

HIGHLIGHT ARTICLE

Management of Borderline Resectable Pancreatic Adenocarcinoma

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Summary

Pancreatic adenocarcinoma is the fourth most common cause of cancer-related death among U.S. men and women. Despite much effort in translational research, pancreatic adenocarcinoma remains a challenging disease with an overall 5-year survival rate less than 5%. To date, the only potentially curative treatment for managing pancreatic adenocarcinoma is surgical resection. However, more than 80% of patients are deemed either unresectable or metastatic upon diagnosis. For borderline resectable disease, although there is no high-level evidence supporting its use, an initial approach involving neoadjuvant therapy is preferred, as opposed to immediate surgery. In this year's ASCO Gastrointestinal Cancers Symposium, several studies were presented with approaches towards treating borderline resectable pancreatic adenocarcinoma. Retrospective studies (Abstract #280, #304, #327) were presented and showed that neoadjuvant chemoradiation were associated with higher rates of negative margin resection and better survival. The tolerability of accelerated fraction radiotherapy with concomitant capecitabine was demonstrated in a phase I study (Abstract #329). More effective therapeutic approaches and prospective studies are needed for this devastating illness. This highlight article will focus on the management of borderline resectable pancreatic adenocarcinoma.

What We Knew About the Management of Borderline Resectable Pancreatic Adenocarcinoma Before the 2012 ASCO GI Cancers Symposium?

During the year 2011, an estimated 44,430 new cases of pancreatic adenocarcinoma were diagnosed in the United States. There were 36,800 deaths that were attributed to pancreatic adenocarcinoma [1]. Pancreatic adenocarcinoma is the fourth most common cause of adenocarcinoma-related death among U.S. men and women [1]. Despite enormous efforts in translational research, the prognosis of pancreatic adenocarcinoma remains extremely poor. The overall 5-year survival rate is less than 5% [2]. To date, the only potentially curative treatment for managing pancreatic adenocarcinoma is surgical resection. However, more than 80% of patients are deemed either unresectable or metastatic upon diagnosis [3].

To improve patient selection for surgery and to increase the likelihood of an R0 resection, an expert

consensus group developed criteria to define tumor respectability in 2009 [4]. Using these criteria, tumors are classified as resectable, borderline resectable, or unresectable. Borderline resectable disease is defined as the absence of evidence of peritoneal or hepatic metastases following a thorough radiological assessment. Radiological findings of tumor abutment on the portal vein or superior mesenteric vein with venous deformity, and limited encasement of the mesenteric vein and portal vein represent the extent of venous involvement. Radiological findings suggesting borderline arterial involvement include encasement of a short segment of the hepatic artery, without evidence of tumor extension to the celiac axis and/or tumor abutment of the superior mesenteric artery involving less than 180 degrees of the artery circumference. This is open to the interpretation of the radiologist and the surgeon, because it is usually not based on operative findings.

An initial approach involving neoadjuvant therapy has been preferred, as opposed to immediate surgery, although there is no high-level evidence supporting its use and it is highly debatable in the setting of borderline resectable disease. Furthermore, no standard neoadjuvant treatment regimen exists for borderline resectable pancreatic adenocarcinoma. Similar paradigms as for locally advanced unresectable disease are being used. They include upfront fluoropyrimidine-based or upfront gemcitabine-based chemoradiation [5, 6, 7] or chemotherapy followed by chemoradiation [5, 8].

Key words Neoadjuvant Therapy; Pancreatic Neoplasms; Radiation

Abbreviations AFRT: accelerated fraction radiotherapy; IOERT: intraoperative electron irradiation

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This highlight article will discuss four abstracts focusing on the management of borderline resectable pancreatic adenocarcinoma published at the 2012 American Society of Clinical Oncology (ASCO) Gastrointestinal Symposium.

What Did We Learn at the 2012 ASCO GI Cancers Symposium?

Borderline Resectable Patients (Abstract #280 [9])

Pimiento *et al.* examined the outcome of multimodality therapy of patients with borderline resectable pancreatic adenocarcinomas. They retrospectively looked at 160 patients with operable pancreatic ductal adenocarcinoma. Among this cohort, 60 patients had borderline resectable tumors. All patient with borderline resectable tumors received neoadjuvant therapy and ultimately 58% received resection. The authors found that the median overall survival was 13.9 months for borderline resectable patients, inferior to 22.6 months for resectable patients. However, the median overall survival was 21.5 months among borderline resectable patients who received resection, similar to resectable patients.

Neoadjuvant Therapy and Margin Status (Abstract #304 [10])

Papavasilou *et al.* studied the influence of margin status and neoadjuvant chemoradiation therapy for borderline resectable pancreatic adenocarcinoma patients. They reviewed 103 patients with borderline resectability. Approximately half of this cohort received neoadjuvant chemoradiation therapy. From the entire cohort, microscopic margin status was positive in 54% of patients. Patients with microscopic positive margins had inferior median overall survival compared with microscopic negative margins (17.2 months vs. 24.9 months, respectively). Patients who

received neoadjuvant therapy had a higher rate of negative margin resection than those who did not receive neoadjuvant chemoradiation (61.7% vs. 38.3%, respectively). The authors concluded that patients with positive margins had worse outcomes and that neoadjuvant chemoradiation was associated with higher rates of negative margin resection.

Intraoperative Electron Irradiation (Abstract #327 [11])

Ashman *et al.* reported their experience treating borderline resectable and unresectable pancreatic adenocarcinoma patients using neoadjuvant chemoradiation followed by surgery with intraoperative electron irradiation. Thirty-one patients who underwent resection were included in this analysis. Median overall survival was 19 months. Patients with R0/R1 resection had a better median overall survival than R2 and unresectable tumors (23 months vs. 10 months). The authors concluded that prognosis was associated with resection margin status. They also suggested performing prospective studies with the use of intraoperative electron irradiation.

Accelerate Fraction Radiotherapy with Capecitabine (Abstract #329 [12])

Chakraborty *et al.* reported a phase I study looking at novel neoadjuvant therapeutic approach using accelerated fraction radiotherapy with concomitant capecitabine for borderline resectable pancreatic adenocarcinoma. With 10 patients enrolled thus far, the authors showed moderate degrees of toxicity, primarily lymphopenia. Other toxicities include hyponatremia and fatigue. The authors concluded that accelerated fraction radiotherapy with capecitabine is relatively safe. Subsequent phase II studies will examine molecular mechanisms of treatment resistance.

Table 1. Updates of 2012 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium.

Abstract	Study design	Enrollment	Treatment	Median survival (months)	Toxicities	Comments
#280 [9] Pimiento <i>et al.</i>	Retrospective	160: 100 resectable; 60 borderline	Resection or neoadjuvant therapy and resection	Resectable: 22.6 Borderline: 13.9 Resected borderline: 21.5	Not applicable	Neoadjuvant therapy associated with higher R0 resection. Overall survival for patients with resected borderline resectable pancreatic adenocarcinoma is similar to resectable patients.
#304 [10] Papavasilou <i>et al.</i>	Retrospective	103 borderline resectable	Neoadjuvant chemoradiation (49.5%)	Positive margin: 17.2 Negative margins: 24.9	Not applicable	Positive margin associated with worse outcome in borderline pancreatic adenocarcinoma. Neoadjuvant therapy associated with higher negative margin resection.
#327 [11] Ashman <i>et al.</i>	Retrospective	31	Neoadjuvant chemoradiation followed by surgery and IOERT	R0/R1 resection: 23.0 R2 or unresectable: 10.0	Not applicable	Neoadjuvant therapy followed by surgery and IOERT may improve prognosis. Survival better with R0/R1 resection vs. R2.
#329 [12] Chakraborty <i>et al.</i>	Prospective phase I	10	Neoadjuvant chemoradiation using AFRT and capecitabine	Not applicable	Grade 3-4 lymphopenia (n=6), hyponatremia, fatigue	Combination AFRT and capecitabine is well tolerated.

AFRT: accelerated fraction radiotherapy; IOERT: intraoperative electron irradiation

The details of these four studies are summarized in Table 1.

Discussion

Management of borderline resectable pancreatic adenocarcinoma remains challenging and requires multi-disciplinary effort. This subgroup of pancreatic adenocarcinoma patients are determined to be potentially resectable. To achieve a favorable long-term outcome, it is critical to identify borderline resectable pancreatic adenocarcinoma and to treat preoperatively to maximize the potential for resection.

An important addition to the National Comprehensive Cancer Network (NCCN) guidelines [13] is a revised set of criteria based on a consensus of the panel members which defines borderline resectable pancreatic adenocarcinoma [4]. There are fewer problems for the conduct of neoadjuvant strategies in borderline resectable tumors, as the consensus is reached upon definition of resectability on imaging and margin positivity by expert radiologists and surgeons. With currently available surgical techniques, patients with borderline resectable pancreatic head adenocarcinoma are at high risk for a margin-positive resection. Therefore, the approach for these patients is to use preoperative systemic therapy and local-regional chemoradiation to maximize the potential for an R0 resection and to avoid R2 resections. In general, patients with favorable responses to preoperative therapy (radiographic evidence of tumor regression and improvement in serum tumor marker levels) are the subset of patients who have the best chance for an R0 resection and a favorable long-term outcome. NCCN guidelines [13] also further underline the importance of upfront systemic therapy prior to administration of chemoradiation therapy as upfront systemic therapy provides for disease control and allows selection of those patients most likely to benefit from subsequent chemoradiation.

Ashman *et al.* reported that neoadjuvant chemoradiation followed by surgery with intraoperative electron irradiation (IOERT) demonstrated promising survival benefit and showed an association of prognosis and resection margin status (Abstract #327 [11]). Survival was superior among patients for whom R0 or R1 resection was achieved (median survival 23 months *vs.* 10 months for R2 or unresected tumors. A study by Papavasiliou *et al.* showed that neoadjuvant chemoradiation was associated with higher rate of negative margin resection (62% *vs.* 38%, $P=0.02$) and better outcomes when compared to patients without neoadjuvant treatment (Abstract #304 [10]). A single institutional review study by Pimiento *et al.* demonstrated an improved overall survival for borderline resectable patients when treated with a multimodality therapy (Abstract #280 [9]). In this study, 58% of treated patients were ultimately resected. These patients had a similar median overall survival compared with resectable patients (21.5 months *vs.* 22.6 months, respectively). Though small in patient

number, the resection rate was higher than previously reported (58% of 60 patients *vs.* 40% of 2,148 patients in a meta-analysis of 19 cohort studies [14]). One may argue that the respectability rate is heavily dependent on what patients are included and how aggressive the surgeons are willing to be. Centers that are willing to resect and reconstruct major vascular structures usually have a higher resectability rate. In this study, not only the resectability rate was high but also the R0 resection rate was higher than previously reported (56% *vs.* 31-35%) [15, 16]. This result suggests that the multimodality therapy is promising and warrants further investigation.

A novel neoadjuvant approach using accelerated fraction radiotherapy with concomitant capecitabine in a phase I study has showed the tolerability (Abstract #329 [12]). A subsequent phase II study of this modality is underway to investigate the efficacy. To date, no randomized phase III trials have yet evaluated the approach of neoadjuvant therapy in borderline resectable disease compared to the approach of taking these patients to surgery upfront. The best regimens to use in the setting of borderline resectable disease remain unknown. Prospective studies of novel agents or combination regimen are needed in the setting of borderline resectable disease.

Conflict of interest The authors have no potential conflicts of interest

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