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HIGHLIGHT ARTICLE

New Developments in the Management of Borderline Resectable Pancreatic Cancer

Highlights from the "2013 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 24-26, 2013

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Summary

The optimal management of borderline resectable pancreatic cancer remains unclear. Neoadjuvant chemoradiation remains the most common approach in the United States, while neoadjuvant chemotherapy alone is also widely utilized and has demonstrated efficacy but there has been no clear consensus about a regimen that would be most beneficial in this setting. We will discuss three abstracts that were presented in the 2013 ASCO Gastrointestinal Cancers Symposium in which various regimens were evaluated in the neoadjuvant setting.

What We Knew About Management of Borderline Resectable Pancreatic Cancer Before the 2013 ASCO Gastrointestinal Cancers Symposium?

Pancreatic cancer is the fourth projected cause of cancer related mortality in 2012. The high mortality associated with this malignancy is highlighted by the fact that 43,920 new cases were estimated for 2012 but the projected mortality was as high as 37,390 based on recent cancer statistics [1].

One of the goals of curative treatment for pancreatic cancer is surgical resection with negative margins. Borderline resectable pancreatic cancers have a very high likelihood of having positive margins which portends a very poor prognosis. This includes portal or superior mesenteric vein involvement. Survival of patients with positive margins and/or vein involvement is similar to patients who have not undergone resection. Overall survival is 10 to 18 months. This is an active area of investigation where novel regimens leading to improved R0 resection rates could improve disease free and overall survival. Several chemotherapy regimens alone or with radiotherapy were evaluated in the 2013 ASCO Gastrointestinal Cancers Symposium with an emphasis on neoadjuvant chemoradiation with an attempt to achieve R0 resection [2, 3, 4]. However, a clear set of guidelines about neoadjuvant therapy has not emerged and ongoing trials are still needed. We are presenting a summary of the abstracts from the recent 2013 ASCO Gastrointestinal Cancers Symposium which discusses the trials of the past year addressing this issue.

Keywords Neoadjuvant Therapy; Pancreatic Neoplasms; Radiosurgery

Abbreviations BRPC: borderline resectable pancreatic cancer; SBRT: stereotactic body radiation therapy

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What Did We Learn in the 2013 ASCO Gastrointestinal Cancers Symposium?

Rates of Pathological Response Following Neo-adjuvant Induction Chemotherapy and SBRT (Abstract 221) [5]

M Chuong *et al*. evaluated the rates of pathological complete response in 35 patients after neoadjuvant induction gemcitabine based chemotherapy followed by stereotactic body radiation therapy (SBRT) in borderline resectable pancreatic cancer (BRPC). Tumor regression grade (TRG) scores were determined independently by a College of American Pathologist (CAP) and an MD Anderson pathologist and were correlated for survival. The CAP TRG scores from best to worse response were 0 (n=3), 1 (n=13), 2 (n=15) and 3 (n=4). The MD Anderson scores from best to worst were similar: IV (n=3), III (sizable pools of cellular mucin; n=6), IIB (n=11), IIA (n=10), and I (n=5). This study suggested a survival benefit based on pathological response seen with neoadjuvant gemcitabine based therapy with subsequent stereotactic body radiation therapy.

Neoadjuvant Chemoradiation Therapy with 5-FU, Cisplatin, Mitomycin C and Heparin to Achieve an Increase Disease Free and Overall Survival (Abstract 315) [6]

T Hibi *et al*. assessed the safety profile and efficacy of a combination regimen of triple chemotherapy with 5-FU, mitomycin C cisplatin and heparin in addition to a 40 Gy dose of radiation therapy in 24 borderline resectable pancreatic cancer patients. There were significant grade 3-4 hematological toxicities seen although there were no severe gastrointestinal toxicities seen. The 5-year overall survival and disease free survival rates after surgery were 52.6% and 36.3%, respectively.

Extended Upfront Neoadjuvant Chemotherapy Alone in BRPC (Abstract 236) [7]

V Picozzi *et al*. presented the results of their trial using upfront chemotherapy alone with gemcitabine and docetaxel in 58 patients with 5-FU based chemoradiation therapy offered to patients who were not candidates for an R0 resection (n=12). Twenty-nine patients achieved R0 resection and 72% (n=21) R0 resection patients remained disease free at 16 months with a median overall survival of over 20 months. Four out of 12 patients who received chemoradiation therapy without R0 resection remained disease free so that overall 25 out of 58 patients (43%) remained progression free in the study. The median overall survival for all patients was 27 months. This study suggested the use of neoadjuvant chemotherapy alone as a reasonable option in borderline resectable pancreatic cancer.

Table 1 summarizes the findings of the three abstracts discussed above.

Discussion

Long term survival in pancreatic cancer is attained only in patients who are able to undergo complete surgical resection with negative margins. This has led to the importance of accurately identifying patients with borderline pancreatic cancer who can benefit from neoadjuvant therapy to increase the rate of R0 resection.

The consensus definition of borderline pancreatic cancer includes:

- no distant metastases;
- venous involvement of the superior mesenteric/ portal vein demonstrating tumor abutment with impingement and narrowing of the lumen, encasement of the superior mesenteric/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction;
- gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis; and
- tumor abutment of the superior mesenteric artery not to exceed greater than 180 degrees of the circumference of the vessel wall [8].

Approximately one-third of patients presenting with locally advanced pancreatic cancer will be borderline resectable [9]. In principle, the application of multimodality therapies to downstage these patients to resectability could have the greatest therapeutic impact. Portal vein involvement treated in the past with resection has been associated with an increased surgical risk with overall cancer survival being poor. Today with endoscopic ultrasound, we can preoperatively identify patients prior to surgery who will have true vein involvement *versus* inflammation. This helps determine who should go to the operating room to achieve a complete surgical resection. The use of neoadjuvant therapy has been very promising in borderline resectable patients to increase the number of patients for surgery with curative intent who otherwise would have had positive margins and never have a chance for surgical resection.

Neoadjuvant chemoradiotherapy approaches have focused on optimizing the radiation fields, dose, and

Table 1. Highlights of the 2013 ASCO Gastrointestinal Cancers Symposium abstracts on borderline resectable pancreatic cancer.

	Abstract 221 [5]	Abstract 315 [6]	Abstract 236 [7]
Number of patients	35	24	58
Chemotherapy	Gemcitabine, docetaxel, capecitabine	5-FU, cisplatin, mitomycin C	Gemcitabine, docetaxel
Radiation	5-fraction SBRT, median 35 Gy	40 Gy (2 Gy/day)	In 12 patients along with 5-FU (who did not qualify for R0 resection)
Radiological response	NA	Progression disease: 29% (n=7)	Partial response: 60% Stable disease: 32% Progression disease: 8%
CA 19-9 response	NA	NA	72% (median decline 85% from baseline CA 19-9)
R0 resection	NA	100% (17/17 who underwent surgery) or 71% of total patients	50% (n=29)
Toxicity	NA	Hematological grade 3-4: 38%	NA
Survival	NA	5-year overall survival: 52.6% 5-year disease free survival: 36.3%	27 months

NA: not available, SBRT: stereotactic body radiation therapy

techniques. The emergence of intensity-modulated radiation therapy over conventional 3D conformal techniques, has allowed for target volumes to be more precisely defined and to avoid more normal tissue. More recently, emerging radiotherapy technologies, including stereotactic body radiotherapy, image-guided radiotherapy and proton radiotherapy are being applied in this arena.

The question of using upfront combination chemotherapy alone instead of chemoradiation remains an important area of research. An optimal regimen still remains elusive at present although FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, leucovorin) has shown a survival benefit in the metastatic setting [10] and should be evaluated in the neoadjuvant setting in clinical trials.

These three abstracts show new approaches to treatment of the borderline resectable pancreatic cancer patient, including novel chemotherapy regimens and novel radiotherapy technologies. All three studies show promising outcomes and await investigation in larger clinical trial settings.

Conflicts of interest The authors have no potential conflicts of interest

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