Borderline Resectable Pancreatic Cancer

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Abstract Borderline resectable pancreatic cancer (BRPC) is an evolving diagnostic entity that blurs the distinction between resectable and locally advanced pancreatic cancer (Varadhachary et al. *Ann Surg Oncol* 13:1035–1046, 2006). Until recently the management of this disease has been poorly defined; however, consensus guidelines have been developed regarding the proper management of this diagnostic entity. Recent studies have shown that if appropriately identified and treated, this subset of disease can have outcomes similar to pancreatic cancer that is defined as resectable (Laurence et al. *J Gastrointest Surg* 15:2059–2069, 2011). The aim of this review is to outline the current consensus on definitions, workup and management of BRPC, and also provide a summary of issues that require progress as defined by the International Study Group of Pancreatic Surgery (ISGPS).

Keywords Borderline · Pancreatic cancer · Pancreas · Whipple · Pancreaticoduodenectomy

Background

Pancreatic cancer is the fourth leading cause of cancer related deaths in men and women despite being the tenth most common site of new cancer diagnoses [2]. The poor outcomes associated with this disease are caused in large part by a

majority of patients presenting with advanced disease at the time of initial diagnosis. Currently, at the time of diagnosis, approximately 53 % of patients have metastatic disease, while another 25 % have locally advanced disease [3]. The prognosis of patients with pancreatic cancer is dismal, as the 1 and 5-year relative survival rates are 27 and 6 %, respectively [2].

Pancreatic cancer comprises of a large variety of individual cancer types; however 80 % are adenocarcinomas [4]. Surgery remains the mainstay of treatment for pancreatic cancer. Historically, this disease has been divided into two groups, resectable or unresectable. The disease was considered unresectable in the presence of metastatic disease or due to the involvement of adjacent vasculature. With advancements in neoadjuvant therapy, as well as in surgical techniques, the determination as to when the disease is resectable versus unresectable has become less clear, giving rise to a new subset of this disease now described as BRPC. It is estimated that approximately one third of patients diagnosed with pancreatic cancer will fall into the category of BRPC [5].

Definition of BRPC

Currently, there is an overall agreement that patients with a patent portal vein (PV), patent superior mesenteric vein (SMV), a clear fat plane between the tumor, celiac axis and superior mesenteric artery, and no distant disease are considered to have resectable disease [6]. However, as the tumor begins to abut, and in turn invade, one or more of these structures, there is still debate over what constitutes resectable disease. It has been observed that the surface area of the tumor contacting these vessels directly correlates with probability of invasion. With PV or SMV encasement greater than 180°, the probability of invasion is around 80 %, while encasement of 270° or greater results in near 100 % likelihood of invasion. Therefore, the current working definition of borderline

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resectable tumor classifies tumors that have circumferential tumor abutment with the SMV, PV, or superior mesenteric artery (SMA) involvement equal to or less than 180°. The definition has also been expanded to include short segment (defined as less than 1.5 cm) encasement of the SMV or portal vein that is amenable to venous resection with subsequent reconstruction. Tumors involving the SMA with abutment less than 180° have been included in the category of BRPC. Tumors involving the SMA with abutment greater than 180° requiring resection and subsequent arterial reconstruction are currently considered to have unresectable disease. Encasement of the gastroduodenal artery (GDA) up to its origin from the hepatic artery or involving a short segment of hepatic artery has been included in the definition of BRPC. Additional CT imaging-based criteria have also been used to determine resectability of disease. These criteria include presence of a teardrop-shaped deformity of the SMV as well as the presence of dense periarterial soft tissue, both denoting a strong likelihood of vascular invasion and thus unresectable disease [6]. Additionally, the National Comprehensive Cancer Network (NCCN) defines BRPC as venous involvement of PV/SMV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal allowing for safe resection and replacement, encasement of the GDA up to the hepatic artery with short segment encasement, or direct abutment of the hepatic artery without extension to the celiac axis and abutment of SMA less than 180° [7, 8]. See Table 1 for NCCN definition of resectability status.tgroup

Current Approach to Diagnostic Workup

Historically, the determination of resectability status of pancreatic status was done at the time of surgical exploration. However, with advancements of imaging technology, it is now

feasible to appropriately stage patients and create a treatment plan preoperatively in most cases [9]. The benefits of high resolution CT using a “pancreas protocol” as the imaging modality of choice is uniformly agreed upon. Such a protocol should achieve an optimal balance between visualization/resolution of normal pancreatic and malignant parenchyma as well as of liver parenchyma and arterial and venous vessel enhancement/visibility [3]. This protocol is accurate in predicting resectability in over 80 % of tumors and over 90 % successful in identifying vascular invasion. The largest limitation of CT is its inability to detect small volume metastatic disease involving the liver and peritoneum. It is estimated that 20–30 % of patients undergoing diagnostic work-up for pancreatic cancer using CT alone have unsuspected metastases [10, 11]. Another available imaging modality is magnetic resonance cholangiopancreatography (MRCP) combined with magnetic resonance angiography (MRA). The combination of these modalities for determination of resectability provides an accuracy rate of around 90 % [12, 13]. Mesenteric angiography to determine vascular involvement has been replaced by CT scan with lower morbidity without any compromise in accuracy [14].

There are a large number of proponents for the use of endoscopic ultrasonography (EUS) in the preoperative work-up of pancreatic cancer [15, 16]. The advantage of utilizing EUS is that it provides the opportunity for guided fine needle aspiration (FNA) for confirmation of disease as well as histological analysis [17]. This modality has been shown to potentially be the most sensitive method for identifying and assessing small lesions less than 2 cm in the pancreas. With regard to tissue biopsy, it has been proposed that use of EUS-FNA is preferred over percutaneous techniques in order to prevent seeding of malignant cells along the biopsy needle

Table 1 NCCN guidelines, version 2.2014, defining resectability status

Localized and resectable	Borderline resectable	Unresectable
No distant metastasis	No distant metastasis	Distant metastasis
No radiographic evidence of SMV or PV distortion	Venous involvement of the SMV or PV with distortion or narrowing of the vein or occlusion of the vein with suitable vessel proximal and distal, allowing for safe resection and replacement.	Greater than 180° SMA encasement, any celiac abutment
Clear fat planes around CA, HA, and SMA	GA encasement up to the hepatic artery with either short segment encasement or direct abutment of the HA without extension to the CA Tumor abutment of the SMA not to exceed 180° of the circumference of the vessel wall	Unreconstructible SMV/portal occlusion Aortic invasion or encasement Metastasis to lymph nodes beyond the field of resection

CA celiac axis; HA hepatic artery; PV portal vein; SMA superior mesenteric artery; SMV superior mesenteric vein

tract [18, 19]. The disadvantages of EUS are that it is very observer-dependent and the technology is not available in all centers.

Venous Involvement

Many studies that have looked at indications for operative exploration and resection in the presence of mesentericoportal axis involvement reported no difference in morbidity, mortality, and survival rates from those patients who underwent standard resection, and outcomes were in fact better than in patients without operative treatment because of venous involvement [20–24]. On the contrary, Worni et al. demonstrated an increase in intraoperative and postoperative morbidity but no increase in operative mortality in patients undergoing concomitant vascular resections [25]. The ISGPS strongly recommends operative exploration and resection in the presence of reconstructable mesentericoportal axis involvement while recommending against the use of neoadjuvant treatment protocols in BRPC patients with isolated venous involvement [3]. They have further proposed to classify the venous resections to help with more detailed, evidence-based future recommendations. Type 1—partial venous excision with direct closure; type 2—partial venous excision using a patch; type 3—segmental resection with primary veno-venous anastomosis; and type 4—segmental resection with interposed venous conduit and at least two anastomoses. Portal venous tumor invasion has been shown to be a negative prognostic factor [3], and the depth of tumor invasion is even more accurate for determining survival [26]. Deeper portal vein invasion into the tunica media or intima was an independent prognostic factor for poor survival.

Arterial Involvement

A meta-analysis by Mollberg et al. showed a perioperative morbidity (median 53.6 %) and mortality (median 11.8 %) in patients undergoing arterial resection. Further, the survival analysis did not show a benefit of arterial resection compared to venous resection [27]. The ISGPS does not recommend arterial resections on a routine basis in patients with BRPC. However they suggest that patients categorized as borderline resectable due to suspicion of arterial infiltration on imaging should undergo surgical exploration given the inadequate differentiation between fibrous adhesions and true cancerous invasion [3, 28, 29]. Neoadjuvant treatment protocols have not shown improved tumor clearance in BRPC patients [30]. For this reason, there is no level I evidence recommending neoadjuvant therapy regimens in patients with arterial infiltration. However, a similar one year survival rate was demonstrated with neoadjuvant chemoradiotherapy when

compared to patients with resectable disease [1]. The status of the superior mesenteric artery margin has been deemed to be the most important predictor of survival because it is the most frequently involved positive margin [31]. The current consensus is to follow the Royal College of Pathologists recommendations for specimen examination and the R1 definition based on the European criteria, which defines a positive resection margin if tumor cells are ≤ 1 mm from the margin [3].

Role of Neoadjuvant Chemoradiation

Recent trials of neoadjuvant chemoradiation, which included various agents such as 5-FU, gemcitabine, cisplatin, paclitaxel, etc. in BRPC, demonstrate a median overall survival from 12 to 40 months [32]. The rationale for neoadjuvant treatment in borderline resectable pancreatic cancer includes: 1. Providing an observation period during neoadjuvant treatment to allow the discovery of initially occult metastases and thus avoiding unnecessary surgery. 2. It provides assurance that all patients receive radiation and chemotherapy, as a large number of those undergoing initial surgery do not receive adjuvant therapy because of postoperative complications, poor recovery, or metastases. 3. Percentage of positive margin resections is less after preoperative therapy [32].

Miscellaneous Factors

New studies are evaluating the role of systemic inflammation in the prognosis of patients with BRPC. Patients with a low modified Glasgow prognostic score, which corresponds to a lower systemic inflammatory response, had better survival than those with advanced inflammation [33]. Similarly, preoperative serum levels of carbohydrate antigen 19-9 (CA 19-9) have been shown to be useful in assessing potential benefits in survival with surgery but not for prediction of resectability [3].

Technical Aspects

Long term survival after a diagnosis of pancreatic cancer is best achieved in patients who are able to undergo operative resection with negative margins. The median overall survival of patients who undergo complete resection with negative margins ranges between 12 and 26 months, with some institutions demonstrating 5 year survival rates of up to 40 % [34, 35]. The basics of a Whipple procedure will not be discussed here, but the intricacies involved during the resection of a BRPC are highlighted.

The accuracy of preoperative CT in determining whether or not the tumor can be separated from the SMV-PV depends on the anatomic relationship of the tumor to this venous confluence, but is not 100 %. Consistent with this observation, the current consensus statement implies that surgeons who perform PD should be experienced with techniques for venous resection and reconstruction [31]. Borderline resectable pancreatic cancers may require venous resection, a more complex arterial dissection, or both. The SMV and the splenic vein join and become the PV posterior to the pancreatic neck. The jejunal branch of the SMV usually passes behind the SMA after draining the proximal jejunum and then enters the posterior- medial aspect of the ileal branch of the SMV to form the main trunk of the SMV [36]. The jejunal branch can occasionally pass anterior to the SMA, making the dissection of the SMV from the uncinate process easier. The jejunal branch-SMV confluence is important because the jejunal branch can be easily injured during dissection of uncinate process tumors if great care is not taken. Hemorrhage from an injured jejunal branch can result in an SMA injury in an attempt to suture the site of venous bleeding if the SMA is not completely exposed. Therefore, exposure of the SMA medial to the SMV should be accomplished before dissecting the SMV when a difficult venous dissection is anticipated and in all cases in which venous resection and reconstruction are being considered. When the pancreatic tumor is inseparable from the posterior-lateral aspect of the SMV or its ileal branch, the jejunal branch can be approached from the left of the SMV by opening the root of the small-bowel mesentery to the right of the SMA, and medial to, or to the left of, the SMV. After exposing the SMA, the soft tissue of the mesenteric root between these vessels is divided until the jejunal branch is identified as it courses posterior to the SMA. The SMA passes caudally after leaving the aorta and normally gives off two inferior pancreaticoduodenal arteries (IPDAs) which perfuse the pancreatic head and uncinate process. The more distal IPDA often originates from a jejunal branch arising from the proximal SMA. The SMA is usually posterior and medial to the SMV and it is common for a pancreatic head tumor that abuts the SMA to be inseparable from the SMV [36].

The ability to separate the SMV-PV confluence from the pancreatic tumor successfully should not be assumed to indicate that the tumor does not extend to the lateral or anterior wall of the SMA. The relationship of the low density tumor, as seen on CT imaging, to the SMA should be known by the surgeon before surgery from high quality cross-sectional images. Unlike the mesenteric veins, the SMA is surrounded by a sheath of autonomic neural tissue and lymphatics extending posteriorly to the SMA and celiac ganglia. This neural tissue can be a conduit for microscopic tumor extension from the site of the primary tumor in the pancreas to the SMA [37]. The SMA margin may be microscopically positive even when gross tumor is not evident during the SMA dissection, an

observation in support of the use of neoadjuvant chemoradiation in patients at risk for a positive SMA margin because of tumor abutment on CT images. Isolated involvement of the jejunal branch of the SMV may be managed by division and segmental resection of this branch without reconstruction as long as the ileal branch remains intact and is of good caliber (at least 1.5 times the diameter of the SMA). Similarly, tumors that involve the ileal branch of the SMV, in the rare setting in which the jejunal branch is uninvolved and preserved, may be managed by ligation and short-segment resection of the ileal branch without reconstruction. Involvement of the confluence of the ileal and jejunal branches in association with more proximal involvement of the common trunk of the SMV may be successfully managed by ligation of the jejunal branch of the SMV along with concurrent segmental resection and reconstruction of the main SMV trunk (and proximal ileal branch) with or without an interposition vein graft. If the splenic vein is left intact, the PV remains immobile and an interposition graft is usually necessary to connect the ileal branch to the main SMV. Cusack et al. initially reported the use of an internal jugular vein interposition graft for this purpose and this particular surgical technique has been further refined since that time [36, 38].

Fig. 1 Illustration of the different forms of reconstruction of the SMV and SMV-PV confluence. (Modified from Tseng JF, Raut CP, Lee JE, et al.: Pancreaticoduodenectomy with vascular resection: margin status and survival duration, *J Gastrointest Surg* 8[8]:935–949; 2004.)

Reconstruction of the ileal branch is always preferred over the jejunal branch as the jejunal branch is usually posteriorly located and extends into the proximal left jejunal mesentery, making access for an anastomosis technically difficult. Division of the jejunal branch and resection of the confluence of the jejunal and ileal branches with reconstruction of the ileal branch (caudal to the tumor) and the main SMV (cephalad to the tumor) can be performed only if the ileal branch is of adequate caliber [36]. Different forms of reconstruction of the SMV and SMV-PV confluence is illustrated below (Fig. 1) [21].

When the tumor is adherent to a small aspect of the lateral or posterior wall of the SMV-PV, a tangential resection with a vein patch is possible. The greater saphenous vein works well for a patch in this type of reconstruction. Occasionally, a vein patch can be avoided if the tumor involves the lateral wall of the SMV-PV confluence directly across from the splenic vein junction. In this case a pie-shaped defect in the vein can sometimes be repaired transversely (analogous to a pyloroplasty). Ligation of the splenic vein frequently allows for an end-to-end primary anastomosis of the SMV to the PV. Splenic vein preservation is necessary when the IMV does not enter the splenic vein to allow for collateral decompression of the stomach and spleen. If IMV decompression of the ligated splenic vein is not present, the splenic vein can be sewn to the left renal vein. Interposition grafting is necessary in most patients in whom the SMV is resected and the splenic-SMV-PV junction is left intact [36, 38, 39].

Future Directions

Borderline resectable pancreatic cancer is a diagnostic entity whose principles of management continue to be in evolution. The recent consensus conference with the proposed recommendations adds some uniformity to the definition and management of patients with borderline resectable pancreatic cancer. With these guidelines and the increasing use of ongoing research, we will be able to select the appropriate candidates for surgery. Selecting the appropriate surgical candidates is crucial for achieving a R0 resection in the borderline resectable patient population and obtaining survival rates comparable to patients considered to be in the resectable category.

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