

Borderline Resectable Pancreatic Cancer: Concepts and Controversies

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Abstract

Pancreatic cancer is a lethal malignancy which is increasing in incidence. Surgical resection offers the best chances of cure for a potentially resectable adenocarcinoma of pancreas which can be supplemented by appropriate adjuvant treatment further. However, 40% of the cases are diagnosed with a distant metastasis at presentation and the remaining 30- 40% are diagnosed as a locally advanced and unresectable. The definition of resectability has been debatable and the term borderline resectable pancreas was introduced. The optimal approaches to manage these tumors are controversial and not yet standardised. While these tumors may be resectable with high probability of incomplete resection, if they are not downstaged with prior neoadjuvant chemotherapy or chemoradiotherapy. Neoadjuvant chemotherapy with single agent or with multiple agents with or without concurrent radiotherapy have been tried since ages and these modalities have wide range of conversion to R0 resection ranging from 4%- 80%. Majority of the patients despite curative R0 resection require adjuvant chemotherapy either alone or in combination with radiotherapy. This review discusses the controversies related to the management of borderline adenocarcinoma pancreas.

Keywords: Borderline Pancreatic Cancer; Vascular Reconstruction; Controversies

Abbreviations: MDACC: Anderson Cancer Center; NCCN: National Comprehensive Cancer Network; AHPBA: Hepato-Pancreato-Biliary Association; SMA: Superior mesenteric artery; NACT: neoadjuvant chemotherapy; NACT: Neoadjuvant Chemoradiation; BRPC: Borderline Resectable Pancreatic Cancer; OS: Overall Survival; 5-Fu: 5- fluorouracil.

Introduction

Pancreatic cancer is the lethal malignancy and is the fourth leading cause of death in United States. Pancreatic

adenocarcinoma is the most aggressive among all known histologies of pancreatic cancer. It has a dismal prognosis too with median survival ranging from 15- 23 months and 5 – year overall survival (OS) is hardly 15-20% [1,2]. Historically the localized pancreatic cancer (PC) is treated with surgery followed by adjuvant therapy but this is not true with borderline resectable pancreatic cancer (BRPC) [3]. Nevertheless, currently R0 surgical resection is the mainstay of the treatment and the only modality to offer best chances of long term survival. There is a new entity described in the literature as BRPC, where subgroup of patients respond so well following neoadjuvant therapy

that borderline resectable PC becomes amenable to R0 resection. Thus, it becomes crucial to detect the potentially resectable tumor accurately and to offer the appropriate treatment modality to the selected patients and high quality multi-detector computerised tomography (MDCT) is the imaging modality of choice to address this issue. In this review we shall briefly discuss the approach to management of BRPC and we have also tried to resolve existing controversies in the management of BRPC.

Anatomical Definition of BRPC and Resectability Concerns

Like any other visceral malignancy, resectability in PC was also defined by the presence of limited pancreatic disease and absence of distant metastasis. Borderline resectability has always been an elusive condition where different definitions have been proposed by different organisations and none of them is universally acceptable. NCCN in 2008, proposed definition for BRPC. Later, in 2009 MD Anderson cancer centre, and American Hepato pancreatobiliary association (AHPBA)/Society for Surgery of the Alimentary Tract (SSAT)/Society of Surgical Oncology (SSO) also suggested new definitions of borderline PC. Definitions proposed by AHPBA was slightly different from the one proposed by MD Anderson where tumor- vessel relationship was defined by

encasement or abutment of Superior mesenteric artery (SMA)/ portal vein (PV) by either $\geq 180^\circ$ or $\leq 180^\circ$ (**Table 1**). Further in 2014, Tran, et al. simplified this classification by defining Tumor-vein circumference interface (TVI) which is very much helpful in decision making and planning for venous reconstruction. This TVI grouping is as follows; (i) no interface, (ii) $\geq 180^\circ$ of circumference or occlusion, (iii) $\leq 180^\circ$ of interface. Details of each system are as follows in table [4-7]. In brief, BRPC can be defined as tumor limited to pancreas with limited involvement of re-constructible vascular structures whereas locally advanced pancreatic cancer (LAPC) is defined as involvement of celiac axis and /or $> 180^\circ$ encasement of SMA/SMV or PV where reconstruction is not feasible [5].

The multi-institutional trial for patients with BRPC was conducted by Alliance for Clinical Trials in Oncology (Alliance A021101), in cooperation with the Southwest Oncology Group, Eastern Cooperative Oncology Group, and Radiation Therapy Oncology Group, under the support of National Cancer Institute (NCI). The study design employed induction chemotherapy with neoadjuvant chemoradiation per protocol followed by surgery and adjuvant chemotherapy. This trial proposed a new definition of BRPC by radiological criteria according to MDCT findings (Table 1) [8,9].

Organisations/ Centres	Tumor and SMV/PV relation	Tumor and SMA relation	Tumor and Celiac axis relation	Tumor and Common hepatic artery
NCCN	*Severely narrowed or occluded *Reconstruction is possible	*Abutment present	*Fat planes with celiac axis and tumor maintained	*Abutment *short segment encasement
AHPBA	*Abutment *Encasement *Occlusion with reconstruction feasibility	*Abutment	*No abutment *No encasement	*Abutment *short segment encasement
MDACC	*Occluded but reconstruction is feasible	*Abutment	*Abutment	*Abutment *short segment encasement
Alliance (A021101)	* $>180^\circ$ contact/ reconstruction possible	* $<180^\circ$ contact	*Reconstructable interface between and vessel	* $<180^\circ$ contact

Table 1: Various definitions of Anatomic Borderline PC according to the tumor-vessel relationship on MDCT [4-10]

Treatment Concerns and Strategies for BRPC

Literature published in the recent past emphasized that the patients with BRPC after R₀ resection had survival equivalent to those with primary resectable PC, though the chances of postoperative histopathologically positive margins always remains the main concern [11,12].

Vascular Involvement: The Decisive Factor in the Management of BRPC

Tumor vessel interface is the most critical step when the treatment for BRPC is planned. A systematic review by Siriwardana, et al. authors have highlighted the

oncological outcomes of 1646 patients where PV or SMV had been resected and the reported rates of median postoperative morbidity and mortality were 42% and 5.9% respectively with no improvement in OS [14]. However, Since then, multiple published studies have shown that venous resection and reconstruction in BRPC does not affect postoperative morbidity, mortality and survival [14-16]. Another meta-analysis reported that there was no difference in perioperative morbidity, mortality or 5-year survival among patients who underwent pancreatic surgery with or without venous resection and vascular reconstruction in BRPC does not comprise OS [17].

On the contrary, two other studies conducted by Castleberry et al. and Worni, et al. found that surgeries involving vascular reconstructions of SMV/PV were associated with increased postoperative morbidity and mortality. However, these researches had used the National Surgical Quality Program database and National Inpatient Sample database respectively which may have involved biases within the data [18,19]. Studies focussing on arterial resection (AR) involving SMA or hepatic artery are very scarce, but proponents of AR do suggest that the oncological outcome is better following AR than offering palliative treatment to these patients [20,21]. However, other authors propose that morbidity and mortality increases significantly after such reconstruction [22]. A meta-analysis including 366 patients also verifies that, though the AR is associated with increased morbidity and mortality but patients undergoing AR had improved survival compared to those who did not undergo AR [23]. Bockhorn, et al. and Ouaisi, et al. also supported the results. Though, such reconstructions must be accomplished in highly selected patients with good performance status [20,23].

Margin Status

The definition of R1 resection has not been uniform in the past. European organisation defines the resection as margin positive if, tumor is present \leq 1mm of the resected margin where as AJCC suggest define positive resection margins when tumor cells are present at the edge of resected specimen. These two slightly different criteria of margin positivity leads to inconsistent reporting of data and hence the results also differ. The oncological outcome after curative resection for BRPC with or without SMV/PV or is highly dependent on histopathological status of margin. The resection is aimed at achieving R₀ resection as patients with positive margin status perform similar to

the patients who did not undergo surgery and survival rates in both the groups is poor [24-26].

Adjuvant or Neoadjuvant Treatment for BRPC; The Rationale

The intent of neoadjuvant therapy, by definition is to administer treatment prior to curative surgery in patients with potentially resectable disease however, in BRPC the neoadjuvant treatment is also intended to improve R₀ resection rates. Various clinical trials have been conducted in the past to justify the implication of NACT or concurrent NACT/RT in BRPC. We tried to summarize the results of the landmark studies conducted so far to address this issue, which is better, chemotherapy or chemo ratio therapy in neoadjuvant setting.

Comparative Studies and Standardisation of Neoadjuvant treatment

Sequencing of Neoadjuvant Treatment; The Rationale

Literature suggests that neoadjuvant therapy offers many advantages over adjuvant therapy and few of those are as follows; (i) It identifies the patient with aggressive tumor biology; (ii) efficacy of radiation therapy is increased; (iii) decreased radiation induced toxicity to adjacent normal tissue; (iv) decreased rate of positive margin status; (v) It increases the rates of resectability of BRPC by downstaging the borderline tumor [27,28].

Hereby, we tried to discuss the landmark published studies and their end results in table 2, which may guide us to determine which modality is better in neoadjuvant setting i.e; NACT or NACT/RT [9,29-34].

Numerous retrospective studies published so far, demonstrate improved median OS by incorporation of concurrent NACT/RT over NACT alone in neoadjuvant setting (Table 2). A retrospective review of 73 patients of pancreatic adenocarcinoma by Choung et al, demonstrates that R₀ resection status was achieved in 31 of 32 patients (96.9%) who had BRPC though median OS was comparable (20 months) studies favouring NACT only [31]. However, RCT phase II study by Landry et al demonstrates equivalent median OS of 26.3 months by NACT alone but because of small sample size (n= 21 patients) this result cannot be extrapolated to the general population of BRPC [9].

Author (Year)	Study design	Sample size	Number of BRPC cases	Neoadjuvant treatment modality	Proportion of study population turned resectable (%)	R ₀ resection status achieved (%)	Median OS (month)
Landry, et al. 2010	Prospective RCT phase II trial	21	21	Gemcitabine based NACT only	24%	60%	26.3
Mehta, et al. 2001	Retrospective; single institution	15	15	5-FU based NACT/RT	60%	100%	30
Katz, et al. 2012	Retrospective; single institution	129	115	Group I ; NACT(Gemcitabine)followed by NACT/RT Group II ; NACT(Gemcitabine) alone	84%	95%	33
Choung, et al. 2013	Retrospective; single institution	73	57	Group I ; NACT(Gemcitabine)followed by NACT/RT Group II ; NACT(Gemcitabine)alone	56%	96%	16.4
Kang, et al. 2012	Retrospective;	202	35	NACT/RT (Gemcitabine)	91%	87%	26.3
Stokes, et al. 2011	Retrospective; single institution	170	40	Cisplatin based NACT/RT	46%	75%	23
McClaine, et al.	Retrospective; single institution	29	29	NACT and NACT/RT both	46%	67%	23.3

Table 2: Studies and their end results in BRPC

In a recent meta-analysis of neoadjuvant therapy for BRPC, researchers have found that out of 134 patients of BRPC, 31.6% were down staged to R₀ resection after incorporating NACT or NACT/RT. Median OS was 22.3 months in resected patients, whereas OS in all patients was 11 months [35]. In another recently published retrospective review by Lloyd, et al. oncological outcomes of concurrent NACT/RT, NACT alone and induction chemotherapy followed by chemotherapy with radiation were compared and authors concluded that induction chemotherapy followed by chemotherapy with radiation resulted in improved OS over either chemotherapy alone arm or concurrent NACT/RT arm. Median OS for these study groups were 21.5 months vs. 13.9 months and 12.5 months respectively (p <0.05). These observations were quite similar to the found in abovementioned studies (table 2). Literature supports that approximately 30% of patient population may become resectable after NACT/RT both however, as different researchers have used inconsistent definitions for BRPC and therefore, it is difficult to propose the standardised guidelines for definitive neoadjuvant treatment strategy for BRPC [36].

Though FOLFIRINIX- based and Gemcitabine based neoadjuvant chemotherapies are the most commonly

used regimens worldwide for BRPC but superiority of one over the other is still controversial. Another meta-analysis conducted in 2016 by Tang et al, suggested that FOLFIRINOX- based regimen had a better R₀ resection rates (60%) whereas with Gemcitabine the achieved R₀ resection rates were 58%. After FOLFIRINOX regimen, 72% patients became resectable and in Gemcitabine arm, only 67% turned out resectable. Though the patients on FOLFIRINOX had higher grade III/IV toxicities but resection rates and R₀ margin status were higher in this group [37].

Adjuvant Treatment

BRPC always has a very high likelihood of loco regional recurrence and distant metastasis, if adjuvant treatment is not administered. Multipler and omised clinical trials have been conducted to assess the benefit of adjuvant chemotherapy with or without radiation therapy (table 3). These trials cannot be compared with one another because of different study designs and different definition of BRPC adopted by researchers. However, OS was comparable (20- 24 months) in all the landmark trials [38-44].

In literature, various retrospective studies have reported promising results of adding adjuvant chemotherapy over chemo radiotherapy for BRPC. A recently published GEMCOR LAP 07 phase III study , showed that adjuvant chemo radiation does increase

progression free survival (6.1 vs. 3.7 months; $p = 0.02$) however, it fails to show improvement in median overall survival over adjuvant chemotherapy alone arm (16.5 vs. 15.3 months, respectively; $p = 0.9$) [44].

Study (year)	Patient number	Radiotherapy (XRT)	Chemotherapy	OS(months)	p value
GITSG (1985) vs. Observation	43 vs. 11 mo	No	5-Fu (bolus)	20	<0.05
EORTC (1999) vs. observation	114	No	5- Fu (infusion)	17.1 vs. 12.5 mo	<0.05
ESPAC1 (2004)	541	Yes	5-Fu (bolus)	19.4 mo No effect of XRT	<0.05
RTOG 9704 (2006)	442	Yes	Gemcitabinevs. 5-Fu infusion	-	>0.05
CONKO-001 (2007)	354	NA	Gemcitabine	13.4 vs. 6.9 mo	<0.05
ESPAC 3 (2010)	1088	NA	Gemcitabine	No difference	>0.05
GERCOR LAP 07 Phase III study (2016) Erlotinib	449	Yes	Gemcitabine	-	0.09

Table 3: Important Randomised controlled trials for adjuvant treatment for BRPC

Conclusion

Pancreatic adenocarcinoma itself is a detrimental disease with unfavourable outcome in majority of the patients. BRPC poses challenge in management as till date, not any dedicated guidelines have been proposed to manage this entity. Though, vascular resections and reconstructions options have carved a way to treat these tumors surgically, but yet, ambiguity persists in administering adjuvant treatment. Moreover, extensive vascular resection may lead to delayed postoperative recovery which may further delay adjuvant treatment as well. Literature suggests timely incorporation of adjuvant chemotherapy with or without radiation may improve disease free survival as well as median overall survival with high rates of loco regional control. The ongoing randomised control trial may further widen our view to treat this entity more efficiently which may resolve the existing controversies.

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