

Resectability criteria in cephalo-pancreatic cancer

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Abstract. Background: Since pancreatic cancer is often diagnosed at an advanced stage the issue of how to manage invasive tumors has been raised in the literature. The curative treatment remains the surgical resection. What we aimed to assess in this review article is the extent to which an invasive tumor can receive an indication for resection. Methods: Articles concerning the management of pancreatic cancer were retrieved using the key words pancreatic cancer, vascular involvement and pancreatic cancer metastases. The database we used pertained to PubMed. Results: There is an ongoing debate on whether surgery is indicated in the case of arterial involvement advising caution when selecting patients for this type of intervention. Venous involvement, however, can and should be treated surgically since its postoperative outcome is similar to that of patients without venous invasion. Lastly, when dealing with metastases a surgical intervention is indicated in cases where they are few and easily resectable, without any harm occurring to healthy tissue.

Key Words: pancreatic cancer, vascular involvement, metastases.

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Introduction

Pancreatic cancer is one of the most aggressive solid malignancies ranking as the 5th leading cause of cancer death (Iglesias et al 2009). In spite of the progress of the last decades the 5-year survival rate still remains at 5% (Wolfgang et al 2013). Only 20% of the pancreatic tumors can be resected, due to the advanced stage of the disease at the moment of diagnosis (Howlander et al 2010). The only potentially curative method is tumor resection with adjuvant chemotherapy, therefore early diagnosis and correct staging are the most important goals in the preoperative era. Due to its retroperitoneal location, pancreatic cancer symptoms are not specific and there are no tests allowing early diagnosis. Abdominal computed tomography (CT) and magnetic resonance imaging (MRI) should be utilized when suspecting pancreatic cancer in order to confirm and assess its resectability. CT allows the observation of the primary tumor and its relation to the superior mesenteric artery (SMA), celiac axis, superior mesenteric vein (SMV), portal vein (PV) and also with distant organs. CECT (contrast-enhanced CT) is the "golden-standard" in diagnosing pancreatic cancer and it is sufficient to initiate a management plan. The accuracy of CECT in predicting surgical resectability is between 80-90% (Karmazanovsky et al 2005). MRI accuracy for vascular involvement is quite similar to that of CECT. Due to the costs and duration of the examination, Buchs et al (2010) have recommended that MRI be done for patients not able to benefit from CECT or if there are inconclusive findings on the CECT. Additional imaging techniques may also highlight other aspects such as vascular invasion in endoscopic ultrasonography (EUS), recurrent tumors in fludeoxyglucose-positron emission tomography scanning, and a more accurate staging in laparoscopy. EUS is also useful in cases where the CECT has not identified a pancreatic mass, but the suspicion

of pancreatic cancer remains. Also, the method can be used to obtain biopsies from the mass (Hidalgo 2010).

Resectability criteria

Pancreatic tumors can be divided into three categories: resectable, borderline resectable and unresectable. Resectable tumors have been defined as having no metastases, no superior mesenteric artery, celiac or hepatic artery encasement and a normal portography. Borderline resectable tumors have abnormal portography but possibility of reconstruction, abutment on the celiac or superior mesenteric artery, or invasion of the stomach, colon or mesocolon. Unresectable tumors have been defined as having distant metastases or lymph-node metastases outside the dissection field; superior mesenteric artery, celiac or hepatic artery (HA) encasement; or portal or superior mesenteric venous invasion with obstruction and no possibility of reconstruction. Also, if the patients have other serious conditions they are not to be considered for radical resection (Nakao 2012). Resectability can be influenced by variant vascular anatomy thus making it important to identify it preoperatively. For example, jejunal branches inserting high on the SMV near the PV confluence can make vascular resection and reconstruction very difficult. Also, an aberrant right hepatic artery arising from SMA requires a careful dissection of the hepatic pedicle (Pietryga et al 2015).

Vascular involvement

The main objective of oncological resection is obtaining free margins (R0) and excising a minimum of 12-15 lymph nodes (Hidalgo 2010). Multiple studies from the literature concluded that a more extensive resection does not bring survival improvement but increases postoperative morbidity (Hidalgo 2010).

The management of a possible tumor adhesion to a vein or an artery is one of the most challenging issues for the surgeon. When facing a vascular invasion, there are three options: to leave the tumor attached to the vessel resulting in a grossly positive margin, to try to separate the tumor from the vessel with a considerable hemorrhage risk, or to perform a partial or segmental resection of the portion of invaded vessel with reconstruction.

Arterial invasion

The narrowing of the SMA, HA or celiac trunk is usually due to a locally advanced cancer, but peritumoral fibrosis can also appear as a malignant mass. This situation is often very difficult to define before or even during surgery.

Yekebas et al (2008) showed that arterial resection can be a safe procedure in cases with confirmed vascular invasion, with morbidity and mortality rates comparable to pancreaticoduodenectomies without arterial resection. In the case of curative surgery, the 2- and 5-year survival rates for patients with arterial invasion are 35% and 15%, respectively. The same rates have been stated in patients without arterial invasion that underwent curative surgery.

Arterial reconstruction depends on the vessel involved. If there is celiac or hepatic invasion, the reconstruction can be done either by end-to-end anastomosis, by interposition of a venous or arterial graft, or using a prosthesis. If the SMA is involved, an aortic anastomosis may be necessary.

According to several authors (Li et al 2004; Vicente et al 2014), arterial resection seems to be justified in highly selected patients with the purpose of achieving a free margin resection.

However, arterial invasion usually includes extensive involvement of the mesenteric neural plexus, rendering radical resection oncologically unsound because often, the histological examination finds R1 margins (Imamura et al 2004). Also, arterial invasion means that the tumor has an aggressive behavior and the micrometastatic spread due to this is thought to limit the oncological benefit of a surgical excision (Srinesvas et al 2007). The most extensive literature review regarding arterial resection in pancreatic cancer published by Mollberg et al (2011) included 26 studies and 2609 patients (366 who underwent pancreaticoduodenectomy with and 2243 who underwent pancreaticoduodenectomy without arterial resection). The meta-analyses cited by Mollberg et al (2011) revealed that arterial resection significantly increased the risk for immediate postoperative mortality [Odds ratio (OR)=5.04; 95% confidence interval (CI), 2.69-9.45; $p<0.0001$; $I^2=24\%$], a poor 1-year [OR=0.49; 95% CI, 0.31-0.78; $p=0.002$; $I^2=35\%$] and 3-year survival rate [OR=0.39; 95% CI, 0.17-0.86; $p=0.02$; $I^2=49\%$] compared with patients without arterial resection. An increased perioperative mortality [OR=8.87; 95% CI, 3.40-23.13; $p<0.0001$; $I^2=5\%$] and a low 1-year survival rate [OR=0.50; 95% CI, 0.31-0.82; $p=0.006$; $I^2=40\%$] was also revealed when comparing to patients undergoing venous resection. Mollberg et al (2011) concluded that arterial resection in patients undergoing pancreaticoduodenectomy for pancreatic cancer is associated with a poor short and long-term outcome.

Venous invasion

Portal vein resection is indicated when tumor-free margins can be obtained (Nakao 2012). In the reconstruction of the portal vein, homo/auto-graft vessel transplantation (Kikuchi et al

1956; Asada et al 1963; Sigel et al 1965), or the use of an artificial vessel (Moore et al 1951; Longmire et al 1966) have been reported. The ideal technique in portal vein reconstruction is the end-to-end anastomosis (Cassebaum 1971; Norton et al 1975; Fortner 1973). The reconstruction of the SMV/PV can be performed in a variety of ways depending on the degree of involvement. Patch or primary closure can be done for partial involvement, with patch reconstruction often using the greater saphenous vein. Segmental reconstruction of the SMV can be performed with an interposing vein graft using the internal jugular, renal vein or superficial femoral vein (Fuhrman et al 1996; Poon et al 2004).

Siriwardana et al (2006) have reviewed the outcome of PV resections in the largest report from the literature on PV-SMV resection in pancreaticoduodenectomies. Fifty-two non-duplicated papers were studied that have provided relevant data from 1646 patients. Histologically confirmed PV invasion was determined in 668 (63.4%) of 1054 PV resection cases. Positive margins were found in 346 (39.8%) of 870 patients with PV resection in 23 studies, with a positivity mean of 0–85%. Postoperative morbidity was reported to be 9-78%, with a median of 42% per cohort. The mortality after portal vein resection was found to be 5.9% (73 out of 1235 patients in 39 studies). The mortality rate of PV resection used to be over 20% at the beginning of the era of PV resection, but has decreased to less than 5% in the last years. Median survival used to be 13 months, and one-year, three-year and five-year survival rates were 50, 16 and 7% respectively.

Recent reports concluded that the results of venous resection and vascular reconstruction in patients with limited involvement of the SMV and PV are similar to that of patients without vein involvement (Nakao, 2012).

Revikumar et al (2014) published a UK multicenter retrospective cohort study comparing pancreaticoduodenectomy with vein resection (PDVR), standard pancreaticoduodenectomy (PD), and surgical biliary and gastric bypass (SB). One thousand five hundred eighty-eight consecutive patients with T3 cephalo-pancreatic cancer undergoing surgery between late 1998-mid 2011 were included. The primary parameters measured were overall survival (OS) and immediate postoperative mortality. As a secondary objective, postoperative morbidity was measured. The authors concluded that there was no significant difference in postoperative deaths in the three groups and a similar OS between PD and PDVR, both significantly better compared with SB.

Yu et al (2015), in a meta-analysis of 22 retrospective studies (2890 patients) compared both postoperative outcomes and OS, in patients with standard pancreaticoduodenectomy versus those with additional venous resection. The study found differences in median tumor size ($p<0.001$), lymph node metastasis ($p=0.03$), R0 resection rate ($p<0.001$), pancreatic fistula ($p=0.01$) as the major postoperative complication, and 5-year survival ($p=0.03$). There was no reported difference between the groups regarding postoperative morbidity, mortality and one-year, three-year survival. Patients from the venous resection group who received R0 resection had a significantly better survival compared with those who received R1 resection. This was true for both two-year ($p<0.001$) and five-year ($p=0.00002$) survival. It was shown that if the patients had actual tumor infiltration, their survival

rate would be lower than that of the patients with peritumoral inflammation.

Metastases

Metastasectomy can be considered in very fit patients who have isolated metastases. Although resection of liver metastases has shown mixed results in terms of improving survival as compared to a palliative procedure only, pulmonary and brain metastasectomy has improved survival in a carefully selected group of patients (Arnaoutakis et al 2011).

The literature suggests that if the metastasis diameter is less than 5 mm, they cannot be detected by CECT or MRI. That is why up to 12% of occult liver metastasis and peritoneal carcinomatosis are discovered only at the moment of exploratory laparotomy (Toomey et al 2013). There is still a controversy regarding the management of these types of cases, especially when occult liver metastases are discovered simultaneously with a resectable pancreatic mass. If the surgeon decides to perform a duodenopancreatectomy, he has to choose between doing a synchronous or metachronous hepatectomy (Lu et al 2015).

Singh et al (2010) reports three cases of synchronous metastasectomy and pancreaticoduodenectomy, patients who died at 7, 14 and 18 months postoperatively, without being able to prove a clear OS benefit.

Klein et al (2012) studied a group of 22 patients who underwent pancreaticoduodenectomy with synchronous liver segmentectomy (7 patients, 32%) or enucleation of the hepatic metastases (15 patients, 68%). They reported a median OS of 7.6 months (± 9.94 months), with a two-year survival of 5% (one patient). None of the patients reached the five-year survival mark.

Adam et al (2006) reported a 5-year survival rate over 25% and a median OS of 1,7 years for patients who had liver metastasectomies with primary pancreatic cancer resection.

Shrikhande et al (2007) suggested that there is an acceptable risk in performing liver metastasectomies synchronous with duodenopancreatectomies in selected patients. The postoperative mortality and morbidity rates for 29 patients with hepatectomies and R0/R1 duodenopancreatectomies were 0% and 24.1%, compared with 4.2% and 35.2% in 287 patients with R0/R1 standard duodenopancreatectomies.

In a systemic review of the literature Michalski et al (2008) identified 103 cases with pancreatic cancer and liver metastasis that benefited from a pancreaticoduodenectomy. Patients with hepatectomy had a significantly longer median OS (11.4 vs. 5.9 months, $p=0.038$), and a complication (24.1-26%) and mortality rate (0-4.3%) similar to that of standard duodenopancreatectomies. They concluded that experienced pancreatic surgical centers could chose patients with metastases as candidates for resection.

Romanian expertise

In our country, there are some tertiary centers specialized in pancreatic surgery. In 2007, Popescu et al describe the technical version of pancreaticoduodenectomy by posterior approach and present the first 10 patients outcomes and the advantages of the method: early assessment of resectability, sparing an aberrant right hepatic artery originating from the superior mesenteric artery, facilitation of portomesenteric venous resection, complete mesopancreatic excision and correct lymphadenectomy.

Subsequent papers of the same team (Dumitrascu et al 2011; Popescu et al 2011a; Popescu et al 2011b; Dumitrascu et al 2010) supports and strengthen these benefits, especially regarding local recurrence, which seems to develop most rarely. Moldovan et al (2012) published a series of sixteen patients with duodeno-pancreatectomy and PV/SMV resection, representing one author's experience, showing that the posterior approach allows an oncologically safe en bloc resection and a reduced time for venous reconstruction. Brasoveanu et al (2015) report a case of pancreatoduodenectomy en bloc with both venous and arterial resection. Bartos et al (2014) propose a protocol for pre, intra and postoperative management of patients with pancreatoduodenectomies, which facilitates case selection, identifies risk factors for complications and offers solutions to ameliorate the outcome of these patients. Also for accuracy of the intraoperative diagnosis and management of pancreatic tumors, Cirimbei et al (2013) reveals the role of intraoperative ultrasound, which enables a complete and correct diagnosis, with an accurate staging, and aids in establishing the adequate therapeutic attitude.

What are the prospects?

Currently the most effective treatment for pancreatic cancer remains the surgical approach followed by chemotherapy. A future challenge in treating pancreatic cancer will be to find new therapies that target the cancer and its surroundings and also the cancer stem cells. Recent findings regarding pancreatic stellate cells and the stroma have shifted the focus to the role in desmoplasia pancreatic cancer development. This will hopefully open new prospects in the research of new cancer treatments.

The goal is to personalize treatment by combining newly discovered drugs with classical chemotherapy and radiation, based on specific biomarkers. This, in turn, the authors predict, will increase patient's survival (Rossi et al 2014).

The role of neoadjuvant chemotherapy is to reduce tumor size and even possibly, to obtain a downstaging of said tumor. Also, it is used in patients who are suspected to have a systemic spread of the cancer. If future imaging of these patients confirms the suspected diagnosis they will be spared of an unnecessary major resection (Winner et al 2015). This type of approach is used mainly in borderline tumors which can become resectable (Fathi et al 2015).

Alamo et al (2014) published the following arguments for neoadjuvant therapy in pancreatic cancer: (1) down-staging of the tumor to achieve an margin free resection; (2) some of borderline tumors can be down-staged to resectable; (3) radiation therapy is more effective prior to surgery, when there is a proper blood supply of the tissue; (4) neoadjuvant treatment may prevent dissemination of neoplastic cells during surgery; (5) patients with occult metastatic disease detected only after neoadjuvant treatment can be spared of an unnecessary laparotomy; (6) post-operative outcomes and recovery are not affected by the neo-adjuvant therapy.

Current studies suggest that laparoscopic pancreatic surgery is feasible and provides some benefits: decreased blood loss, reduced post-operative pain, shorter length of stay and faster functional recovery. But it is a complex technique which demands long learning curves. Also, there are still debates regarding the oncological outcomes. There are more data needed on tumor recurrence and patient survival (Anderson et al 2014).

The most important aspect of pancreatic cancer surgery is to identify new diagnostic methods which will allow an early detection of the tumor, in a resectable stage.

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