoperative neoadjuvant (radio) chemotherapy in locally advanced pancreatic cancers in order to select the patients who would benefit from a resection (*e.g.*, those without occult systemic disease at the time of diagnosis). The question of whether neoadjuvant treatment with more aggressive (radio) chemotherapies will decrease the size of the local tumor and will lead to true downstaging of PDAC remains unanswered.

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