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TOPIC HIGHLIGHT

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Selection criteria in resectable pancreatic cancer: A biological and morphological approach

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Abstract

Pancreatic ductal adenocarcinoma (PDA) remains one of the most aggressive tumors with a low rate of survival. Surgery is the only curative treatment for PDA, although only 20% of patients are resectable at diagnosis. During the last decade there was an improvement in survival in patients affected by PDA, possibly explained by the advances in cancer therapy and by improve patient selection by pancreatic surgeons. It is necessary to select patients not only on the basis of surgical resectability, but also on the basis of the biological nature of the tumor. Specific preoperative criteria can be identified in order to select patients who will benefit from surgical resection. Duration of symptoms and level of carbohydrate antigen 19.9 in resectable disease should be considered to avoid R1 resection and early relapse. Radiological assessment can help surgeons to distinguish resectable disease from borderline resectable disease and locally advanced pancreatic cancer. Better patient selection can increase survival rate and neoadjuvant treatment can help surgeons select patients who will benefit from surgery.

Key words: Pancreatic ductal adenocarcinoma; Pancreatic cancer; Borderline resectable pancreatic cancer; Pancreatic surgery; Pancreatic cancer staging

Core tip: The aim of this work was to improve identification of patients with pancreatic ductal adenocarcinoma, who will benefit from pancreatic resection. Duration of symptoms and level of carbohydrate antigen 19.9 in patients with resectable disease should be considered to avoid R1 resection and early relapse. Radiological assessment can help surgeons to distinguish resectable disease from borderline resectable disease and locally advanced pancreatic cancer.

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INTRODUCTION

Despite recent advances in cancer therapy, pancreatic ductal adenocarcinoma (PDA) remains one of the most aggressive tumors and is among the four most frequent causes of tumor-associated deaths in both men and women in the European Union and the United States[1,2]. Surgical resection still represents the only curative treatment for PDA, although only a small fraction of tumors is amenable to surgical resection at diagnosis[3-6]. Moreover, among patients who undergo surgery, 30% develop early recurrence as a result of misdiagnosed aggressive disease[6]. The aim of this paper is to review the current available data on factors related to adverse prognosis in

patients with resectable PDA.

EPIDEMIOLOGY

Only 20% of patients with PDA are resectable at diagnosis and 5-year overall survival (OS) after curative resection is only 20%[4-8]. During the last decade survival rates of PDA have remained dismal with a 5-year OS of 15%-20% after pancreaticoduodenectomy and 8%-15% after distal pancreatectomy[9,10]. In the 1990s there was no improvement in 5-year OS, which was even lower (2.3%-2.7%) compared with the 5-year OS rate observed in the late 1980s (2.5%-3.1%)[11]. Despite progress in diagnostic procedures, most cases are still metastatic at diagnosis, and are not amenable to radical surgery and even when curative surgery is performed, most patients will eventually relapse[11]. In a large, retrospective, study of a high-volume centre in Italy, Barugola *et al*[12] compared the survival time-trends in a selected population of patients affected by resectable PDA. There were 114 (21%) resections in 1990-1999 and 430 (79%) in 2000-2008. The length of hospital of stay (16 d *vs* 10 d) and postoperative mortality (2.6% *vs* 1.1%) significantly decreased over time. The median disease-specific survival significantly increased from 16 mo in the first period to 29 mo in the second period. Resection performed in 1990-2000 was an independent predictor of poor outcome, indicating that long-term survival after surgery for resectable PDA significantly improved in the last decade. This improvement is possibly explained by the advances in cancer therapy but also by better patient selection by pancreatic surgeons. As regards oncological progress, in recent years several efforts have been made to develop effective drugs for pancreatic cancer. In particular, two recent randomized clinical trials that included patients with metastatic PDA demonstrated significantly better survival for the treatment groups compared with control groups of patients treated with gemcitabine[13,14]. Conroy *et al*[14] showed that patients treated with FOLFIRINOX (5-fluorouracil, oxaliplatin, and irinotecan) had improved survival compared with a gemcitabine alone group, with a median OS of 11.1 mo *vs* 6.8 mo with an objective response rate of 31.6% *vs* 9.4%. Similarly, Von Hoff *et al*[13] have shown a better survival in patients with PDA treated with gemcitabine plus nab-paclitaxel compared with gemcitabine alone. In this work, OS was 8.5 mo in the treatment group compared with 6.7 mo in the control group. The increase in objective response rate due to improvement in oncological treatments can also have the consequence of increasing the number of resectable patients[15]. Better patient selection has probably modified the survival of patients with PDA because of changing resectability criteria. Among those who undergo surgical resection, up to 30% of patients die of disease within 1 year after surgery[6,16]. In this subgroup, recurrence is early, and survival rates are comparable to those observed in patients with advanced disease undergoing antitumoral therapies alone[17]. The risk of early failure after surgery could be associated with the following: (1) inadequate preoperative radiological staging; (2) lack of radical surgery; and (3) differences in tumor aggressiveness. Undoubtedly, what is common to patients who will recur early, is disease with more aggressive biological behavior.

All of these patients are resectable at diagnosis, but probably the difference with the others patients is the biological characteristics of the tumor. In addition, there is a relationship between hospital volume with long-term survival in patients with cancer subjected to pancreatectomy, probably due to patient selection and technical expertise at the major centers that are responsible[18]. Therefore, it is necessary to select patients not only on the basis of surgical resectability, but also on the basis of the biological nature of the tumor.

Preoperatively, we can identify specific criteria to be recognized in order to select those patients who will actually benefit from surgical resection. Focusing on these criteria, we suggest a step-by-step approach for patients with pancreatic cancer; the first step is to consider their clinical and laboratory factors and then their radiological features.

CLINICAL AND LABORATORY CRITERIA

In order to select patients who will benefit from a surgical approach, we have to consider not only the imaging but also other parameters such as symptoms, risk of mortality related to the patient's comorbidity, and the level of carbohydrate antigen (CA),19.9. Symptoms of PDA depend on the site of the pancreatic lesion; for pancreatic head tumors, jaundice is the first sign, whereas for pancreatic body/tail tumors, pain is the most frequent symptom. Duration of symptoms > 40 d is an important parameter associated with a higher risk of early recurrence among patients who undergo surgery[6]. Although the reason behind abdominal pain in PDA remains unclear, it is likely that this represents the result of pancreatitis or tumoral invasion of the retroperitoneal nerves[10,19,20]. The presence of invasion of the retroperitoneal nerves, which causes pain, means that the tumor is over the gland, thus, despite radiological resectability, it should be considered as a borderline or locally advance disease. Nevertheless, not all patients with a resectable PDA are also fit for surgery. Before planning pancreatic resection therefore, it is mandatory to assess carefully the surgical risk of each patient. Several studies have demonstrated that elderly patients have an increased risk of morbidity after pancreaticoduodenectomy (PD), in particular related to postoperative pancreatic fistula, although morbidity and mortality rates are acceptable[21]. It could be therefore justified to offer PD to elderly patients who do not have significant comorbidity[21]. Brozzetti *et al*[22] have compared two group of patients (Group A > 70 years and Group B < 70 years). They showed significantly higher operative morbidity and mortality in Group A and they concluded that, although an aggressive surgical approach is justified

in elderly patients with pancreatic adenocarcinoma, surgical complications that lead to reoperation are responsible for high mortality in elderly patients. In addition to general causes, such as concomitant disorders, reduced functional reserve, poor tolerance to stress, and the texture of the pancreatic remnant, there are specific prognostic factors affecting pancreaticojejunostomy leakage and related mortality.

Another important parameter related to the aggressiveness of disease is the level of CA19.9. CA19.9 has been used for the diagnosis, prognosis, and follow-up of pancreatic cancer patients. Preoperative CA19-9 is strongly associated with tumor stage. A decrease in CA19.9 level is the best index of improved prognosis[23,24]. In contrast, patients with increased CA19.9 after resection had a significantly shorter median survival time. In another study published by Montgomery *et al*[25], patients who had CA19.9 < 180 U/mL in the first 3 mo after surgery had improved survival. Lower preoperative CA19.9 values correlated not only with a lower pathological stage, but also with increased post-resection survival. The presence of preoperative CA19.9 < 1000 U/mL was associated with a median survival of 28 mo compared with 12 mo in patients with CA19.9 > 1000 U/mL[23]. CA19.9 > 200 U/mL in patients with resectable PDA is associated with a higher risk of early failure after resection for pancreatic cancer. The importance of CA19.9 levels as a prognostic marker in PDA has been demonstrated in several other studies that have evaluated the decrease in CA 19-9 after anti-tumor therapy. Yang *et al*[26] have shown that patients who had a CA19.9 decrease of > 90% following chemoradiotherapy (CRT), had a significantly improved median survival compared with those who had not (16.2 mo *vs* 7.5 mo). The median survival of patients with a CA19.9 level lower than the median post-CRT value was 10.3 mo, compared with 7.1 mo for those with a CA19.9 level greater than the median. After CRT, CA19.9 < 50 U/mL also had a meaningful prognostic significance. In the neoadjuvant therapy setting, the measurement of CA19.9 is an essential variable in the evaluation of possible surgical resection of tumors that exhibit a response to treatment.

RADIOLOGICAL CRITERIA

The diagnostic phase and the resectability assessment of PDA should always involve a multidisciplinary evaluation. In this setting, it is important to offer patients the expertise of a high-volume center and dedicated multidisciplinary team (MDT). The importance of MDTs has been widely demonstrated for other malignancies[27,28]. Similarly, Pawlik *et al*[29] have analyzed the impact of MDTs in the management of patients with pancreatic cancer. They analyzed 203 patients with computed tomography (CT) that revealed locally advanced/unresectable disease (35%), metastatic disease (18%), and locally advanced disease with metastasis (1%). After an accurate review of the imaging, the clinical stage of the disease was modified in 19% of patients. Overall, 48 out of 203 (24%) patients had a change in their recommended management based on clinical review of their case by the pancreatic MDT. As a consequence, the quality of imaging as well as the expertise of radiologists contributes significantly to better patient selection. Imaging should include at least one high-quality technique such as CT or magnetic resonance imaging. CT should be performed according to a defined pancreas protocol such as triphasic cross-sectional imaging and thin slices. Optimal multiphase imaging techniques include a non-contrast phase, plus arterial, pancreatic parenchymal and portal venous phases of contrast enhancement with thin cuts (3 mm) through the abdomen[30]. The arterial phase shows excellent opacification of the celiac axis and the superior mesenteric artery, whereas the superior mesenteric, portal and splenic veins and the pancreas itself are opacified in the venous phase. Likewise, the detection of liver metastasis is optimal in the latter phase. Weg *et al*[31] and Kopka and Grabbe[32] have noted that a slice thickness of 2-4 mm is superior to 5-10 mm in the detection of small liver metastases. Moreover, the introduction of multidetector CT imaging has allowed the acquisition of these thinner slices in liver imaging, resulting in improved detection rates of liver metastases[33]. Vascular involvement is another important finding that can be assessed preoperatively by CT scan. A classification of vascular involvement in pancreatic cancer has been defined by the MD Anderson Group[34]. This classification includes two separate entities: (1) borderline resectable: PDA that is defined as a tumor with an abutment ⩽ 180° (one half or less) of the circumference of the superior mesenteric artery (SMA) and/or with a short-segment encasement/abutment of the common hepatic artery (typically at the gastroduodenal origin) and/or with short-segment occlusion with suitable vessel above and below in superior mesenteric vein (SMV) or portal vein (PV); and (2) locally advanced: PDA that is defined as a tumor with an encasement > 180° of the SMA and/or with an encasement and no technical option for reconstruction usually because of extension to the celiac axis/splenic/left gastric junction or the celiac origin, and/or with occlusion of the SMV/PV without an option for reconstruction. Nonoperative management for locally advanced pancreatic cancer (LAPC) is largely accepted[15,35-37]. Neoadjuvant treatment with combination chemotherapy results in a higher resection rate compared with single agent chemotherapy (33% *vs* 27%) as confirmed by Gillen *et al*[38] in their meta-analysis. In contrast, the optimal management for borderline resectable tumors is still debated. Compared with resectable PDA, borderline tumor is characterized by a higher risk of positive-margin resection with a subsequent higher risk of recurrence[34]. Although the prognosis of borderline resectable patients is significantly better than that of LAPC, survival rates are worse than those of resectable tumors[39]. Moreover, the role of arterial resection (AR) during pancreatectomy in borderline tumors has been analyzed in a recent systematic review published by

Mollberg *et al*[40]. Perioperative morbidity rates of patients with AR ranged from 17% to 100% (median 53.6%) with a median mortality rate of 12% (range: 0%-45.5%) compared to 2.6% in standard pancreatic resection[29,30]. Pancreatectomy with AR then increases the risk of mortality fivefold, without significant advantages in terms of long-term survival. These results demonstrate that the artery involvement by PDA, implies a more aggressive tumor biology, and these neoplasms should be considered as locally advanced despite the feasibility of surgical resection. Also, the involvement of the splenic artery has been demonstrated to be an adverse prognostic factor in body/tail PDA[41]. Neoadjuvant therapy is specifically beneficial in borderline resectable tumors and increases the fraction of resectable tumors. Katz *et al*[42] reported that 78% of patients completed neoadjuvant therapy and restaging, and 41% of them eventually underwent pancreatectomy. In this light, they suggest that neoadjuvant treatment could be considered to select properly patients who can benefit from surgery.

FURTHER DIAGNOSTIC TOOLS TO ASSESS RESECTABILITY

In several cases of patients with seemingly resectable tumors, clinical and radiological work-up could be lacking and further examinations are warranted in order to clarify doubtful findings (*i.e.*, elevated CA19.9 or persistence of abdominal pain). It has been observed that, in about 15% of patients with radiologically resectable PDA, surgery does not improve survival[43]. These patients are at high risk of early death despite radical surgery and they should be identified preoperatively using additional tests. Endoscopic ultrasound (EUS) is complementary to CT in the staging of the disease and in the detection of vascular invasion (SMA, SMV, and celiac axis) and lymph node metastasis[44,45]. Also EUS with fine needle aspiration (FNA) is preferable to CT-guided FNA in patients with resectable disease because of better diagnostic yield, safety, and potentially lower risk of peritoneal seeding[30]. EUS could be also helpful for obtaining a cytological grading of the tumor preoperatively. Among patients with borderline resectable PDA, the presence of a poorly differentiated or anaplastic tumor is another factor that shifts the management toward neoadjuvant treatment[6]. Nevertheless, the accuracy of FNA in the assessment of tumor grading has not been validated so far. Diagnostic staging laparoscopy to rule out metastasis not visible at standard imaging is routinely used in some institutions prior to surgery or chemoradiation or in patients with high risk for disseminated disease. Selective use of laparoscopy may be more appropriate and will probably be a more cost-effective approach[46]. The role of positron emission tomography (PET) with ^{18}fluorodeoxyglucose is still unclear, although it may be considered after formal pancreatic CT protocol in patients with high risk of metastasis, but it is not a substitute for high-quality, contrast-enhanced CT[30]. Nowadays, PET-CT favorably alters management more often when used for therapeutic monitoring compared to staging or restaging[47].

Beyond these imaging techniques, genetic status of a pancreatic carcinoma can be used to predict widespread metastatic failure. Several studies have demonstrated that there are different genomic alterations in PDA[48,49]. The most important are point mutations of *KRAS, CDKN2A/p16*, *TP53*, amd *SMAD4/DPC4*. Yonezawa *et al*[50] have analyzed the genetic abnormalities in precursor lesions such as pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, mucinous cystic neoplasms and their relation to PDA. They have found that KRAS mutation in PDA is 75%-100%, and SMAD4/DPC4 inactivation is seen in 55% of PDA patients. The low expression levels of SMAD4 are associated with an high rate of lymph node metastasis and poor survival[49]. Tanaka *et al*[51] have reported that loss of SMAD4 protein expression and chromosome 18q deletion were distinctly associated with metastasis. Determinations of DPC4 status at initial diagnosis may be of value in stratifying patients into treatment regimens related to local control *vs* systemic therapy[52]. Locally advanced carcinomas from patients with no documented metastatic disease uncommonly showed loss of DPC4 expression (22%) as compared with carcinomas from patients with extensive metastatic burden in which the rates of DPC4 loss approached 75%. In this setting, patients with DPC4-positive carcinomas would receive greater clinical benefit from intensive local control by CRT compared to patients with DPC4-negative carcinomas in which systemic chemotherapy alone may be more appropriate[53]. The advantage of SMAD4/DPC4 expression as a prognostic indicator is that it is potentially assessable preoperatively or during staging laparoscopy, whereas other factors, such as margins, perineural invasion and lymph node status are determined only after resection.

CONCLUSION

Surgical resection is still the only curative treatment for PDA. Oncological treatments have improved survival in patients with pancreatic cancer, also by increasing the rate of down staging and consequently of resectability. This improvement is probably also due to better patient selection by pancreatic surgeons. Nevertheless, current definitions of resectable, borderline resectable and locally advanced tumors are based only on radiological parameters and do not take into consideration the biology of the disease. Indeed, in borderline resectable disease a clear advantage in terms of survival has not been demonstrated for up-front surgery. Furthermore, surgery for borderline resectable is burdened by a high rate of morbidity and mortality that does not improve survival. In this light, a new concept of borderline pancreatic cancer has to include clinical and biological aspects (type and duration of symptoms, CA19.9 level, and immunohistochemistry). The selection of patients who will benefit from surgery has to be improved in the setting of an MDT discussion

that also considers further examinations.

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