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TOPIC HIGHLIGHT

2015 Advances in Pancreatic Cancer

Management of borderline resectable pancreatic cancer

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Abstract

Pancreatic cancer is the fourth most common cause of cancer death in the United States. Surgery remains the only curative option; however only 20% of the patients have resectable disease at the time of initial presentation. The definition of borderline resectable pancreatic cancer is not uniform but generally denotes to regional vessel involvement that makes it unlikely to have negative surgical margins. The accurate staging of pancreatic cancer requires triple phase computed tomography or magnetic resonance imaging of the pancreas. Management of patients with borderline resectable pancreatic cancer remains unclear. The data for treatment of these patients is primarily derived from retrospective single institution experience. The prospective trials have been plagued by small numbers and poor accrual. Neoadjuvant therapy is recommended and typically consists of chemotherapy and radiation therapy. The chemotherapeutic regimens continue to evolve along with type and dose of radiation therapy. Gemcitabine or 5-fluorouracil based chemotherapeutic combinations are administered. The type and dose of radiation vary among different institutions. With neoadjuvant treatment, approximately 50% of the patients are able to undergo surgical resections with negative margins obtained in greater than 80% of the patients. Newer trials are attempting to standardize the definition of borderline resectable pancreatic cancer and treatment regimens. In this review, we outline the definition, imaging requirements and management of patients with borderline resectable pancreatic cancer.

Key words: Pancreatic cancer; Surgery; Chemotherapy; Radiation; Borderline

Core tip: The diagnosis and treatment of borderline resectable pancreatic cancer (BRPC) remains unclear. The definition of BRPC is not uniform and generally refers to regional blood vessel involvement by the tumor. Recent attempts have been made to standardize the definition of BRPC. Neoadjuvant therapy is recommended in the hopes of obtaining negative surgical margins and consists of chemotherapy and radiation therapy. Data for therapeutic approaches is primarily

derived from single institution retrospective series. In this article, we review the definition, imaging modalities for diagnosis and treatment of patients with BRPC.

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INTRODUCTION

Pancreatic cancer is the fourth most common cause of cancer death in the United States with 48960 incident cases and 40560 deaths estimated in 2015[1]. Despite the recent advances in therapeutic interventions, the 5-year relative survival rate remains approximately 6%. At initial presentation, approximately 50%-55% of the patients are found to have metastatic disease, 20%-25% have locally advanced disease and only 20% have resectable disease[2]. Surgery provides the only curative option with long term survivors. Modern advances in surgical techniques have substantially decreased post-operative mortality and morbidity, especially in high volume centers[3]. Improvement in imaging modalities has led to better delineation of resectable disease and spares patients from unnecessary surgery[4]. Yet, of those patients who undergo potentially curative resections, the 5-year survival remains abysmal at 20%[1].

Despite the fact that the progress has been slow, there has been improvement in systemic therapies for the treatment of pancreatic cancer. Gemcitabine remained the standard of care option for unresectable pancreatic cancer for a long time. Recently, two randomized clinical trials have demonstrated superior efficacy over single agent gemcitabine in the setting of metastatic and locally advanced disease. Conroy *et al*[5] reported a phase Ⅲ trial comparing the combination of 5-fluorouracil, folinic acid, oxaliplatin and irinotecan (FOLFIRINOX) to gemcitabine. The median survival was significantly better with FOLFIRINOX at 11.1 mo compared to 6.8 mo with single agent gemcitabine. The response rates were higher in the combination group as well (31.6% *vs* 9.4%). However, increased grade 3 or 4 toxicities with FOLFIRINOX limits this therapy to highly selected patients. The addition of nab-paclitaxel to gemcitabine has demonstrated improvement in median survival (8.5 mo *vs* 6.7 mo), progression free-survival (5.5 mo *vs* 3.7 mo) and response rates (23% *vs* 7%)[6]. The higher response rates observed with this regimen makes them very appealing for downstaging tumors. Further, since the objective of systemic treatment for borderline resectable pancreatic cancer is the possibility of margin negative surgery and potentially cure, higher toxicities may be acceptable in this group of patients. This is in contrast to patients with metastatic disease where the primary aim is to improve survival by a few months while maintaining a good quality of life.

Involvement of blood vessels by tumor frequently renders the possibility of resection with negative margins problematic in patients with non-metastatic pancreatic cancer. Patients with negative margins have significantly improved survival compared to patients who have gross disease at the resection margin[7]. The term "borderline resectable pancreatic cancer" has no universal definition but, in general, denotes patients with pancreatic cancer that abuts regional blood vessels such that there is a high risk for margin-positive resection[8]. Tumor abutment refers to solid tumor contact of ⩽ 180 degrees of circumference of blood vessel and encasement refers to greater than 180 degree of contact. Unfortunately, the current pancreatic staging system by the American Joint Committee on Cancer (AJCC) does not differentiate this subgroup of patients with those tumors encasing blood vessels termed locally advanced disease. In this staging system, patients with portal vein, superior mesenteric vein or superior mesenteric artery involvement are considered unresectable. All patients with vascular involvement and no metastatic disease are grouped under stage Ⅲ disease.

Staging work up

Pre-operatively, diagnostic imaging is utilized for differentiating pancreatic cancer into resectable, borderline resectable or unresectable disease. The National Comprehensive Cancer Network (NCCN) recommends multidetector computerized tomography (CT) angiography, acquiring thin, preferably sub-millimeter sections using a pancreatic protocol. The images are to be obtained in the non-contrast, arterial, pancreatic parenchymal and portal venous phase contrast enhancement. The multiphasic protocol helps in assessment of vascular invasion of tumors by selective visualization of arterial (superior mesenteric artery, celiac axis, gastroduodenal artery) and venous (superior mesenteric vein, portal vein, splenic vein) structures. Pancreatic protocol CT has an excellent sensitivity (89%-97%) and negative predictive value[9]. However, CT is not very accurate for predicting resectability (45%-79%) as it is not very sensitive to detect small hepatic and peritoneal metastases[9]. Pancreatic magnetic resonance imaging (MRI) can also be used as an adjunct for staging, especially for patients with a contrast allergy. MRI is similar to CT in respect to providing details of tumor anatomy for resectability status but is less widely utilized. The role of positron emission tomography (PET) scan for patients with borderline resectable disease remains unclear. PET scans may help, however, in detecting metastatic disease in addition to CT scans and spare patients from unnecessary surgery[10,11]. Thus, PET scans may be used as adjuncts to CT scans especially in patients with a high risk of advanced disease.

Endoscopic ultrasound (EUS) is a complementary modality to CT scan and is utilized in many centers.

Table 1 Criteria for resectability

	NCCN	AHPBA/ SSAT/SSO	MD Anderson	Intergroup (Alliance)
Celiac artery	No abutment for pancreatic head cancer. For body/tail, ≤ 180° contact	No abutment or encasement	Abutment	Tumor-vessel interface < 180° of vessel wall circumference
CHA	Solid tumor contact ≤ 180° allowing for reconstruction	Abutment or short segment encasement	Abutment or short-segment encasement	Reconstructable short-segment interface of any degree
SMA	Solid tumor contact ≤ 180°	Abutment	Abutment	Tumor-vessel wall interface < 180° of vessel wall circumference
SMV/PV	Solid tumor contact > 180° or contact of ≤ 180° with contour irregularity or thrombosis allowing for safe reconstruction	Occlusion	Occlusion	Tumor-vessel interface ≥ 180° of vessel wall circumference and/or reconstructible occlusion

CHA: Common hepatic artery; SMA: Superior mesenteric artery; SMV: Superior mesenteric vein; PV: Portal vein; NCCN: National Comprehensive Cancer Network; AHPBA/SSAT/SSO: Americas Hepato-Pancreato-Biliary Association/Society for Surgery of the Alimentary Tract/Society of Surgical Oncology.

It is particularly useful for assessment of vascular invasion, especially of the portal vein. EUS is not a good modality for involvement of the superior mesenteric artery. EUS is routinely performed for patients with borderline pancreaticcancer for pathologic diagnosis. Tissue confirmation is not necessary for patients undergoing upfront surgery but should be obtained prior to initiation of neoadjuvant therapy. EUS-guided fine needle aspiration or biopsy is safe and is associated with a low complication rate[12-14]. Further, there is decreased potential for peritoneal seeding compared to percutaneous biopsy.

Staging laparoscopy is performed routinely at selected centers to detect occult metastatic disease, especially peritoneal involvement. It can thus be performed prior to surgery or prior to initiation of neoadjuvant therapy to avoid non-curative surgery and potentially prevent unnecessary complications associated with laparotomy[15]. At some institutions laparoscopy is reserved for patients with a higher chance of metastatic disease, including markedly elevated tumor markers or symptomatic patients. Despite the fact that staging laparoscopy can detect occult disease even in patients who had undergone good quality imaging studies, this procedure is not routinely utilized.

Classification

The definition of borderline resectable pancreatic cancer (BRPC) is not uniform. Some series have included patients based on anatomic imaging criteria for BRPC alone while others include patients with clinical factors. Recently, attempts have been made to clearly define borderline resectable disease and differentiate it from clearly resectable or unresectable disease. Table 1 lists the different classification systems utilized for defining borderline resectable pancreatic cancer including those proposed by the National Comprehensive Cancer Network (NCCN), MD Anderson, Americas Hepato-Pancreato-Biliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract (AHPBA/SSO/SSAT) and the Intergroup[16-18]. Due to complexities involved in making these distinctions, it is very important that all cases of non-metastatic pancreatic cancer are discussed by a multidisciplinary team in high volume centers.

The NCCN panel has recently updated the guidelines and the definition of borderline resectable pancreatic cancer is included in the Table 1.

Vascular involvement

One of the key concepts for defining borderline resectable pancreatic cancer is the possibility of benefit of surgery in patients with vessel involvement. Vascular reconstruction is frequently the limiting factor during pancreatectomy in these patients. Siriwardana *et al*[19] in 2006 reported outcomes on 1646 patients from 52 studies with portal vein or superior mesenteric vein resections. Median postoperative morbidity was 42% with mortality of 5.9%. Median survival was only 13 mo with 5-year survival of only 7%. This study concluded that pancreatic surgery requiring resection of the portal vein did not improve outcomes. However, this study was limited by relatively older studies from 1996-2005 and heterogeneity of the studies included in the review. Since then, multiple single institution studies from high volume centers have demonstrated similar morbidity, mortality and survival for patients who underwent pancreatic surgery with or without venous involvement[20-24]. Zhou *et al*[25] in 2012 published a meta-analysis of 19 nonrandomized studies comprising 2247 patients. There was no difference in perioperative morbidity, mortality or 5-year survival among patients who underwent pancreatic surgery with or without venous resection. These studies suggest that venous resection with pancreatectomy is safe and feasible and can lead to improvement in long term outcomes. However, the results should be interpreted with caution as there may be publication bias as well as underreporting of morbidity data. Further, studies using National Surgery Quality Improvement Program database and National Inpatient Sample database demonstrated increases in morbidity and mortality with the addition of venous resection to pancreatic resection[26,27]. However, the limitations of these studies include the use of an administrative database, no distinction between venous or arterial resection and the

inability to differentiate between planned and unplanned vascular resections.

There is even limited data for arterial resection during pancreatectomy for pancreatic cancer. Some studies have demonstrated similar morbidity and mortality with the addition of arterial resection to pancreatic surgery[28,29]. However, a meta-analysis including 366 patients from 26 studies demonstrated significantly greater peri-operative morbidity and mortality with arterial resection[30]. This study also found that despite increased complications, patients undergoing pancreatic and arterial resection had improved survival compared to those patients who did not undergo resection. Similar results have been reported in other studies from high volume centers[31,32]. Thus, arterial resection should be limited to highly selected patients.

Treatment

Patients with borderline resectable pancreatic cancer are preferentially treated with neoadjuvant therapy to enhance the potential to facilitate margin negative, or R0, resection. Some patients with micrometastatic disease initially may have progressive disease on subsequent restaging scans after neoadjuvant therapy and thus are spared from unnecessary surgery. These patients would have been unlikely to benefit from pancreatic resection. It is generally acceptable that multimodality treatment is required for this patient population, although some centers have pursued a strategy of neoadjuvant chemotherapy alone[33]. In the adjuvant setting, up to 25% of patients are unable to receive treatment secondary to post-operative complications[34,35]. For these reasons, at some centers, neoadjuvant therapy is recommended even for resectable pancreatic cancer but is not the standard of care at this time[36].

There is no standard of care for the type of neoadjuvant therapy in this patient population. Treatment typically consists of a combination of radiation therapy and chemotherapy. The treatment regimens are usually reported from a single institution experience and are largely retrospective in nature. The chemotherapy regimen, dose and duration of radiation and type of radiation are different in these reports making cross-comparison very difficult. Moreover, the definitions of resectability have not been uniform in these studies. The most commonly cited resectability criteria are similar to the NCCN and MD Anderson anatomic imaging criteria while some studies have classified patients as borderline if they have a marginal performance status for surgery or have findings on imaging indeterminate for metastases.

After neoadjuvant therapy, depending on the case series, approximately 50% of the patients are able to undergo resection. After treatment, the change in tumor size by the Response Evaluation Criteria In Solid Tumors (RECIST) is low, around 10%-20%. RECIST response did not correlate with survival among patients who underwent pancreatic resection after neoadjuvant therapy, suggesting that RECIST criteria is a poor determinant of benefit in these patients[37]. There is the possibility that the tumor near the vessel can be replaced by fibrous tissue which may not be easily discernible on CT scan[38].

There have been four small prospective trials reported in the literature that have evaluated neoadjuvant therapy for patients with borderline resectable cancer (Table 2). Landry *et al*[39] reported the multi-institutional randomized phase II trial comparing two neoadjuvant regimens. Patients in arm A (n = 10), received concurrent gemcitabine and radiation while patients in arm B (n = 11) received induction chemotherapy with gemcitabine, cisplatin and 5-fluorouracil followed by 5-flourouracil based radiation. Three patients in arm A and two patients in arm B underwent resection. The median survival of resected patients was 26.3 mo. These outcomes were consistent with previous retrospective studies[40,41]. The trial was terminated early due to poor accrual. Another phase II trial evaluated the role of neoadjuvant therapy in patients with resectable or borderline resectable pancreatic cancer[42]. Thirty nine patients with borderline resectable disease were identified using NCCN criteria and were treated with gemcitabine and oxaliplatin for two cycles. Radiation was administered with the first cycle of chemotherapy to a total dose of 30 Gy in 15 fractions. Pancreatic resection was performed in 63% of patients and 84% of those patients had R0 resection. The median survival of resected patients was 25.4 mo. Similar results were observed with other small clinical trials[43,44].

The data on clinical outcomes after neoadjuvant therapy for borderline pancreatic cancer is primarily derived from retrospective single institution experience. One of the first restrospective studies from MD Anderson included 160 patients with pancreatic cancer who received pre-operative therapy, including 84 patients who met radiologic criteria for borderline resectable disease[40]. Patients were treated with a variety of neoadjuvant regimens including chemotherapy or chemoradiotherapy with a gemcitabine based regimen being most common. Resection was performed in 38% of the patients with negative margins in 97% of the subjects. The median survival for resected patients was 40 mo and for all patients was 21 mo. In the follow up report, 115 patients who met AHPBA/SSO/SSAT criteria for borderline resectable pancreatic cancer were included[37]. Despite the fact that partial response by RECIST criteria was observed in only 12% of the patients, 70% of the patients underwent resection and only 5% of the patients had positive margins.

Stokes *et al*[41] evaluated capecitabine based chemo-radiation in 40 patients with borderline resectable pancreatic cancer. Patients received external bean radiation in conventional fractionation (50.4 Gy in 28 fractions) or in an accelerated protocol (50 Gy in 20 fractions). Radiation was targeted at the gross tumor as

Table 2 Selected neoadjuvant studies for borderline resectable pancreatic cancer

Ref.	Study type	*n*	Regimen	Resection	R0 resection	Median OS (resected patients)	Median OS (all patients)	Definition
Katz *et al*[40]	Retrospective	84	5-FU, paclitaxel, gemcitabine or capecitabine + RT; Gemcitabine based chemotherapy	38%	97%	40 mo	21	MDA
Turrini *et al*[70]	Retrospective	49	5-FU/cis + RT 45 Gy for 5 wk	18%	100%	24 mo	14 mo	MDA
Chun *et al*[71]	Retrospective	74	5-FU or gem + RT	100%	59%	23	23	Other
Stokes *et al*[41]	Retrospective	40	Capecitabine + RT	46%	75%	23	12	MDA
Katz *et al*[37]	Retrospective	115	Gem followed by gem or 5-FU or capecitabine + RT; Gem or 5-FU or capecitabine + RT	70%	95%	33	22	NCCN
Mellon *et al*[45]	Retrospective	110	GTX X 3 cycles followed by SBRT	51%	96%	19	34	NCCN
Landry *et al*[39]	Randomized phase II	21	Gem + RT; Gem/cis/5-FU followed by 5-FU/RT	24%	100%	26	19.4 mo; 13.4 mo	Other
Lee *et al*[44]	Prospective trial	18	Gem/capecitabine X 3-6 cycles	61%	82%	23	16	NCCN
Kim *et al*[42]	Phase II study	39	Gem/Ox + RT	63%	84%	25	18	NCCN
Motoi *et al*[43]	Phase II study	16	Gem/S1 X 2 cycles	NA	87%	NA	18	MDA
Takahashi *et al*[46]	Prospective	80	Gem + RT followed by Gem	54%	98%	NA	NA	Other

NCCN: National Comprehensive Cancer Network; MDA: MD Anderson; 5-FU: 5-flurouracil; NA: Not available; RT: Radiation therapy.

well as draining lymphatics with a margin ranging from 0.5-2 cm (excluding the para-aortic and porta-hepatis location) utilizing intensity modulated radiation therapy (IMRT) and image guided radiation therapy. Pancreatic resection was performed in 46% of the patients with R0 resection in 87.5% of patients. Accelerated fraction radiation wasn't associated with increased severe toxicities. A report from Moffitt Cancer Center included 110 patients with BRPC treated with induction chemotherapy followed by stereotactic body radiation therapy (SBRT)[45]. The majority of the patients received combination of gemcitabine, docetaxel and capecitabine for 3 cycles. Surgical resection of the tumor was performed in 51% of the patients with R0 resection rate of 96%. Interestingly, 4 (7%) patients had complete pathologic response and a total of 28 (50%) patients had College of American Pathology Tumor Regression Grade 0-1. The median survival for all BRPC was 19 mo.

Radiation type

The neoadjuvant radiation strategies presented above for borderline pancreatic cancer vary greatly from center to center with respect to dose and technique. This ranges from a conventionally fractionated approach all the way to a SBRT approach and everywhere in between. Moreover, some series report the integration of radiosensitizing chemotherapy, consisting largely of continuous infusion 5-flurouracil (5-FU) or gemcitabine.

Standard fractionation has been used in upfront resectable patients with good outcomes and has been adopted at many centers as a strategy for borderline resectable patients[41,46-48]. With standard fractionation, > 90% pathologic response was achieved in 16%-37% and resection rates are around 50%[41,46]. In the report by Stokes *et al*[41], there was a trend for increased survival and a statistically significant increase in > 90% pathologic response in patients that received accelerated fractionation. Takeda *et al*[49] report their results of a phase Ⅰ and Ⅱ trial looking at accelerated hyperfractionation in borderline pancreatic cancer patients. A total of 35 patients were treated with concurrent gemcitabine and accelerated hyperfractionated radiation 1.5 Gy given twice daily to a total dose of 30 Gy (phase Ⅰ) or 36 Gy (phase Ⅱ) targeting the tumor and regional metastatic lymph nodes with a > 1 cm margin utilizing a 4-field technique. No acute grade ⩾ 3 non-hematologic toxicity was observed. Three fourth of the patients underwent surgical resection with all being R0 resections. Greater than 90% pathologic response to neoadjuvant treatment was observed in 23% of patients. Median survival was 41.2 mo in the patients that underwent surgical resection. This, along with the report by Stokes *et al*[41], suggests a benefit in response rates with accelerated fractionation concurrent with chemotherapy.

The radiation dose and volume treated depends on many factors including technique as well as chemotherapy used. Patients treated with the radiation sensitizing chemotherapy agent 5-FU can be treated to a higher dose and a larger volume, targeting the gross tumor as well as draining lymphatics[41]. When concurrent full dose gemcitabine is utilized, caution on the total dose of radiation as well as the volume being treated is indicated. In the prospective trial, only the gross tumor with a 1 cm margin and a total dose of 30 Gy in standard fractionation was used[42].

IMRT and/or SBRT can be used to increase the biologically effective dose and data suggests there may be potential for improved outcomes in the setting of pancreatic cancer not amenable to upfront resection.

The University of Michigan data reporting dose escalation with IMRT (recommended dose of 55 Gy in 25 fractions) in the locally advanced setting with full dose gemcitabine shows promising results as far as toxicity and R0 resection rates[50]. The most recent Radiation Therapy Oncology Group 1201 trial is a phase II trial looking at local *vs* systemic treatment escalation stratified by SMAD4 expression[51]. SMAD4 has been identified and shown to correlate with patterns of failure, either locally destructive failure *vs* metastatic disease in a rapid autopsy study done at John Hopkins[52]. These results will add to the knowledge of dose escalation with IMRT. SBRT along with chemotherapy prior to or after was initially established in locally advanced pancreatic cancer and was shown to be an effective treatment strategy with low rates of toxicity[53-57]. More recently, results from a phase Ⅱ trial reported by Herman *et al*[58], showed that in locally advanced pancreatic cancer patients treated with SBRT (33 Gy in 5 fractions) there were minimal acute and late toxicity (2% and 11%, respectively). The results published by group at Moffitt Cancer Center incorporating SBRT demonstrated that 51% of the BRPC patients underwent surgical resection with 96% being R0 resections[59]. The median dose was 30 Gy (range 28-30) to the gross disease and 40 Gy (25-50 Gy) to the area of vessel abutment. No prophylactic draining lymphatics were in the treatment volume. There were few acute and late grade $\geqslant$ 3 toxicity (7%). With 14 mo of follow up, there were no recurrences in this subset of patients and there was a rate of pathologic complete response of 7%. SBRT allows for escalating and personalizing the dose to each patient based on specific tumor location, vasculature abutment, and proximity to critical normal tissues with no increase in toxicity or peri-operative mortality and allows for the time course from systemic therapy to potential resection to be shorter since the duration of therapy is only one week. No prospective data is yet available in the BRPC setting incorporating SBRT but the available evidence merits further investigation of this novel approach.

Lastly, interest has been generated on the potential of proton therapy to improve outcomes for pancreatic cancer patients. Proton therapy over five days has been successfully integrated with capecitabine for upfront resectable patients on a phase Ⅰ/Ⅱ study with low rates of toxicity[60]. MD Anderson has compared 3-dimentional conformal radiation (3DCRT), IMRT, and passive-scattering proton therapy dose escalation (72 Gy) plans for pancreatic tumors[61]. Overall they found 3DCRT to be inadequate for coverage and IMRT to be more conformal in high gradient dose regions which would be beneficial for dose escalation in patients with organs at risk in close proximity, as seen in pancreatic cancer. Proton therapy had the advantage of a low integral dose but this would not affect dose escalation. Thompson *et al*[62] reported their dosimetric comparison of IMRT, double scattering and pencil beam scanning proton therapy. They found again that proton beam therapy would unlikely result in dose escalation over IMRT. Proton therapy resulted in decreased dose in the low-intermediate dose range but increased dose in the mid to high dose region, with unclear clinical significance.

The optimal technique and dose of radiation therapy is unclear; however, dose escalation with IMRT and/or SBRT show promising results in increasing R0 resection rates with low toxicity.

DISCUSSION

The margin status is very important to the clinical outcomes after pancreatic resection. The goal of the resection is to obtain R0 resection as patients with gross disease at the margins (R2 resection) do not benefit from surgical resection and have similar outcomes as patients without surgery[63-65]. Microscopic disease at the margin (R1 resection) is associated with a poor prognosis but is not consistent across all studies[63,66,67]. The definition of R1 resection has not been uniform in the past which makes interpretation of data from various studies problematic. AJCC criteria define positive resection margins when tumor cells are present at the edge of resected specimen whereas European criteria defines positive margins if tumor cells are present within $\leqslant$ 1 mm of resected margins[68]. The location of margins has prognostic impact as well. In one study, R1 status at the anterior or posterior margins was not relevant for outcomes[69].

Recently, there has been improvement in systemic therapies for metastatic pancreatic cancers that has improved response rates over single agent gemcitabine. The FOLFIRINOX regimen and gemcitabine/nab-paclitaxel combination is associated with response rates of 31% and 23% compared to less than 10% with single agent gemcitabine. These regimens may increase the probability of margin negative resection and the ability to obtain an R0 resection. There are additional toxicities associated with these combination regimens, especially FOLFIRINOX, including neutropenic fever. The Intergroup trial (ALLIANCE A021101) is evaluating neoadjuvant FOLFIRINOX followed by capecitabine based chemoradiotherapy. The dose of 5-FU has been modified to make it more tolerable. Patients who undergo resection will also receive adjuvant gemcitabine. The criteria for resection have been clearly defined through consensus and may become the new standard for resectability.

CONCLUSION

Management of borderline resectable pancreatic cancer continues to evolve. Prior studies have been complicated by low accruing trials, largely retrospective single institution experiences, and different classification criteria, chemotherapy regimens and radiotherapy type and schedule. There is an urgent need to apply uniform criteria for defining borderline pancreatic cancer. The patients should be classified and treated with a

multidisciplinary approach at high volume centers. Patients should undergo a pancreas protocol CT scan and EUS to determine the resectability status. Ideally, these patients should be treated on a clinical trial protocol. The ability to obtain negative margins is of the utmost importance for improving the outcomes of these patients. Newer aggressive chemotherapy regimens may help improve the resectability rate. These regimens followed by SBRT or IMRT may have a role in treatment. Induction chemotherapy followed by chemoradiation is the most commonly utilized approach but is not uniform. Newer trial designs incorporating uniform classification and treatment strategy will help standardize treatment for patients with borderline resectable pancreatic cancer.

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