Editorial Commentary

Redefining resectability in pancreatic cancer after neoadjuvant therapy: are we any closer?

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Pancreatic resection with negative margins offers the only potential cure within a multimodal treatment strategy that includes chemotherapy with or without radiotherapy for patients with pancreatic cancer. Traditionally the definition of resectability in pancreatic cancer was focused on the location of the tumour to major vascular structures surrounding the head of pancreas as described by a variety of organisations around the world, with subtle differences in definitions for resectable, borderline resectable and locally advanced pancreatic cancers (1). Our understanding of pancreatic cancer has evolved from 'surgical resection with negative margins offering the only potential hope of a cure' to managing pancreatic cancer as a systemic disease from the outset. The adoption of neoadjuvant therapy (NAT) has become standard practice in many pancreatic centres worldwide and recent evidence has shown improved overall survival and disease free survival in patients with all stages of pancreatic cancer (2). The adoption of NAT provides clinicians with a window of opportunity to observe and identify patients with favourable tumour biology as demonstrated by control of tumour growth by chemotherapy. The definition of resectability in pancreatic cancer therefore requires to be updated for patients undergoing NAT to include an assessment of tumour biology. This issue was addressed by Dr. Oba and colleagues at the symposium 'New criteria of resectability for pancreatic cancer' which was held during the 33rd meeting of the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) (3). The aim of this symposium was to bring together experts in the field of locally advanced pancreatic cancer with western and eastern experience to reach a consensus opinion of which factors should be included to address updated guidelines on resectabilty in pancreatic cancer that reflects recent developments in defining resectability after NAT. This is particularly important as we continue to accumulate evidence supporting NAT for borderline resectable pancreatic cancer (4,5).

This symposium has considered patient fitness for surgery as based on the Eastern Cooperative Oncology Group (ECOG) which has been shown to be an independent predictor of survival in patients with pancreatic cancer (6). This highlights a role for prehabilitation programmes in patients with borderline resectable and locally advanced pancreatic cancer. Although early results from studies have shown that such programmes might improve post-operative outcomes it effect on overall survival remains to be seen (7). This symposium has focused however on a dynamic assessment of tumour biology to be taken into consideration

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along with an anatomical assessment of resectability.

Identifying tumour response by imaging remains challenging. The ability to identify tumour regression based on the RECIST criteria remains difficult as viable tumour is replaced by fibrotic or inflammatory tissue (8). There is evidence that the use of positron emitted tomography/computed tomography (PET-CT) can help identify tumour response with a drop in maximum Standardised Uptake Values (SUVmax) following NAT demonstrating a response to chemotherapy (9). These results have been confirmed by further large studies (10) demonstrating that reduced metabolic activity in pancreatic cancer following NAT as demonstrated on CT PET is an accurate measure of tumour response and is associated with improved survival.

The use of MRI in pancreatic imaging is increasing and MRI PET like CT PET can accurately identify reduced metabolic activity highlighting disease response in locally advanced pancreatic cancer (11). A pilot study from The Netherlands has shown, that 3 Tesla (3 T) contrast enhanced and diffusion weighted (DWI) magnetic resonance imaging (MRI) was more sensitive than CT at identifying tumour response following NAT (12). They described a Halo sign where viable tumour was replaced by fibrotic tissue. A higher R0 resection rate was seen in patients with a HALO sign but this was not statistically significant (66.7% *vs.* 20.0%, P=0.242). Although promising, the study was limited to 20 patients and larger studies are required to confirm these findings. The identification of patients with fibrosis at the resection margin rather than viable tumour would facilitate the selection of those likely to undergo a R0 resection which is associated with improved survival (5).

The role of endoscopic ultrasound scan (EUS) and elastography was not explored in this symposium but EUS has been shown to play an important role in the diagnosis of pancreatic cancer and to provide an accurate assessment of the stage of tumour (13). EUS has shown promise at assessing tumour response/progression in patients with gastric cancer following NAT (14). Despite some promising results (15) at assessing tumour response following NAT in pancreatic cancer its role remains to be fully elucidated. A European multicentre study (PEACE) is currently underway exploring the utility of contrast enhanced ultrasound (CEUS) as a predictor of treatment efficiency in locally advance pancreatic cancer and results may further confirm the utility of CEUS in this setting.

Whilst decreasing CA19-9 levels have been shown to reflect response to chemotherapy in some studies (16) results are conflicting (17) and not all patients have elevated CA19-9 levels prior to commencing chemotherapy. This symposium has highlighted a lack of serum markers to identify tumour response. There is ongoing work investigating molecular subtypes of pancreatic cancer through EUS guided biopsy of the tumour. Molecular subtyping of pancreatic cancer has identified that different subtypes with varying response profiles to treatment and overall survival (18) however this is yet to be translated to serum biomarkers that can assess response to NAT. Similarly Micro RNAs have been investigated in the setting of patients with inoperable pancreatic cancer undergoing palliative chemotherapy (19) and has shown promise at mapping response to treatment. The role of micro RNAs however in assessing response in patients with LA pancreatic cancer remains to be elucidated. The conclusions of this symposium were rightly that further work is required to develop biomarkers to assess tumour response to NAT to help identify those patients with favourable tumour biology.

Pancreatic resection for PDAC is shifting towards a more aggressive surgical approach for fewer patients. Whilst the evidence supports that major vascular resection can be safely carried out and is associated with improved overall survival (20) it is also associated with higher morbidity rates. Patient selection is therefore paramount to focus such aggressive surgical approaches on patients with favourable tumour biology and those likely to undergo a R0 resection that may benefit instead an aggressive surgical approach following NAT. This symposium represents a transition in our understanding that patient selection for pancreatic resection no longer relies on anatomical considerations but a functional assessment of tumour biology. With results from the ESPAC5 trial reporting a survival benefit following NAT in borderline resectable pancreatic cancer (4), it is likely that this will become the standard of care and it is paramount that restaging after treatment is standardised. A multi-modal approach will be required and further research studies are essential to identify a combination of blood biomarkers and imaging modalities such as MRI, PET-CT and CEUS that predict tumour response to NAT to facilitate improved patient selection and therefore improve patient outcomes.

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