Regression grading in post neoadjuvant treated pancreatic cancer

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Abstract

Neoadjuvant chemoradiation (NCRT) is emerging as an important treatment modality in borderline resectable pancreatic ductal adenocarcinoma (PDAC) in an attempt to reduce tumour stage and improve resectability. Currently, there are several systems utilised to grade tumour regression in PDAC; the most widely used of these are the Evans, MD Anderson (MDA) and College of American Pathologists (CAP) systems. There is also significant institutional variation in handling and reporting tumour regression in post treated PDAC. As a result, there is a need for a standardised and reproducible method of handling and assessing these specimens in routine practice. This review aims to provide an overview of histological grading in neoadjuvant treated pancreatic cancer, focussing on the different regression grading systems with particular attention to the three most frequently recommended and used systems. In addition, we briefly outline the handling of post-treated pancreatic resections and the spectrum of histological features encountered in these specimens.

Keywords cancer; grading; pancreas; regression

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains to be an extremely aggressive cancer with dismal prognosis. The vast majority of patients present with unresectable disease (80−85%)[1−4] and in the remaining patients with potentially resectable disease (15−20%), the 5-year survival rate is only approximately 20%.[1]

At present, the surgery-first approach followed by adjuvant treatment (AT) confers the best chance of survival[5,6] with chemotherapy administered without radiation demonstrating greater survival benefits.[6,7]

In the last two decades, there has been an impetus for employing neoadjuvant chemoradiation therapy (NCRT) as an additional treatment modality in PDAC.[8−14] This was initially trialled in resectable PDAC as this mode of treatment was thought to offer several theoretical advantages, including: 1/effective administration of chemoradiation in well-oxygenated cells that have not been compromised by the surgical procedure 2/identifying the subset of patients with micro-metastatic disease that usually relapse soon after surgery, will avoid being subjected to the morbidity of unnecessary surgery 3/a better chance of achieving a margin negative (R0) resection 4/reduction in the risk of intraoperative tumour cell implantation during surgery.[5,15,16] However, these purported benefits did not support the routine clinical use of neoadjuvant therapy in resectable PDAC[5] as the survival benefits were comparable to patients who were treated by surgery alone and paradoxically worse than patients treated with single/combination AT (Figure 1).[5,17] In addition, it was also felt that delaying surgery could potentially result in disease progression.

However, subsequently, NCRT was found to be of greater benefit in the group of patients with "borderline resectable" tumours resulting in improvements in survival comparable to those with resectable disease. This group is comprises approximately 30−40% of all patients presenting with PDAC.[17−20]

It is well established that NCRT can significantly alter histological appearance of tumours. However, the degree of change is variable and is highly dependent on the patient's response to treatment. Typically, the histological tumour response to treatment is evaluated by tumour regression grading. The latter has been shown to be useful in monitoring patient response and may also serve as a good prognostic indicator. Giving credit to this assertion, studies carried out on other neoadjuvant treated gastrointestinal tumours (ie. oesophagus and colorectum) have demonstrated that evidence of pathological regression correlates with better long-term outcome disease-free survival.[21−24] Several grading systems have been proposed[8,25−30] and have been used interchangeably. The most widely used of these are the Evans,[8] College of American Pathologists' (CAP)[30] and MD Anderson grading systems (modified CAP and Evans system).[27]

This review aims to provide an overview (including historical perspective) of histological grading in neoadjuvant treated pancreatic cancer, focussing on the different regression grading systems with particular attention to the three most frequently recommended systems. In addition, we briefly outline the criteria of borderline resectable disease, the handling of post-treated pancreatic resections and the spectrum of histological features encountered in these specimens.

Borderline resectable PDAC: criteria and the role of preoperative therapy

Borderline resectable PDAC is a group of tumours that lies between the nebulous territory of resectable and locally advanced disease. NCRT in this setting has been shown to be beneficial with a radiological reduction in the size of tumours and subsequent resectability.[18] Borderline resectable disease is defined as tumours that exhibit encasement of a short segment of the hepatic artery, without evidence of tumour extension to the coeliac axis/abutment of the superior mesenteric artery (SMA) involving less than half (<180°) of the circumference of the artery/short segment of the superior mesenteric vein (SMV), portal vein (PV) or superior mesenteric portal vein (SMPV) confluence with a possibility of vascular resconstruction.[19] The definitions of borderline disease proposed by American Hepatopancreaticobiliary Association (AHABA)/Society of Surgical

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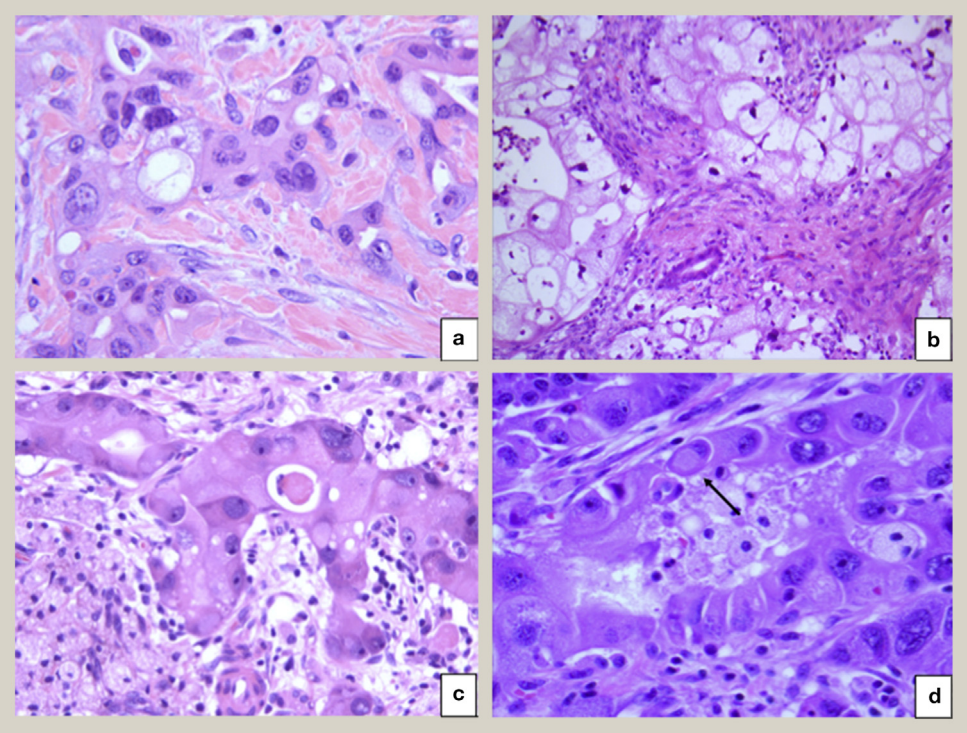

Figure 1 (**a**) Tumour cells with enlarged nuclei, vacuolated and densely eosinophilic cytoplasm (×400). (**b**) Clear cell change in tumour cells distinguished by large polygonal cells with abundant clear to amphophilic cytoplasm and wrinkled nuclei (×200). (**c**) Groups of polygonal to pyramidal cells with abundant "vaguely" granular oncocytic cytoplasm, enlarged nuclei and prominent nucleoli (×400). (**d**) Focal rhabdoid change (arrow) seen in tumour cells with distinct globular hyaline intracytoplasmic inclusion resulting in the eccentric margination of nuclei (×400). All H&E.

Oncology (SSO)/Society for Surgery of the Alimentary Tract (SSAT), MD Anderson Cancer Centre group and The Alliance for Clinical Trials in Oncology (Alliance) are outlined in Table 1.

Specimen dissection and tissue sampling

Currently, there is no standardized practice to sampling pancreatic resection specimens treated with NCRT. In addition, as observed by Verbeke et al.,[31] these specimens are often difficult to dissect as they are invariably distorted by fibrosis secondary to chemoradiation and may often include additional attached structures, such as the superior mesenteric vein or portal vein. While there is some degree of institutional and regional variation in dissection techniques, there are three most frequently utilised methods and these will be briefly discussed here.

The longitudinal opening along the main pancreatic and bile ducts was initially the preferred mode of dissection for pancreaticoduodenectomy specimens.[32,33] However, some argue that this method is technically challenging as the ducts are frequently obstructed and/distorted by the tumour mass and

Commonly used definitions for borderline resectable disease

Vessel	AHPBA/SSO/SSAT[20]	MD Anderson[19]	Alliance 2013[20]
SMA	Abutment	Tumour abutment <180° (one half or less) of the circumference of the artery	Tumour vessel interface <180° of vessel wall circumference
HA	Abutment or short segment encasement	Short segment encasement/abutment of the common HA (typically at the gastroduodenal origin)	Reconstructible short segment interface of any degree between tumour and vessel wall
CA	No abutment or encasement	Abutment of the artery	Tumour vessel interface of <180° of vessel wall circumference
SMV/PV	Abutment, encasement or occlusion	Short segment occlusion with suitable vessel patency above and below	Tumour vessel interface >180° of vessel wall circumference and/reconstructible occlusion

AHPBA/SSO, SSAT = Hepatopancreaticobiliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract; SMA = superior mesenteric artery; HA = hepatic artery; CA = coeliac artery; SMV/PV = superior mesenteric vein/portal vein.

Table 1