Original Article

Histopathologic tumor response after induction chemotherapy and stereotactic body radiation therapy for borderline resectable pancreatic cancer

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Background: While clinical outcomes following induction chemotherapy and stereotactic body radiation therapy (SBRT) have been reported for borderline resectable pancreatic cancer (BRPC) patients, pathologic response has not previously been described.

Methods: This single-institution retrospective review evaluated BRPC patients who completed induction gemcitabine-based chemotherapy followed by SBRT and surgical resection. Each surgical specimen was assigned two tumor regression grades (TRG), one using the College of American Pathologists (CAP) criteria and one using the MD Anderson Cancer Center (MDACC) criteria. Overall survival (OS) and progression free survival (PFS) were correlated to TRG score.

Results: We evaluated 36 patients with a median follow-up of 13.8 months (range, 6.1-24.8 months). The most common induction chemotherapy regimen (82%) was GTX (gemcitabine, docetaxel, capecitabine). A median SBRT dose of 35 Gy (range, 30-40 Gy) in 5 fractions was delivered to the region of vascular involvement. The margin-negative resection rate was 97.2%. Improved response according to MDACC grade trended towards superior PFS (P=061), but not OS. Any neoadjuvant treatment effect according to MDACC scoring (IIa-IV *vs.* I) was associated with improved OS and PFS (both P=0.019). We found no relationship between CAP score and OS or PFS.

Conclusions: These data suggest that the increased pathologic response after induction chemotherapy and SBRT is correlated with improved survival for BRPC patients.

Keywords: Radiation therapy (RT); pancreatic cancer; chemotherapy

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Introduction

Despite advances in treatment over the past several decades, pancreatic ductal adenocarcinoma (PDAC) remains a devastating disease with limited survival for the majority of patients. Only those who undergo margin-negative (R0) surgical resection have a reasonable likelihood of long-term disease control and potential cure. Unfortunately, only 15-20% of patients have resectable disease at diagnosis with the remainder presenting with distant metastatic or locally advanced tumors. Even after successful resection the expected 5-year survival is less than 20% (1).

Borderline resectable pancreatic cancer (BRPC) patients are unlikely to undergo R0 resection at initial diagnosis although they are more likely to do so after preoperative chemotherapy and radiation therapy (RT) (2,3). Preoperative RT for BRPC is typically delivered using conventional fractionation. In recent years stereotactic body radiation therapy (SBRT) has become increasingly used for BRPC

based on emerging data suggesting significant local effect with minimal toxicity (4-7). Furthermore, SBRT is completed in no more than 5 fractions, thus providing a much shorter overall treatment time and increased patient convenience compared to conventionally fractionated RT that is delivered over 5.5 weeks. Prospective evaluation of SBRT for BRPC is currently ongoing (NCT01992705, NCT01360593) in an attempt to verify its safety and efficacy in ultimately achieving an R0 resection.

Several important prognostic factors have been identified in resected PDAC cancer patients including margin status (8,9), lymph node involvement (10-12), and CA 19-9 level (13-15). The degree of histopathologic tumor response, or tumor regression grade (TRG), after preoperative therapy is another emerging prognostic factor and has been evaluated in patients with various cancers including those of the head and neck, rectum, and esophagus (16-20). Emerging data suggest that TRG is also a significant independent prognostic factor for PDAC after chemotherapy alone or chemoradiation (21-23). A retrospective study from MD Anderson Cancer Center (MDACC) described a significant correlation between TRG score and survival in 223 pancreatic cancer patients who received neoadjuvant chemoradiation (21). In that study, patients with less residual tumor had more favorable pathologic findings (less frequent positive margins and lymph node involvement) and improved survival on multivariate analysis. One strategy to improve histopathologic tumor regression is through RT dose intensification, which can be achieved using SBRT (22). We evaluated the effect of TRG on clinical outcomes in BRPC patients who received preoperative therapy including SBRT.

Methods

After obtaining Institutional Review Board approval, a pancreas cancer database maintained in the Department of Radiation Oncology was queried to identify BRPC patients treated with induction chemotherapy followed by SBRT at our institution between 2009 and 2012. As was previously reported, SBRT was delivered to the primary tumor using a 5-fraction approach using 5-6 Gy per fraction including dose painting the region of vessel abutment by tumor up to 8 Gy per fraction provided all normal tissue constraints could be respected, particularly for the stomach, duodenum, and small bowel (4). Fiducial markers were routinely used for target delineation and daily image guidance. Patients were treated either with respiratory gating or abdominal compression. Four weeks after treatment all patients underwent restaging PET/CT and pancreas protocol CT scans. Patients determined to be fit for surgery, without evidence of metastatic disease, were recommended to have surgical exploration and surgical resection, if appropriate. Surgery was performed typically between 6-8 weeks after SBRT completion. Only patients who underwent definitive surgery with curative intent were included in this analysis.

Resected specimens were examined at the time of grossing to identify the tumor site. If no residual grossly visible tumor was identified, the entire residual area with fibrosis was submitted for evaluation. All of the slides were reviewed and one expert pancreatic pathologist (B.A.C.) reviewed all pancreatic resection specimens. The amount of residual tumor was assessed by evaluating all of the sections derived from the tumor bed. Each patient's tumor specimen was assigned two TRG scores (*Table 1*), one from the College of American Pathologists (CAP) Cancer Protocols and the other from the MDACC. The CAP method is a 4-tiered system in which a grade of 0 indicates a pathologic complete response (pCR) and a grade of 3 indicates either poor or no response (24). The published MDACC method used in this study is a 5-tiered system in which a pCR is indicated by a grade of IV, and no to minimal (<10%) tumor cell destruction is indicated by a grade of 1 (25).

Each patient's TRG scores, using both scoring methods, were evaluated with respect to progression free survival (PFS) and overall survival (OS) using the Kaplan Meier method. OS was determined from the start of induction chemotherapy to date of death or last follow up if the patient was still alive. PFS was determined from the start of induction chemotherapy to the date of first recurrence, death, or last follow up.

Results

Of a total 57 BRPC patients who completed induction chemotherapy and SBRT and underwent surgical resection, the initial 36 consecutive patients were included in this study. Patient and tumor characteristics are described in *Table 2*. The median age was 63 years (range, 45-81 years) and 18 patients were female (51.4%). The pancreatic head was involved in 30 patients (85.7%) with the remainder involving the body/tail (14.3%). Most were clinically staged as T3 (91.4%) and N0 (54.3%).

The most commonly delivered induction chemotherapy (85.7%) was a combination of gemcitabine, docetaxel, capecitabine (GTX) and it was generally well tolerated

Table 1 Tumor regression grade scores and corresponding definitions according to the CAP and MDACC methods

TRG scores	Definition
CAP	
0	No viable residual tumor (complete response)
1	Marked response (minimal residual cancer with single cells or small groups of cancer cells)
2	Moderate response (residual cancer outgrown by fibrosis)
3	Poor or no response (extensive residual cancer)
MDACC	
IV	No viable residual tumor (complete response)
III	<10% viable-appearing tumor cells
IIb	Destruction of 51-90% of tumor cells
IIa	Destruction of 10-50% of tumor cells
I	<10% or no tumor cell destruction

CAP, College of American Pathologists; MDACC, MD Anderson Cancer Center; TRG, tumor regression grades.

Table 2 Patient, tumor, and treatment characteristics

Variables	N	%
Total patients	36	
Age at diagnosis, median [yr]	63 [45-81]	
Gender		
Male	17	47.2
Female	19	52.8
Histology		
Adenocarcinoma	35	97.2
Adenosquamous carcinoma	1	2.8
Primary tumor location		
Head	30	83.3
Body	5	13.9
Tail	1	2.8
Clinical T stage		
3	34	94.4
4	2	5.6
Clinical N stage		
0	20	55.6
1	16	44.4
Induction chemotherapy		
GTX	30	83
Gemzar alone	5	13.9
Gemzar/cisplatin	1	2.8
Prescription RT dose to region of tumor-vessel abutment, median (Gy)	35 (32.5-40)	

GTX, Gemzar, Taxotere, Xeloda.

Table 3 Assigned TRG after induction chemotherapy, stereotactic body radiation therapy, and surgery per the CAP and MDACC

TRG	N	%
CAP		
0	4	11.1
1	13	36.1
2	15	41.7
3	4	11.1
MDACC		
IV	4	11.1
III	6	16.6
IIb	11	30.6
IIa	11	30.6
I	4	11.1

TRG, tumor regression grade; CAP, College of American Pathologists; MDACC, MD Anderson Cancer Center.

as the majority of patients received the prescribed chemotherapy regimen (82.9%) consisting of Gemzar, Taxotere and Xeloda (GTX). All patients completed the prescribed SBRT course, with none experiencing significant acute toxicity. A median dose of 35 Gy (range, 32.5-40 Gy) was prescribed to the region of vessel abutment while the remainder of the primary tumor was treated to a median dose of 30 Gy (range, 25-30 Gy). Most patients underwent a pancreaticoduodenectomy (88.6%) after a median 5.6 weeks (range, 4.6-9.1 weeks) from SBRT completion. Of the 36 total patients, 35 were resected with negative surgical margins (97.2%).

Most patients had moderate to significant tumor regression. Complete response was present in four patients and was reflected by CAP grade 0 and MDACC grade IV. CAP grades of 0, 1, 2, and 3 were assigned to 4 (11.1%), 13 (36.1%), 15 (41.7%), and 4 (11.1%) patients, respectively. MDACC grades of IV, III (M), IIB, IIA, and I were assigned to 4 (11.1%), 6 (16.6%), 11 (30.6%), 11 (30.6%), and 4 (11.1%) patients, respectively (*Table 3*). Therefore only a minority of patients (11.1%) per either grading system had a poor response (CAP grade 3 or MDACC grade I).

Median follow-up was 13.8 months (range, 6.1-24.8 months). Median OS was 22.5 months and median PFS was 14.9 months. Improved treatment response (higher score) according to the MDACC method trended towards superior PFS (P=0.061), but not OS (P=0.134). Any histopathologic

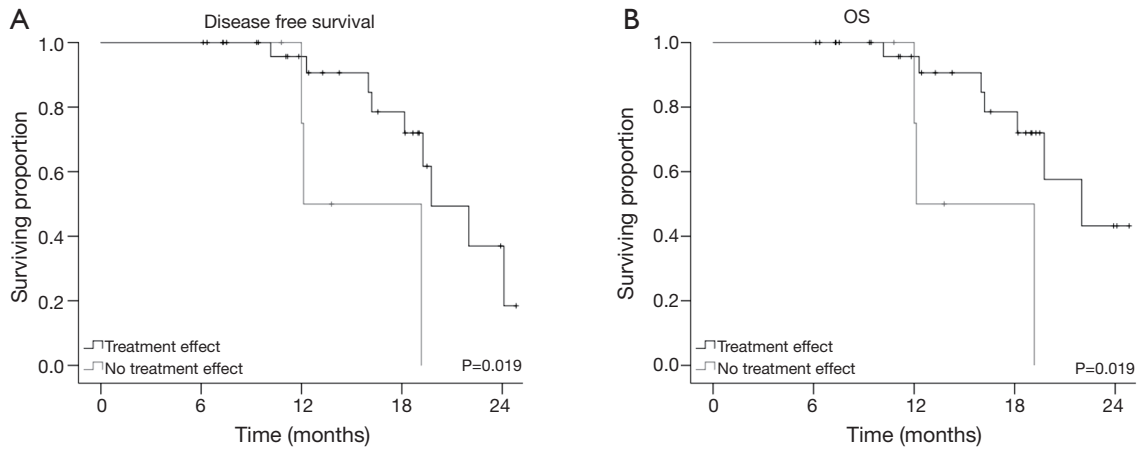

Figure 1 Histopathologic treatment effect according to MDACC tumor regression criteria is associated with superior (A) PFS and (B) OS. MDACC, MD Anderson Cancer Center; PFS, progression free survival; OS, overall survival.

treatment effect (IIA-IV *vs.* I) according to MDACC method predicted for improved OS (22.9 *vs.* 14.5 months) and PFS (15 *vs.* 7.4 months; both P=0.019) (*Figure 1*). We found no significant relationship between CAP grade and either OS or PFS. All four patients with a pCR were alive and without evidence of disease at the time of last follow up. Lastly, no local recurrences have been reported in any patient.

Discussion

While most PDAC patients have unresectable disease at initial presentation, those classified as having BRPC who undergo R0 resection after preoperative chemoradiation potentially can have long-term disease control (2,3). While prospective data support SBRT for PDAC patients with locally advanced unresectable disease (26-29), emerging retrospective evidence for BPRC are encouraging that preoperative regimens including SBRT may effectively increase the likelihood of complete resection with minimal toxicity and in a much more patient-friendly timeframe as compared to conventionally fractionated RT (4,5). Although no prospective SBRT data for BRPC have been published, several clinical trials are ongoing. These trials include one at our institution (NCT01992705), anticipated to support the continued use of pancreatic SBRT.

Several independent prognostic factors have been identified for patients with PDAC including margin status (8,9), lymph node involvement (10-12), and CA 19-9 level (13-15). The degree of histopathologic response after preoperative therapy, or TRG, is another prognostic factor that has been shown to be significantly related to clinical outcomes for various cancers, especially of the gastrointestinal tract (17,20,21,24,25,30-32). In fact, some studies have suggested that the prognostic significance of histopathologic tumor response warrants incorporation of TRG into staging systems for patients who have received preoperative therapy (33-35). Despite this, TRG scores are infrequently used for clinical decision-making, in large part due to the many TRG scoring methods that exist, consequentially leading to a lack of standardization. These different methods essentially utilize varying thresholds for the ratio between residual tumor versus tumor that has been replaced by fibrous or fibromatous granulation tissue (21,22,31,32,36-38). It is clear that validation studies are needed to clarify which method should become the standard.

We evaluated TRG in this study using the methods published by the CAP and MDACC. There were several reasons for this. First, as has been previously mentioned, data is lacking to conclude which method is the "best" among the multiple that have been developed. Thus, we decided to report scores from two separate scoring methods to have a higher likelihood of showing a significant correlation between at least one method with our clinical outcomes. Second, we selected the CAP and MDACC approaches because they are two of the most commonly reported in the literature, which would make our results more generalizable.

Induction chemotherapy and SBRT resulted in most patients having greater than minimal histopathologic effect (~90%) according to CAP (grade 0-2) and MDACC

(grade IV-IIA) criteria. Complete response was achieved in 4 patients (11%). We could not determine the relative contribution of chemotherapy *vs.* SBRT on tumor regression. However, compared to a study from MDACC in which SBRT was not given it is interesting that a higher percentage of significant response defined as CAP grade 0-1 (47% *vs.* 19%) or MDACC grade IV-III (28% *vs.* 19%) was seen in our patients who received SBRT (21). It is important to note that a significant number of patients in the MDACC study received chemoradiation with 30 Gy in 10 fractions, which has a lower biologically effective dose (BED_{10}=39 Gy) compared to 50.4 Gy in 28 fractions (BED_{10}=59.5 Gy) and 35 Gy in 5 fractions (BED_{10}=59.5 Gy), which was the median dose delivered in our study to the region of vascular involvement (39,40). We note that 11 patients in our study safely received up to 40 Gy in 5 fractions (BED_{10}=72 Gy) to the region of vascular involvement. Finally, we recognize that we cannot draw any conclusions from this comparison given our fairly small patient number and the heterogeneity in chemotherapy between studies. However it is plausible that increased tumor regression may be achieved through dose escalation using SBRT.

We found no correlation between OS or PFS and CAP grade. On the other hand, we observed a trend towards superior PFS (P=0.06) with increasing histopathologic response according to the MDACC method. The minority of patients per MDACC criteria (n=4) had a poor response to preoperative therapy, which was associated with significantly worse OS and PFS (both P=0.02). Reasons for limited response after intense multi-agent chemotherapy and SBRT are not known, but could be in part related to the poor inherent radiosensitivity of those tumors (39). Why we found a correlation between the MDACC but not the CAP grading method is also not obvious, but could be because the MDACC grading is 5-tiered (*vs.* the 4-tiered CAP method) and therefore a finer level of distinction could be made between patients with a partial response. As was previously noted, there was good agreement between patients who had minimal or poor response (CAP grade 3, MDACC grade I). The MDACC method is also much more objective, requiring TRG scores to be assigned based on the destruction of a certain percentage of tumor cells. On the other hand, the CAP method is largely subjective, requiring the pathologist to determine TRG based on a "marked", "moderate", or "poor" treatment response.

We recognize that there are several limitations of this study including its retrospective design, small patient number, and relatively limited follow up. We attempted to minimize selection bias by evaluating an initial group of consecutive BRPC patients treated at our institution using SBRT. We also accounted for interobserver bias in TRG assessment by having only one pathologist with expertise in PDAC (B.A.C.) evaluates all tumor specimens.

This is the first study to characterize TRG in BRPC patients after undergoing preoperative therapy with induction chemotherapy followed by SBRT. While we could not isolate TRG as a result of SBRT alone, we believe that SBRT likely contributed significantly to the excellent overall tumor responses that we observed. It remains unclear if the effect of SBRT *vs.* standard fractionation RT differs for BRPC. Even if tumor regression is similar between these two dose fractionation strategies, there are increasingly apparent clinical advantages of SBRT that warrant its continued evaluation.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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