Comparison of 1-, 2-, and 3-Dimensional Tumor Response Assessment After Neoadjuvant GTX-RT in Borderline-Resectable Pancreatic Cancer


ABSTRACT

Background: Facilitation of margin-negative resection is the goal of neoadjuvant therapy regimens used in the treatment of borderline-resectable pancreatic cancer patients. Multiple treatment approaches have shown efficacy in this setting, including neoadjuvant GTX (gemcitabine [Gemzar], docetaxel [Taxotere], and capecitabine [Xeloda]) and radiotherapy (RT). Three-dimensional tumor response may be a more accurate method of assessment compared to traditional 1- and 2-dimensional techniques. We compared these 3 methods in a series of patients who underwent neoadjuvant GTX-RT and surgical resection.

Materials and Methods: This retrospective review included borderline-resectable pancreatic cancer patients treated with neoadjuvant GTX followed by 5-FU chemoradiotherapy with the intent of downstaging to resectability. Tumor was contoured on computed tomography (CT) scans obtained at the following time points: (A) initial staging, (B) CT simulation, and (C) restaging. These contours were used to determine tumor response according to WHO, RECIST, and volumetric criteria.

Results: Fourteen patients all experienced a measurable decrease in tumor volume following neoadjuvant therapy and were deemed suitable for at least surgical exploration. Radiotherapy was delivered to a median 50 Gy (range, 45–52 Gy) in 1.8–2.0 Gy fractions via 3-D conformal (21%) or IMRT (79%). The median percent volume changes before and after CT simulation were −3.4% and −52.6%, respectively. The overall median percent change was −54.5%. The corresponding absolute volume changes were −0.42 cm³ (range, 9.12 to −12.47), −5.31 cm³ (range, 2.06 to −15.93), and −6.72 cm³ (range, 0.53 to −15.47), respectively. Response according to WHO, RECIST, and volumetric methods was identical with the exception of 1 patient.

Conclusion: This is the first study to quantify volumetric tumor change objectively as a result of neoadjuvant chemoradiotherapy for the treatment of borderline resectable pancreatic cancer. Our data suggest that tumor response to neoadjuvant therapy is essentially equivalent between 1-, 2-, and 3-dimensional assessment methods.


Despite advances in the multidisciplinary approach for treating ductal adenocarcinoma of the pancreas, long-term survival remains very poor.1 Pancreatic cancer is likely a systemic disease despite an initial negative metastatic workup, as over 80% of patients will develop distant metastasis after surgical resection.2,3 Despite this, resection is currently the only means of potential cure and an important goal for any neoadjuvant therapy program. Of all newly diagnosed patients, only approximately 20% of patients are diagnosed with resectable disease, and only about 20% of this subset are expected to live at least 5 years.4 M. D. Anderson Cancer Center recently reported their experience of 160 patients in which the median survival for those who completed neoadjuvant therapy and resection was 40 months vs. 13 months for those who did not undergo pancreatectomy (P < .001).5

Address correspondence to: Sarah Hoffe, MD, Department of Radiation Oncology, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, Florida 33612, USA. Phone: 813-745-1678; E-mail: sarah.hoffe@moffitt.org
Margin status is one of the most important prognostic factors in resected patients. In fact, the published literature demonstrates that margin-negative resections (R0) are associated with prolonged survival over either microscopic (R1) or gross (R2) residual disease.6–12 Furthermore, positive margins are associated with survival outcomes similar to those of unresectable patients and increase the recurrence rate after potentially curative resection to approximately 90%.4,13,14

The importance of margin status is best illustrated in borderline-resectable disease. The likelihood of achieving upfront negative surgical margins in these patients is low, usually as a result of tumor abutment of nearby vasculature. Neoadjuvant strategies to enhance the potential of margin-negative resection have ranged from systemic chemotherapy alone, to systemic chemotherapy followed by chemoradiotherapy, to chemoradiotherapy alone, to systemic chemotherapy and radiotherapy (RT), to neoadjuvant chemotherapy and radiotherapy (RT), we evaluated volumetric tumor change in a series of borderline resectable patients. To clarify potential differences between response assessment methods, we compared tumor response according to WHO, RECIST, and volumetric methodologies.10

**MATERIALS AND METHODS**

**Patient Demographics**

This retrospective review included all patients with biopsy-proven adenocarcinoma of the head of the pancreas treated at the H. Lee Moffitt Cancer Center & Research Institute (Tampa, Florida, USA) between February 2006 and April 2010. After receiving approval by our institutional review board, data were retrieved from a database maintained by the Gastrointestinal (GI) Pancreatic Tumor Program. All patients were diagnosed with borderline resectable pancreatic cancer after review at our GI Multidisciplinary Tumor Board. None had received prior chemotherapy or RT to the abdomen or pelvis.

**Staging**

The initial evaluation included a detailed history and physical examination, complete blood count, blood chemistries, and CA 19–9 level. Staging also included a multidetector thin-section pancreatic protocol computed tomography (CT) scan and endoscopic ultrasound (EUS).

**Definition of Borderline-Resectable Pancreatic Cancer**

Borderline-resectable pancreatic cancer was diagnosed based on EUS and CT findings. The definition of borderline-resectable disease used at our institution includes the following criteria: (1) ≤180° circumferential tumor abutment with the superior mesenteric vein (SMV), portal vein (PV), or superior mesenteric artery (SMA); (2) short segment encasement (approximately 1.5 cm) of the PV/SMV amenable to partial vein resection and reconstruction; or (3) gastroduodenal artery encasement up to the origin of the hepatic artery. Involvement of both the PV/SMV and SMA that would require resection and reconstruction of both arterial and venous systems was classified as unresectable. Patients who had encasement of the superior mesenteric artery (SMA), celiac artery, aorta, or inferior vena cava (IVC) were classified as unresectable and thus were not included.

**Neoadjuvant Therapy**

All patients received induction GTX followed by external beam RT with concurrent 5-FU radiosensitization. GTX was administered as follows: gemcitabine 750 mg/m² on days 4 and 11; docetaxel 30 mg/m² on days 4 and 11; capecitabine 750 mg/m² BID on days 1–14. This was repeated every 21 days for a median of 3 cycles (range, 2–10). Capecitabine 750 mg/m² was also delivered during the 3 days prior to gemcitabine administration to prevent, in theory, any gemcitabine-mediated 5-FU metabolism inhibition. Of note, synergistic cytotoxicity occurred only when capecitabine preceded gemcitabine and docetaxel by at least 2–4 days in earlier studies.29 Chemoradiotherapy began 1 week after completion of induction GTX. Continuous infusion 5-FU (225 mg/m²) was administered concurrently with daily radiotherapy.

A single GI radiation oncologist (SEH) treated all patients in this series. The simulation parameters consisted of administering oral Gastrografin 30 min prior to immobilization of the patient in the supine position with arms overhead. CT simulation was performed first in free breathing with IV contrast to set the isocenter. Since studies have shown significant respiratory associated pancreatic tumor motion in the range of 1 cm, a 4-dimensional scan was performed to quantify the degree of tumor movement with respiration.36 The degree of maximum respiratory associated tumor motion in this study was consistently measured to be 1 cm or greater.

Most patients (79%), specifically those diagnosed more recently, were treated with intensity-modulated radiation therapy (IMRT). Several (21%) were treated with 3-dimensional conformal RT prior to the availability of IMRT at our institution. Daily image guidance on the linear accelerator was not available at our institution when these patients were treated.
Given concerns about potential underdosage of moving target volumes with multileaf collimator (MLC)-based IMRT, solid IMRT using compensators was used for the majority of patients in this series. The gross tumor was contoured on the contrasted free-breathing scan and then typically created an internal gross target volume (GTV) by taking into account the position of the tumor at maximum inspiration and expiration. A GTV to planning-target-volume (PTV) expansion of 7–10 mm was generated to create the PTV50. A clinical target volume (CTV) was then drawn by the radiation oncologist to reflect the highest nodal echelon stations at risk. These regions typically included peripancreatic, celiac, superior mesenteric, medial portal hepatic, and para-aortic nodes from T12 to L2. A CTV to PTV expansion of 1 cm was then generated to create the PTV45. The goal of treatment planning was to use a simultaneous integrated IMRT boost such that the CTV received 45 Gy in 25 fractions while the GTV received 50 Gy in 25 fractions. A typical set of isodose curves are illustrated in Figure 1.

**Restaging**

A restaging pancreas protocol CT scan was obtained approximately 4 weeks after completion of neoadjuvant chemoradiotherapy. Each patient’s records were presented at our GI Multidisciplinary Tumor Board following restaging, and all were believed to have had a significant radiographic response to neoadjuvant therapy. As a result, each underwent an exploratory laparotomy and ultimately pancreaticoduodenectomy. Segmental resection of the SMA, PV, or SMV/PV confluence was performed in 2 patients when the operating surgeon could not separate the pancreatic head from these vessels without leaving tumor on the vessel. The operating surgeon and pathologist determined whether an R0 or R1 resection was achieved.

**Tumor Response Analysis**

The pancreatic tumor was contoured by an experienced GI radiologist (JC) on 3 separate CT scans, each obtained at a distinct time point, as follows: (A) initial staging, (B) CT simulation, and (C) restaging. Contouring and volumetric calculations were performed using our radiation treatment planning software (Pinnacle, Philips, Andover, MA).

According to WHO methodology, a cross-product of the maximum diameter in the transverse plane and the largest perpendicular diameter on the same image was calculated. Comparing values prior to and following treatment allowed response to be categorized as follows: complete response (tumor disappearance), partial response (≥50% reduction in cross-product), stable disease (≤50% reduction, <25% increase in cross-product), and progressive disease (>25% increase in cross-product). RECIST guidelines categorize response based on the pre- and post-treatment differences in the largest diameter in the transverse plane alone. Response based on RECIST guidelines is categorized as follows: complete response (tumor disappearance), partial response (>30% reduction in diameter), stable disease (<30% reduction, <20% increase), progressive disease (>20% increase). All 1- and 2-dimensional measurements were made using the same tumor contours drawn for the volumetric calculations.

Tumor response based on volumetric and linear measurements cannot be directly compared. To compare these data, WHO criteria were extrapolated, and the following response categories were created: complete response (tumor disappearance), partial response (>65% volume reduction), progressive disease (>44% increase in tumor volume), stable disease (all other volume changes).

**RESULTS**

Fourteen patients with borderline resectable pancreatic cancer underwent neoadjuvant GTX chemotherapy followed by concurrent 5-FU-based chemoradiotherapy. Patient and treatment characteristics are listed in Table 1. The median age was 65 years (range, 33–82), and most patients were male (79% vs. 21%). A median 3 cycles of GTX were completed, with 1 patient completing 2 cycles and 1 completing 10 cycles. The median RT dose was 5000 cGy (range, 4500–5220) using either IMRT or 3-D conformal RT. For IMRT-based treatment, the median PTV45 and PTV50 volumes were 920.1 cm³ (range, 92.4–1496.5) and 129.9 cm³ (range, 43.6–410.2), respectively. All patients underwent pancreaticoduodenectomy after favorable response to neoadjuvant therapy, with 12 patients (86%) achieving an R0 resection while 2 (14%) had microscopic positive margins.

Table 2 illustrates the duration between initial staging (A), CT simulation (B), and restaging (C). The median interval between A–B and B–C was 34 days (range, 11–78) and 99 days (range, 89–135), respectively. A median 166 days (range, 123–361) elapsed between the start of neoadjuvant therapy and surgical resection.
Figure 2 displays the measured volume change for each patient individually during intervals A–B, B–C, and A–C. Although each patient ultimately had a tumor volume decrease during interval A–C, a significant number were observed to have had a volumetric increase during interval A–B. In fact, 50% had a measured increase at simulation of median 0.86 cm³ (range, 0.02–9.12). Most patients had chemotherapy-induced peritumoral edema and/or inflammation on the CT simulation scan, thus making accurate delineation of the tumor borders difficult. In contrast, 93% of patients experienced a volumetric decrease during interval B–C. Tumor borders were more easily determined on the restaging scan, which was aided by the approximately 4-week interval after RT, during which inflammation and edema were able to at least partially subside.

Table 3 demonstrates the median volumetric change during intervals A–B, B–C, and A–C of −0.42 cm³ (range, 9.12 to −12.47), −5.31 cm³ (range, 2.06 to −15.93), and −6.72 cm³ (range, 0.53 to −15.47), respectively. The median percent volumetric changes before and after CT simulation were −3.4% and −52.6%, respectively. Overall, there was nearly a median 55% percent decrease in tumor volume with respect to interval A–C, as seen in Figure 3.

We compared tumor response based on WHO, RECIST, and volumetric criteria. The contours used to calculate the tumor volume on each scan were used to determine the maximum dimensions needed for the 1- and 2-dimensional methods. There was concordance between all 3 techniques in 13 of 14 patients (93%), as shown in Table 4. One patient had a partial response (PR) by 1- and 2-dimensional methods, but stable disease (SD) by the volumetric method. All methods agreed that 9 patients had SD and 4 had a PR.

DISCUSSION
This is the first study to quantify volumetric tumor change objectively as a result of neoadjuvant chemoradiotherapy for the treatment of borderline-resectable pancreatic cancer. Our data suggest that tumor response to neoadjuvant therapy is essentially equivalent between 1-, 2-, and 3-dimensional assessment methods.

The goal of neoadjuvant therapy strategies in borderline resectable patients is ultimately to facilitate resection with negative margins. Published data suggest that pancreatic fibrosis is common in the setting of tissue injury and inflammation, with activation of quiescent pancreatic stellate cells into myofibroblast-like cells that can express alpha-smooth muscle actin. At restaging, assessment of soft tissue adjacent to vasculature can be complicated by this phenomenon, raising the question as to whether this represents tumor vs. inflammation or fibrosis. This has direct implications in determining tumor response and whether patients are candidates for laparotomy and potential pancreatic resection.

On restaging CT, all patients in this study had noticeable debulking of tumor away from the initially involved vasculature after neoadjuvant therapy. This radiographic response warranted surgical exploration and ultimately pancreaticoduodenectomy in all patients. However, the primary intent of this study was to evaluate response from a volumetric standpoint in comparison to traditional 1- and 2-dimensional methods.

Our data demonstrate that neoadjuvant therapy results in significant tumor volume reduction. The ability to delineate tumor borders accurately was enhanced by the use of thin-slice pancreas protocol CT scan. Interestingly, most of the volume change occurred after CT simulation. In fact, the median decrease prior to and after simulation was 3.4% vs. 51.6%, respectively. It is important to note that such a stark difference is likely related, at least in part, to chemotherapy-induced peritumoral edema and/or inflammation seen at the time of simulation.

Because of the poor ability of CT to visualize soft tissue anatomy, our tumor contours at the time of simulation likely overestimated the actual tumor volume. On the same note, tumor borders were more clearly identified upon restaging. Restaging was performed approximately 4 weeks from completion of neoadjuvant therapy, during which time any inflammation and/or edema had time to at least partially resolve.
Adjuvant therapy that can cause a discrepancy between the planned vs. actual delivered dose.\textsuperscript{45} We have changed our protocol and currently simulate patients 2 weeks prior to the start of RT. We plan to review the relative volumetric changes associated with this temporal approach in a future study.

While our intent was not to measure the relative effect of chemotherapy and RT, our data do suggest that RT plays an integral role in downstaging borderline resectable patients to margin-negative resection. This is in agreement with previously published data.\textsuperscript{6–12} For instance, Pingpank demonstrated that preoperative RT resulted in fewer positive margins and higher rates of margin-negative resection.\textsuperscript{46} While we intended to analyze the relationships between tumor volume change and surgical outcomes, including tissue regression grade, our study size was too small, and nearly all patients achieved negative margins. We plan to study the effect of volumetric change on these parameters in a larger patient population.

Evaluation of tumor response using 1- and 2-dimensional measurements on CT scan is commonly used. World Health Organization guidelines have been in use since 1979, in which a comparison is made between pre- and post-treatment cross-products of the maximum tumor diameter and the largest perpendicular diameter. The WHO criteria evolved into the RECIST guidelines that use a 1-dimensional approach.\textsuperscript{47} The published data suggest that there is good agreement between these 2 methods.\textsuperscript{48,49} However, such 1- or 2-dimensional methods are based on the inherent assumption that the measured volume is symmetrical and that any tumor change occurs equally in all directions.\textsuperscript{50} This is rarely the case, especially of pancreatic tumors, which tend to be highly infiltrative. As a result, tumor response according to WHO and RECIST criteria may significantly overestimate the actual tumor volume.\textsuperscript{32} In addition, 1- or 2-dimensional measurements can be subject to significant interobserver variability, especially for ill-defined lesions such as pancreatic tumors.\textsuperscript{51} Volumetric measurements, which are now more readily attainable due to advancements in imaging technology, may overcome this variability and have been shown to be highly reproducible.\textsuperscript{33,52} The International Cancer Imaging Society has acknowledged that 3-dimensional assessment of response may play a larger role in the future.\textsuperscript{53}

The benefit of volumetric response assessment has been reported.\textsuperscript{32–35} Prasad published their comparison of 1-, 2-, and 3-dimensional techniques in patients with metastatic breast cancer to the liver. While results between the 1- and 2-dimensional techniques were in almost complete agreement, the volumetric measurements were discordant in a considerable proportion of patients.\textsuperscript{54–56} Six of 37 patients who experienced a partial response by the 1- and 2-dimensional methods had stable disease according to 3-dimensional analysis.

Our study did not demonstrate a significant difference between any of the assessment methods. In fact, there was complete agreement in 13 of 14 patients (93%), with 9 having stable disease and 4 having a partial response. The 1 patient with discordant results had a partial response by WHO and RECIST, and stable disease by volumetric analysis. It should be noted that this patient had an overall volume decrease of 64.3%, just shy of the requirement of >65% volume decrease to have achieved a partial response. Given the inherent difficulties accurately identifying soft tissue structures on CT, slight contouring variations easily

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Volume (cm$^3$)</th>
</tr>
</thead>
</table>
| A–B | Median change $-0.42 (-3.4\%)$  
|       | Range $9.12 - 12.47$ |
| B–C | Median change $-5.31 (-51.6\%)$  
|       | Range $2.06 - 15.93$ |
| A–C | Median change $-6.72 (-54.5\%)$  
|       | Range $-0.53 - 15.47$ |

\begin{figure}
\centering
\includegraphics[width=\textwidth]{tumor_volume_change.png}
\caption{Tumor volume change (cm$^3$) for individual patients at various intervals (A–B, B–C, and A–C) during neoadjuvant chemoradiotherapy.}
\end{figure}
Comparison of 1-, 2-, 3-D Response to Neo GTX-RT in PaCa

could have resulted in complete concordance between the 3 methods.

In summary, our comparison of WHO, RECIST, and volumetric assessment methods resulted in near complete concordance. This study also demonstrates that neoadjuvant GTX-RT for borderline resectable pancreatic cancer significantly decreases tumor volume and facilitates downstaging to resectability with negative margins.

REFERENCES

12. Neoptolemos JP, Stocken DD, Dunn JA: Influence of resection margins on survival for pa-
tients with pancreatic cancer treated by adjuvant chemoradiation and/or chemotherapy in the ESPAC-1 randomized controlled trial. Ann Surg 234:758–768, 2001
27. Safran H, Dipetrillo T, Iannitti D: Gemcitabine, paclitaxel, and radiation for locally advanced

Table 4. Stable disease (SD) or partial response (PR) according to WHO, RECIST, and volumetric criteria

<table>
<thead>
<tr>
<th>Patient</th>
<th>WHO</th>
<th>RECIST</th>
<th>Volumetric</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>2</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>3</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>4</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>5</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>6</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>7</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>8</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>9</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>10</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>11</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
</tr>
<tr>
<td>12</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>13</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
<tr>
<td>14</td>
<td>PR</td>
<td>PR</td>
<td>PR</td>
</tr>
</tbody>
</table>

Abbreviations: RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.
Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.