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**Selection criteria in resectable pancreatic cancer: A biological and morphological based 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 but also by the increased consideration of the value of patients’ selection by pancreatic surgeons. In fact, it is necessary to select patients not only on the basis of the surgical resectability but also on the basis of the biological nature of the tumor. Preoperatively specific criteria can be identified in order to select patients who will really benefit of surgical resection. Duration of symptoms, high value of CA 19.9 also in presence of resectable disease should be considered in order to avoid R1 resection and early relapsing. Radiological assessment can help surgeons to distinguish resectable disease from borderline resectable disease and locally advanced pancreatic cancer. A better patients’ selection can increase survival rate and neoadjuvant treatment can help surgeons to select patients’ who will really benefit from surgery.

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

**Core tip:** The aim of this work is to identify better patients, affected by pancreatic ductal adenocarcinoma, who will really benefit for pancreatic surgery of pancreatic resection. Duration of symptoms, high value of CA 19.9 also in presence of resectable disease should be considered in order to avoid R1 resection and early relapsing. 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 tumor-associated deaths in both males and females in the European Union and in the United States[1,2]. Surgical resection still represents the only curative treatment for PDA although only a small fraction of tumors is amenable of surgical resection at diagnosis[3-6]. Moreover among patients who will undergo surgery, 30% of those will recur early as a result of a misdiagnosed aggressive disease[6]. Aim of this paper is to review the current available data on factors related with an adverse prognosis in patients with resectable PDA.

**EPIDEMIOLOGY**

Only 20% of patients are resectable at diagnosis and 5-years overall survival (OS) after curative resection is only 20%[4-8]. During the last decade survival rates of PDA remained dismal with a 5-year OS of 15%–20% after pancreaticoduodenectomy and 8%–15% after distal pancreatectomy[9,10]. In the 90s there was no improvement in 5-year OS, which was even slightly lower (2.3%-2.7%) compared with the 5-year OS rate observed in the late 80s (2.5%-3.1%)[11]. Despite progress in diagnostic procedures, most of cases are still metastatic at diagnosis, and are not amenable of radical surgery and even when curative surgery is performed, most of 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 the period 1990-1999 and 430 (79%) in the period 2000-2008. The length of hospital of stay (LOS) (16 d *vs* 10 d) and the postoperative mortality (2.6% *vs* 1.1%) significantly decreased over time. The median disease-specific survival (DSS) significantly increased from 16 mo in the first period to 29 mo in the second period. The resection performed in the period 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 the increased consideration of the value of patients’ selection by pancreatic surgeons. As regards of oncological progresses, in the last years several efforts have been made in the development of effective drugs in pancreatic cancer. In particular, two recent randomized clinical trials that included patients with metastatic PDA demonstrated a significant better survival for the treatment groups compared with control groups of patients treated with gemcitabine[13,14]. Conroy *et al*[14] show that FOLFIRINOX [5-fluorouracil (5-FU), oxaliplatin, and irinotecan] group have improved survival compared with 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, Van Hoff *et al*[13] have shown a better survival in patients with PDA treated with Gemcitabine plus nab-Paclitaxel compared with patients treated only with Gemcitabine. In this work OS was 8.5 mo in the treatment group compared 6.7 mo in the control group. The increase of objective response rate due to improvement of oncological treatments can lead to a consequent increasing also in the rate of resectable patients[15]. On the other hand, a better patients’ selection, have probably modified the survival of patients with PDA because of changing in resectability criteria. Among those who will undergo surgical resection, up to 30% of patients will die of disease within 1 year after operation[6,16]. In this subgroup, recurrence is very 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 to three factors including (1) inadequate preoperative radiological staging; (2) lacking radical surgery; and (3) differences in the aggressiveness of the disease. Undoubtedly, what is common to patients who will recur early, is a disease with a more aggressive biological behaviour.

All of these patients are resectable at diagnosis, but probably the difference with the others patients is the biological characteristic of the tumor. In addition to that, there is a relationship between hospital volume with long-term survival in patients with cancer subjected to pancreatectomy probably due to patients’ selection and technical expertise at the major centres that are responsible for the results[18]. So it is necessary to select patients not only on the basis of the 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 of surgical resection. Focusing on this criteria, we suggest a step-by-step approach to a patient with pancreatic cancer, the first step is then clinical and laboratoristic factors and then radiological features.

**CLINICAL AND LABORATORISTIC CRITERIA**

In order to select patients who will really benefit of a surgical approach we have to consider not only the imaging but also other parameters such us symptoms, risk of mortality related to patient’s comorbidity and the level of CA19.9. Symptoms of PDA depend on the site of the pancreatic lesion, as for pancreatic head tumors jaundice is the first sign whereas for pancreatic body/tail tumors, pain is the most frequent symptom. The 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 likelihood that this represents the result of pancreatitis or tumoral invasion of the retroperitoneal nerves[10,19,20]. In this light, the presence of abdominal pain should be always considered cautiously as the high risk of a locally advance tumor despite imaging findings of a resectable tumor. Nevertheless, not all the patients with a resectable PDA are also fit for surgery. Before planning a pancreatic resection is therefore always mandatory to carefully assess the surgical risk for each patient. Several studies have demonstrated that elderly patients have an increased risk of morbidity in pancreaticoduodenectomy (PD), in particular related to post-operative pancreatic fistula (POPF) although morbidity and mortality rates are acceptable[21]. It could be therefore justified to offer PD also to elderly patients who do not have significant comorbidities[21]. Brozzetti *et al*[22] have compared two group of patients (group A for patients older than 70 years, group B for patients younger than 70 years). They have shown a significantly higher operative morbidity and mortality in group A and they concluded that although an aggressive surgical approach is justified for elderly patients with pancreatic adenocarcinoma, surgical complications that lead to reoperation are responsible for a 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. The CA19.9 value decrease is the best index of improved prognosis[23,24]. In contrast, patients with an increased CA19.9 after resection had a signiﬁcantly shorter median survival time. In another study published by Montgomery *et al*[25], patients who had a CA19.9 value of less than 180 U/mL in the ﬁrst 3 mo after surgery had an improved survival. Lower preoperative CA19.9 values correlated not only with a lower pathologic stage, but also with an increased post-resection survival. The presence of a preoperative CA19.9 value less than 1000 U/mL is associated with a median survival of 28 mo compared with 12 mo of those patients who had a CA19.9 value > 1000 U/mL [23]. A value of 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 also demonstrated by several other studies that evaluated the decrease of CA 19-9 after anti-tumoral 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 than 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, a CA19.9 value less than 50 U/mL also showed a meaningful prognostic significance. Then in the neoadjuvant therapy setting, the measurement of CA19.9 value is an essential variable in the evaluation of a possible surgical resection of those tumors that exhibited a response to the 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 centre and the expertise of a dedicated multi-disciplinary team (MDT). The importance of MDT has been widely demonstrated for other malignancies[27,28]. Similarly, Pawlik and co-workers[29] have analysed the impact of MDT in the management of patients with pancreatic cancer. In this study, the authors analysed 203 patients with an outside computed tomography (CT) report that described 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 the 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 patients’ selection. Imaging should include at least one high-quality technique 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 multi-phase imaging technique includes 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 coeliac axis and the superior mesenteric artery, whereas the superior mesenteric vein, the portal vein, the splenic vein, and the pancreas itself are well 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 an occlusion of SMV/PV without technical option for reconstruction. A non-operative 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. On the other hand, 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 that of resectable tumors[39]. Moreover, the role of arterial resection (AR) during pancreatectomy in borderline tumors has been analysed 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 of 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 splenic artery has been demonstrated to be an adverse prognostic factor in body/tail PDA[41]. Neoadjuvant therapy is speciﬁcally beneﬁcial in borderline resectable tumours and increases the fraction of resectable tumours. 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 really 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.*, an elevated value of CA19.9 or the persistence of abdominal pain). It has been observed that, in about 15% of patients with radiologically resectable PDA, surgery does not improved 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, celiac axis) and nodes 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 a 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 with 18FDG (PET) 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]. Nowad PET-CT favourably alters management more often when used for therapy 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*, *SMA*D4/DPC4. Yonezawa *et al*[50] have analysed the gene’s abnormalities in precursor lesion such as PanIN, IPMN, MCN and their relation to PDA. They have found that KRAS mutation in PDA is around 75%-100%, and SMAD4/DPC4 inactivation is seen in 55% of PDA. The low expression levels of SMAD4 is already associated with an high rate of lymph nodes metastasis and poor survival[49]. Tanaka *et al*[51], also, 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 settings patients with DPC4 positive carcinomas would receive a greater clinical beneﬁt from intensive local control by chemoradiotherapy 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 fastors, such as margins, perineural invasion and lymph nodes 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 the increased consideration in patients’ 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 term of survival has not been demonstrated for up-front surgery. Furthermore, surgery for borderline resectable is burdened from high rate of morbidity and mortality that not improve survival. In this light, a “new concept” of border-line pancreatic cancer has to include also clinical and biological aspects (type and duration of symptoms, CA19.9 value, immunohistochemically). The selection of patients who will actually benefit from surgery has to be improved always in the setting of a MDT discussion also considering further examinations.

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