### Title

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# Clinicopathological correlation of radiologic measurement of post-therapy tumor size and tumor volume for pancreatic ductal adenocarcinoma

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## Abstract

**Objectives:** Tumor size measurement is critical for accurate tumor staging in patients with pancreatic ductal adenocarcinoma (PDAC). However, accurate tumor size measurement is challenging in patients who received neoadjuvant therapy before resection, due to treatment-induced fibrosis and tumor invasion beyond the grossly identified tumor area. In this study, we evaluated the correlation between the tumor size and tumor volume measured on post-therapy computed tomography (CT) scans and the pathological measurement. Also, we investigated the correlation between these measurements and clinicopathological parameters and survival.

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**Materials and methods:** Retrospectively, we evaluated 343 patients with PDAC who received neoadjuvant therapy, followed by pancreaticoduodenectomy and had pre-operative pancreatic protocol CT imaging. We measured the longest tumor diameter (RadL) and the radiological tumor volume (RadV) on the post-therapy CT scan, then we categorized RadL into four radiologic tumor stages (RTS) based on the current AJCC staging ($8^{th}$ edition) protocol and RadV based on the median. Pearson correlation or Spearman's coefficient (δ), T-test and ANOVA was used to test the correlation between the radiological and pathological measurement. Chi-square analysis was used to test the correlation with the tumor pathological response, lymph-node metastasis and margin status and Kaplan-Meier and Cox-proportional hazard for survival analysis. P-value < 0.05 was considered significant.

**Results:** As a continuous variable, RadL showed a positive linear correlation with the post-therapy pathologic tumor size in the overall patient population (Pearson correlation coefficient: 0.72, P<0.001) and R-GTV (δ: 0.63, p<0.0001). However, there was no correlation between RadL and pathologic tumor size in patients with ypT0 and those with pathologic tumor size of ≤ 1.0 cm. Post-therapy RTS and RadV group correlated with ypT stage, tumor response grades using either CAP or MDA grading system, distance of superior mesenteric artery margin and tumor recurrence/metastasis.

**Conclusion:** Although RadL tends to understage ypT in PDAC patients who had no radiologically detectable tumor or small tumors (RTS0 or RTS1), radiologic measurement of post-therapy tumor size may be used as a marker for the pathologic tumor staging and tumor response to neoadjuvant therapy.

### Keywords

Pancreatic cancer; radiologic tumor size; radiologic tumor volume; tumor response grade; tumor stage

## Background:

Pancreatic cancer ranks third in terms of cancer-related deaths in the United States[1, 2]. Despite the development of new treatment strategies, pancreatic ductal adenocarcinoma (PDAC) continues to have a high mortality rate, which closely parallels its incidence, and is predicted to become the second most common cause of cancer-related deaths in the US by year 2030[3]. The best hope of cure for PDAC patients is surgical resection with negative margins. However, only approximately 20% PDAC patients are good candidates for surgical resection at the time of diagnosis since the disease is usually asymptomatic or shows mild non-specific clinical manifestations in its early stages[4]. Thus, early diagnosis and accurate staging are critical to the optimal treatment plan and to the clinical outcomes for PDAC patients.

Neoadjuvant chemotherapy with or without radiation before surgery in PDAC patients shows comparable benefits to those who underwent surgery first followed by adjuvant therapy[5]. The potential benefits of neoadjuvant strategy include better tolerance and guaranteed delivery of therapy, early treatment of micrometastatic disease, higher rate of a margin negative resection, and selection of patients with favorable tumor biology to undergo major

surgery[6]. Neoadjuvant therapy is increasingly being used to treat patients with potentially resectable PDAC and is now established in practice guidelines for those with borderline resectable PDAC[7]. Our previous investigations showed that preoperative chemoradiationtherapy, combined with meticulous surgical technique, is associated with increased superior mesenteric artery (SMA) margin distance, reduced rates of locoregional recurrence and lymph node positivity, and longer progression-free survival compared with those whose received surgery first[8, 9].

Pathologic examination and tumor staging of pancreatectomy specimens from patients with PDAC who were treated with neoadjuvant therapy are challenging. The current American Joint Committee on Cancer (AJCC) staging system (8$^{th}$ edition) uses only tumor size in maximum dimension to classify primary tumor (pT) stage for pT1-pT3 (pT1 ≤ 2 cm; pT2 > 2 cm and ≤ 4 cm; and pT3 > 4 cm), while the criteria for pT4 tumor defined as tumor involving the celiac axis, superior mesenteric artery and/or common hepatic artery, irrespective of tumor size[10]. However, accurate measurement of tumor size in post-therapy pancreatectomy specimens is extremely difficult, especially for patients who had good response to neoadjuvant therapy, due to the presence of severe fibrosis in both tumor and adjacent non-neoplastic pancreatic tissue induced by neoadjuvant therapy and microscopic invasion of PDAC cells into the adjacent pancreatic tissue. Therefore the gross measurement of tumor size is often inaccurate, especially for those patients who had major responses[11].

Pre- and post-treatment CT scans using pancreatic protocol are routinely used to evaluate the clinical staging, tumor resectability, tumor response and restaging after neoadjuvant therapy and play a key role in the multidisciplinary decision-making for patients with PDAC[12–15]. Previously, we have shown that mass transport properties of PDAC tumors can be derived from pre-therapy CT scans, and correlate with gemcitabine and radiation delivery, tumor heterogeneity and clinical outcomes[16–18]. Furthermore, we measured the differences enhancement at the interface between PDAC and parenchyma (delta) on pre-therapy CT scans, and showed that high-delta tumors contain significantly less stroma and more aggressive mesenchymal features and common pathway mutations, and are associated with poor clinical outcome compared to those with low-delta tumors[19–23]. Finally, we demonstrated that the changes at the PDAC/parenchyma interface on pre- and post- therapy CT scans may serve as an early predictor of therapy response[15]. More recently, we showed that reduction in tumor volume evaluated on pancreatic protocol CT scans was an independent predictor for pathologic major response[13]. In another study evaluating tumor measurements and tumor staging, Kassardjian *et al.* assessed the accuracy of tumor size measurements in 268 PDAC patients using pre-operative CT scan (n=159), endoscopic ultrasound (EUS, n=93) and *magnetic resonance imaging* (*MRI*, n=16) and compared to the gross tumor size reported by pathology. They found that imaging studies underestimated tumor size and T stage when compared the gross tumor size as reported by pathology, however, the overall TNM stage was only rarely altered in their study population[14]. However, the correlations of tumor size and tumor volume measured by CT scan with ypT, tumor response grading and other clinical features in PDAC patients who received neoadjuvant therapy were not investigated. In this study, we aimed to correlate the maximal tumor length (RadL), radiologic tumor stage (RTS) and tumor volume (RadV), as measured on post-therapy pancreas protocol CT scans with clinicopathological parameters and

survival in 343 PDAC patients who received neoadjuvant therapy and pancreaticoduodenectomy. Our study showed that post-therapy RadL, RTS, and RadV may be used as a surrogate maker for ypT and pathologic tumor response.

## Materials and methods:

### Patient population:

This study was approved by the University of Texas, MD Anderson Cancer Center Institutional Review Board (PA14–0646). Retrospectively, we evaluated 398 consecutive patients with histologically confirmed diagnosis of PDAC who received neoadjuvant therapy and pancreaticoduodenectomy at our institution between 1999 and 2012. 343 patients who underwent adequate pre-operative pancreatic protocol CT scans (absence of stents artifacts) after neoadjuvant therapy were included in this study. Patients with PDAC who did not receive neoadjuvant therapy, patients with PDAC arising from intraductal papillary neoplasm, mucinous cystic neoplasm, or other pancreatic neoplasms were excluded. There were 186 males and 157 females with a median age at diagnosis of 64.1 years (range: 34.5 to 85.4 years). Fifty-one patients (14.9%) received neoadjuvant fluoropyrimidine-based chemoradiation, 69 (20.1%) received neoadjuvant gemcitabine-based chemoradiation, 101 (29.5%) received systemic chemotherapy followed by gemcitabine-based chemoradiation, 104 (30.3%) received systemic chemotherapy followed by fluoropyrimidine-based chemoradiation and 18 (5.2%) patients received neoadjuvant systemic chemotherapy alone. The clinical and follow-up information were extracted from a prospectively maintained pancreatic cancer database at the Department of Surgical Oncology at our institution and were verified by reviewing patients' medical records and/or the U.S. Social Security Index if needed. There were 8 (2.3%), 130 (37.9%), 178 (51.9%), and 27 (7.9%) patients with ypT0, ypT1, ypT2, and ypT3, respectively. No patient had a ypT4 tumor.

### Imaging Technique:

Images were obtained using a multiphasic pancreas CT imaging protocol. A volume of 125–150 cc of iodinated contrast was injected at a rate of 3–5 cc/sec. Bolus tracking, with a trigger of 100 Hounsfield Units (HU) rise was utilized as measured at the abdominal aorta. Imaging beginning of the hemidiaphragms was started 20 seconds after the trigger. Scan durations were approximately 5 seconds, depending on the imaging platform/scanner, such that the pancreas was imaged approximately 45 seconds after the start of contrast injection (the pancreatic parenchyma phase). After another 20 second delay, imaging began again at the diaphragms, approximately 65 seconds after the start of contrast injection, to image the abdomen during the portal venous phase of contrast enhancement. All images were reconstructed in the pancreatic parenchyma phase and the portal venous phase to 2.5–3 mm slice thickness (depending on the imaging platform/scanner) for review.

### Tumor size and tumor volume measurement by CT scan:

The pre-operative pancreatic protocol CT scan images after neoadjuvant therapy were imported to the image analysis platform (Velocity AI, Varian Medical Systems, Palto Alto, CA). Using the arterial phase scans, we measured the longest tumor diameter (RadL) in centimeters. Then we used the provided segmentation tool to manually contour the tumor

slice-by-slice on the axial plane, and the software calculated the volume of the contoured tumor in cubic centimeters (RadV). For patients who had no radiologically detectable tumors (n = 25), we recorded the RadL and RadV as zero. The measurements were reviewed by two radiologists (EPT and PRB) who were blinded to the pathology and treatment data. Representative CT scan images for measuring RadL and volumetric contouring of a PDAC are shown in Figure 1. The radiologic tumor stages (RTS) were classified based on the RadL in centimeter using size cut-offs in AJCC 8$^{th}$ edition (RadT0, 0 cm; RadT1 ≤ 2 cm; RadT2 > 2 cm and ≤ 4 cm; and RadT3 > 4 cm)[10]. The RadV were grouped into RadV0 (no tumor identified by radiology, 0 cm$^3$); RadV1 (RadV > 0 cm$^3$ and ≤2.37 cm$^3$) and RadV2 (RadV >2.37 cm$^3$) using the median RadV (2.37 cm$^3$) as a cut-off.

### The pathologic evaluation:

A standardized grossing and reporting systems for tumor type, size, differentiation, extra-pancreatic tissue involvement, margins status, number of lymph nodes examined and number of positive lymph nodes in pancreaticoduodenectomy specimens have been used at our institution since 1990. The tumor size was measured by gross and validated by histologic examination as described by Chatterjee et al[24]. Post-therapy ypT and ypN stages were grouped according to the current AJCC manual, 8$^{th}$ edition[10]. Treatment response was graded using the College of American Pathologists (CAP) tumor response grading[6] and MD Anderson grading systems[25, 26].

### Patient follow up and statistical analysis:

Statistical analysis was performed using the Statistical Package for Social Sciences software for Windows (Version 26, SPSS, Inc., Chicago, IL). A two-sided significance level of 0.05 was used for all statistical analyses. The correlations between the categorical data were analyzed using Chi-square analyses and the means among different pathologic and radiologic groups were compared One-Way ANOVA or Independent-Samples T tests. Spearman's coefficient (δ) was used to test the correlation between the radiological and pathological measurement. Survival analyses were performed using the Kaplan-Meier method and the log-rank test was used to evaluate the statistical significance of differences or using the Cox regression analysis for continuous variables. Disease-free survival (DFS) was calculated from the date of surgery to the date of first recurrence after surgery in patients with recurrence or to the date of last follow-up in patients without recurrence. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the date of last follow-up if death did not occur.

## Results:

### Correlation of Post-therapy mean RadL and mead RadV with pathologic parameters

The means of RadL and RadV of different ypT, ypN and tumor response groups are shown in Table 1. There were significant differences in the means of RadL and RadV among the patients with ypT0, ypT1, ypT2, and ypT3 patients (One-Way ANOVA or Independent-Samples T tests, $P < 0.001$, Table 1 and Figure 2A & 2B). The differences in the means of RadL and RadV were statistically significant for ypT0 vs ypT2 (P < 0.001 and P = 0.049); ypT0 vs ypT3 (P < 0.001 and P = 0.01); ypT1 vs ypT2 (P < 0.001 and P < 0.001); ypT1 vs

ypT3 (P < 0.001 and P < 0.001); and ypT2 vs ypT3 (P < 0.001 and P < 0.001). However, there was no difference in mean RadL (P = 0.68) and mean RadV (P = 0.68) between ypT0 and ypT1 groups. There were also no differences in either mean RadL or mean RadV among the patients with ypN0, ypN1 and ypN2 disease (P > 0.05, Table 1 and Figure 2)

The mean RadL and mean RadV for patients with CAP grade 3 response were significantly bigger than those with CAP grade 0 (P = 0.001 and P = 0.04), CAP grade 1 (P = 0.001 and P = 0.02), and CAP grade 2 response (P=0.04 and P = 0.01). The mean RadL for patients with CAP grade 2 response was bigger than those with CAP grade 1 (P = 0.01) and CAP grade 0 (P = 0.02) responses. However, there was no difference in RadV among those with CAP grade 0, 1 or 2 responses and there was no difference in RadL between CAP grade 1 and grade 0 (P>0.05, Table 1 and Figure 3A). Similarly, the mean RadL for patients with MDA grade 2 response was significantly bigger than those with MDA grade 0 response (P=0.05) and MDA grade 1 response (P=0.001). However, there was no significant difference in RadL among those with MDA grade 0 and 1 responses (P = 0.60, Table 1 and Figure 3B). There was no difference in RadV among the patients with MDA grade 0, grade 1 or grade 2 response (P = 0.14, Table 1).

### The correlation of post-therapy radiologic tumor size and pathologic tumor size.

The correlation between RadL and pathologic tumor size is shown in Figure 4. There was a positive linear correlation between RadL and pathologic tumor size (Pearson correlation coefficient: 0.72, P<0.001, Figure 4A). In patients with ypT1, there was no correlation between post-therapy RadL and pathologic tumor size in 27 patients who had a pathologic tumor size of 1.0 cm or less (Pearson correlation efficient: −0.12, P = 0.55, Figure 4B). Among the eight cases with complete pathologic response (ypT0), only two patients had no radiologically detectable tumor. The remaining six cases had a post-therapy RadL ranging from 0.6 to 2.5 cm. These data suggest that RadL was not a good indicator for pathologic tumor size when PDAC was ≤1.0 cm or had complete pathologic response (ypT0).

### The correlations of the RTS and RadV groups with clinicopathological parameters

The correlations between RTS and RadV groups and clinicopathological parameters are shown in Table 2. Post-therapy RTS correlated with ypT8 (P<0.001), CAP and MDA tumor response grading (P < 0.001 and P <0.001), the distance of superior mesenteric margin (P = 0.04), and local recurrence/distant metastasis (P = 0.049). Post-therapy RadV groups correlated with gender (P = 0.03), ypT8 (P<0.001), CAP and MDA tumor response grading (P < 0.001 and P <0.001), the distance of superior mesenteric margin (P = 0.007) and local recurrence/distant metastasis (P = 0.04). No correlations were identified between RTS or RadV groups and age, ypN8, or differentiation (P>0.05, Table 2). Among 25 patients with no radiologically detectable tumor (RTS0 and RadV0), 20 patients had ypT1 and three patients had ypT2 disease, only two had ypT0 disease.

### The correlation of post-therapy RTS and ypT8 with disease-free or overall survivals.

Survival analysis showed that patients with no radiologically detectable tumor (RadV = 0) had improved disease-free survival with borderline statistical significance compared to those with RadV1 and RadV2 groups (P = 0.05). No correlation between RadV with overall

survival was found (P = 0.15). There were also no significant correlations between post-therapy RTS and disease-free survival (P = 0.38) or overall survival (P = 0.71, Figure 5A–5D). Cox regression analysis using RadL or RadV as a continuous variable also showed no significant correlation between RadL or RadV and disease-free or overall survivals (P > 0.05, data not shown). On the other hand, post-therapy pathologic tumor stage (ypT) correlated significantly with both disease-free survival (P < 0.001) and overall survival (P = 0.002, Figure 5E and 5F).

## Discussion:

The current AJCC staging system (8th Edition) uses only the tumor size to define pT1, pT2 and pT3 for PDAC[10]. Pathologic examination is the gold standard to measure the tumor size for pathologic staging. However, therapy-induced fibrosis in both tumor and adjacent non-neoplastic pancreas and the invasion of PDAC cells into adjacent grossly normal appearing pancreatic parenchyma are common and often make accurate tumor size measurement in post-therapy pancreatectomy specimens very difficult. This is especially true and sometime an impossible task to accurately measure the tumor size in pathology when the tumor demonstrated major pathologic response to neoadjuvant therapy and had only scattered microscopic foci of viable residual PDAC cells in the background of therapy-induced fibrosis on histologic examination, but no tumor could be grossly identified in the specimen[6]. In this study, we measured the post-therapy maximal tumor length (RadL) and tumor volume (RadV) based on pancreatic protocol CT scans and examined their correlations with clinicopathological parameters and survival in 343 patients with PDAC who received neoadjuvant therapy and pancreaticoduodenectomy. We found that post-therapy RadL, RTS, and RadV correlated with ypT stage, tumor response grading and the distance of the SMA margin. In addition, we found that post-therapy radiologic tumor stage (RTS) correlated with tumor recurrence/metastasis. These findings suggested that RadL, RTS and RadV may be used as surrogate makers for ypT and pathologic tumor response.

Multiphasic pancreatic protocol CT scans are routinely used in pancreatic cancer patients to evaluate their clinical stage at baseline, tumor resectability, and tumor response to therapy and for restaging after neoadjuvant therapy[12–15]. Previous study by Kassarjian *et al*[14]. compared the tumor size measurements by various imaging modalities with tumor size as measured by gross examination and found that RTS was concordant with pT in 60.4%, upstaged the tumor in 9.7%, and downstaged the tumor in 29.9%[14]. In this study, we found that RTS was concordant with ypT in 238 (69.4%), downstaged the tumor in 75 (21.9%), and upstaged the tumor in 30 (8.7%) patients. Our study showed better concordant rate between RTS and ypT and a lower number of cases downstaged by RTS than those reported by Kassarjian *et al.*[14]. The differences between these studies may be due to the following reasons: 1. Most patients included in the previous study (76.9%) did not receive neoadjuvant therapy, while all patients in our study received neoadjuvant therapy. 2. Different radiological imaging methods were used between these two studies. The previous study used CT scans, m*agnetic resonance imaging or endoscopic ultrasound* to measure the tumor size, while only pancreas protocol CT scans were used to measure the tumor size in our study. 3. The previous study included 69 (25.7%) cases of PDAC arising in association with IPMN, which were excluded in this study[14]. Nevertheless, both studies demonstrated good

concordance between RTS and pT or ypT, and showed that RTS tends to understage tumor in PDAC patients.

Correlations between post-therapy RadL or RTS as measured on pancreas protocol CT scans and pathologic response, in the setting of pancreatic cancer patients undergoing neoadjuvant therapy have not been reported previously. In this study, we found that RadL, RTS and RadV grouping correlated significantly with tumor response grades based on either CAP grading system or MDA grading system in a large cohort of PDAC patients who received neoadjuvant therapy and pancreaticoduodenectomy. Although we did not observe significant correlation between either RTS or RadV grouping with patient survival, the RTS and RadV grouping correlated with the distance of the SMA margin, which is the most common site for local recurrence of PDAC after pancreaticoduodenectomy. Consistent with these findings, we found that RTS and RadV group correlated with tumor recurrence/metastasis during the follow up after surgery. These findings highlight the importance of radiologic measurement of post-therapy tumor size and tumor volume tumor in the clinical management of PDAC patients.

Although post-therapy RadL showed a strong correlation with pathologic tumor size in our study population, it should be noted that 6 of 8 (75%) cases with complete pathologic response (ypT0) had a post-therapy RadL ranging from 0.6 to 2.5 cm (4 RTS0 and 2 RTS2) in this study. In addition, we did not observe significant correlation between post-therapy RadL and pathologic tumor size in patients with pathologic tumor size of 1.0 cm or less. These data suggest that RadL was not a reliable predictor for pathologic tumor size if the patient has a complete pathologic responses to neoadjuvant therapy or the post-therapy tumor is 1.0 cm or less in size. This concept is consistent with our finding that there was no significant differences in either mean RadL or mean RadV among the patients with CAP grade 0 and those with grade 1 responses. On the other hand, only 2 of 25 (8%) patients in our study who had no radiologically identifiable tumor (RTS0) were found to have a complete pathologic response (ypT0). The tumor size measured by CT scans understaged the tumor in 23 of 25 (92%) patients with RTS0. Therefore, CT scans may not reliably identify patients with complete pathologic response for PDAC patients who receive neoadjuvant therapy. Similar findings have been also reported in other malignant neoplasms[27–29]. Compared with CT scans, pancreatic MRI has been reported to be better in evaluating the volume of small tumors and to facilitate contouring of pancreatic tumors[30]. A recent study of an MRI based tumor response grading system for rectal cancer integrated multiple parameters, i.e., radiologic response, residual tumor, fibrosis and mucin to generate a score from 1 to 5, with grade 1 indicating complete radiologic response to treatment and grade 5 indicating no response[31]. This newly proposed MRI grading system showed significant correlations with pathologic tumor response and survival outcomes[31]. Future studies are needed to evaluate the utility of MRI in the accurate staging of small tumors and to evaluate tumor response in patients with PDAC.

In conclusion, although RadL tends to understage post-therapy pathologic tumor stage (ypT) in PDAC patients who had no radiographically detectable tumor or small (≤1 cm) tumors (RTS0 or RTS1), post-therapy RadL shows significant correlations with pathologic tumor size and tumor response grading. Radiographic tumor stage (RTS) and radiographic volume

(RadV) group correlate with ypT stage, tumor response grades, the distance of the SMA margin and development of recurrence/metastasis. Radiologic measurements of post-therapy tumor size and volume on CT scans may be used as a marker for pathologic tumor staging and tumor response to neoadjuvant therapy.

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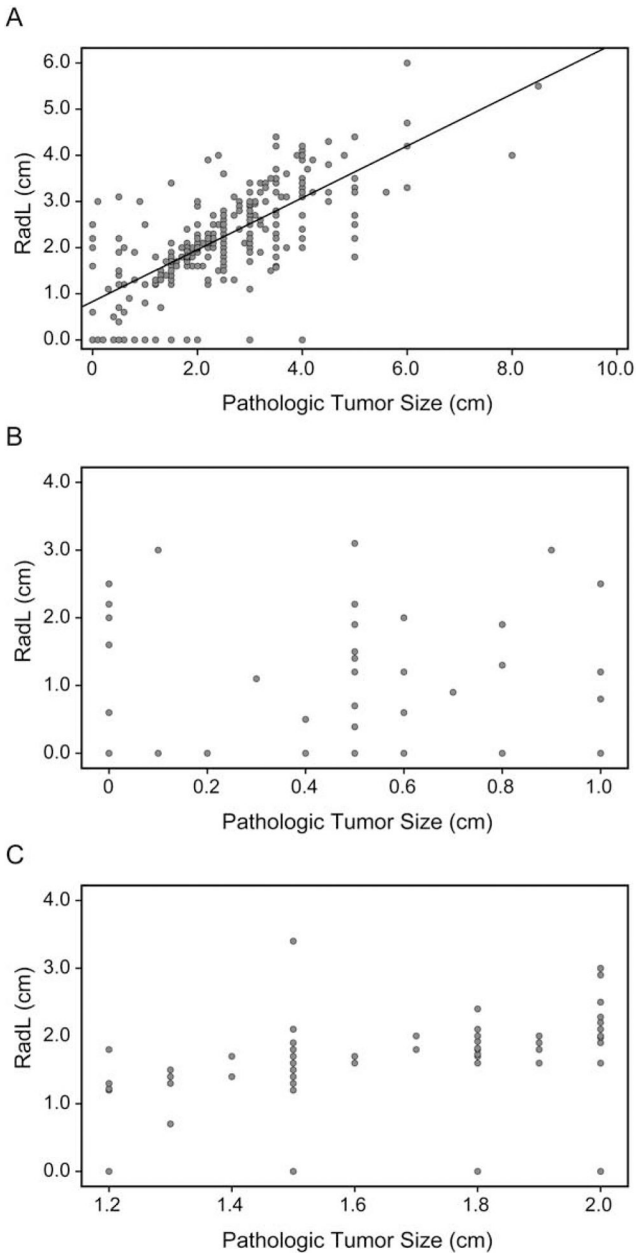


**Figure 1:**
Representative computed tomography (CT) images showing post-therapy longest tumor diameter (RadL) and volume measurements (RadV). Volumetric contouring of the PDAC tumor interpolated in the axial (A), coronal (B) and sagittal (C) planes, and 3D rendering of the contoured volume (D).

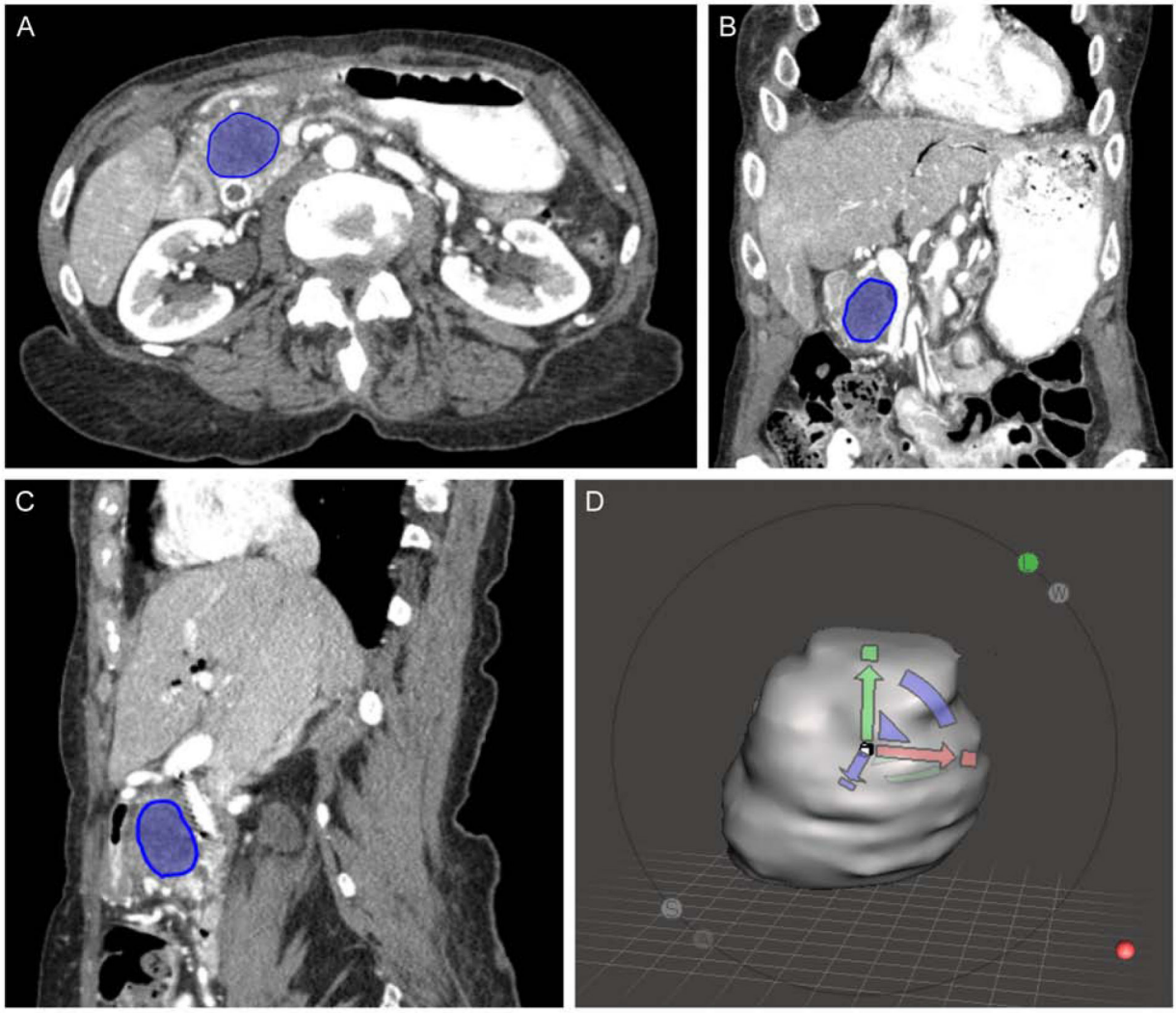


**Figure 2:**
Boxplots of post-therapy RadL and RadV in correlation with post-therapy pathologic tumor (ypT) stage. Boxplots of RadL (A) and RadV (B) among different ypT groups are shown.

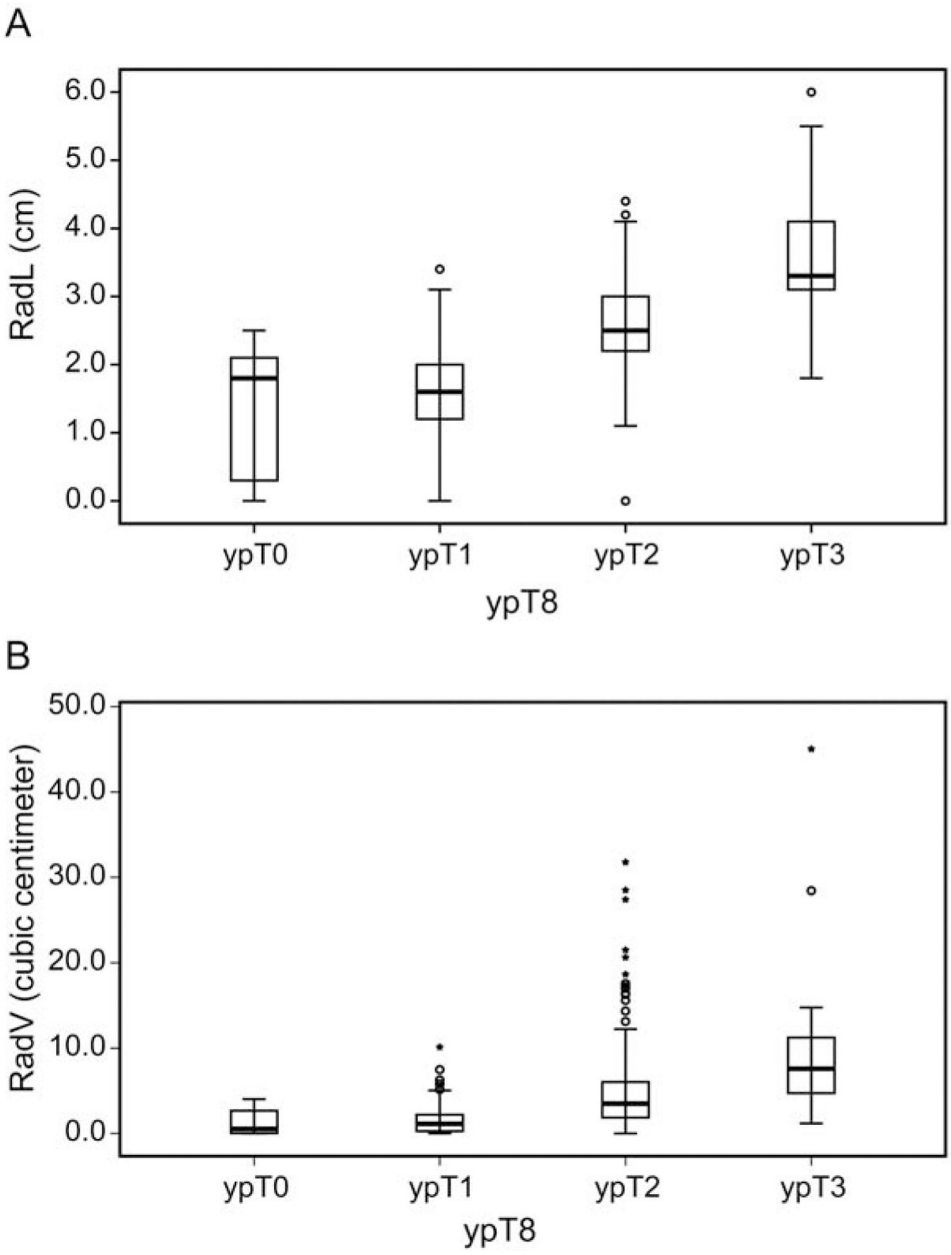


**Figure 3:**
Boxplots of post-therapy RadL in correlation with the College of American Pathologists (CAP) tumor response grading (A) and MD Anderson Cancer Center (MDA) tumor response grading (B).

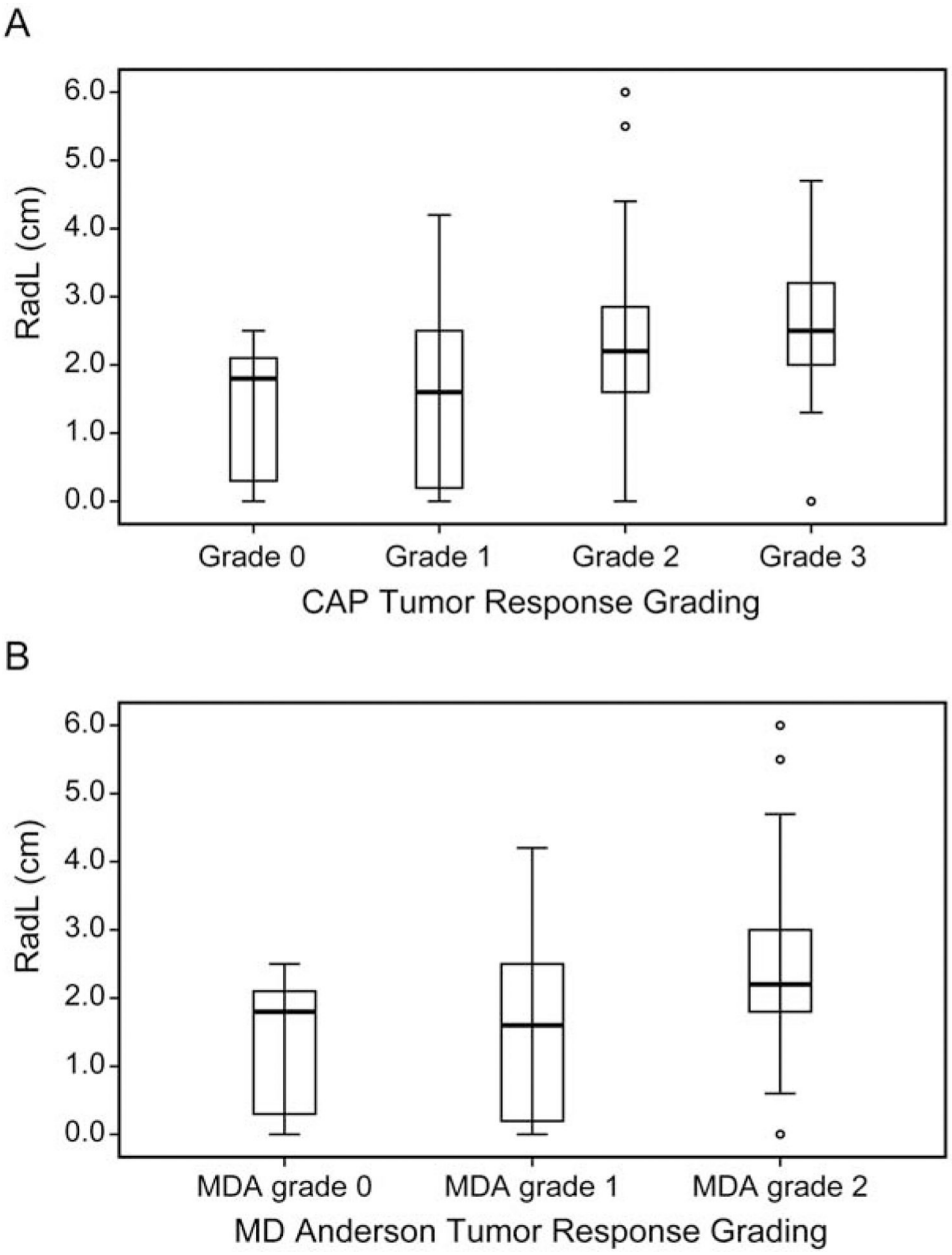


**Figure 4.**

Scatter plots showing the correlation between post-therapy RadL and post-therapy pathologic tumor size in overall patient population (A) and patients with ypT1 tumors (B).

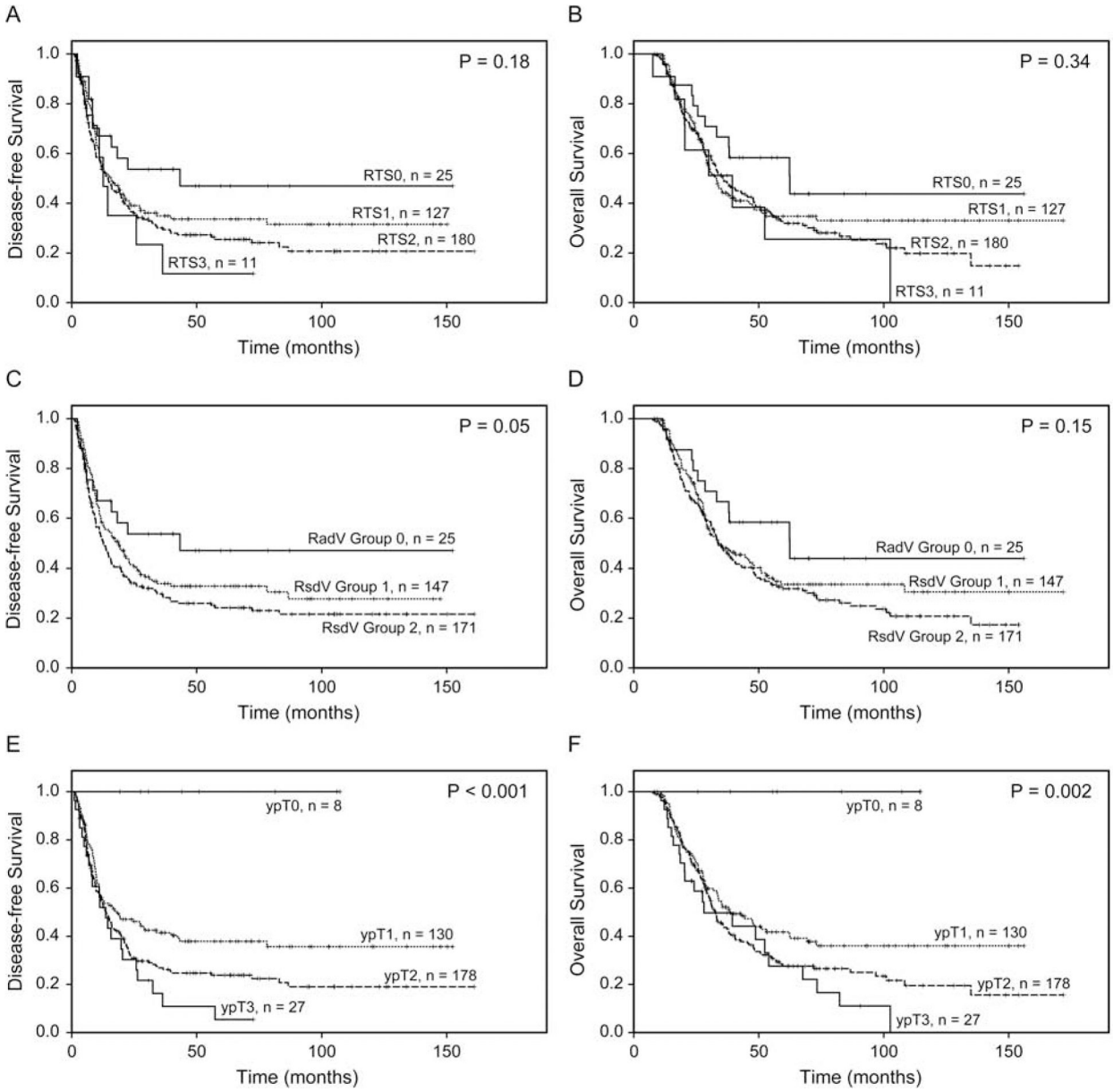


**Figure 5.**

Kaplan-Meier survival curves of disease-free and overall survival stratified by post-therapy radiologic tumor stage (RTS) (A and B), RadV group (C and D) and ypT8 (E and F).

**Table 1.**

The Mean RadL and RadV Among Different ypT, ypN and Tumor Response Grading Groups

| | No of Patients | Mean RadL (± SD, cm) | P value | Mean RadV (± SD, cm) | P value |
|---|---|---|---|---|---|
| ypT0 | 8 | 1.36 ± 1.01 | <0.001 | 1.32 ± 1.58 | <0.001 |
| ypT1 | 130 | 1.49 ± 0.80 | | 1.57 ± 1.73 | |
| ypT2 | 178 | 2.60 ± 0.77 | | 5.06 ± 5.33 | |
| ypT3 | 27 | 3.56 ± 0.96 | | 9.61 ± 8.94 | |
| ypN0 | 157 | 2.08 ± 1.12 | 0.06 | 3.65 ± 5.73 | 0.50 |
| ypN1 | 124 | 2.35 ± 0.99 | | 4.32 ± 4.85 | |
| ypN2 | 62 | 2.33 ± 0.89 | | 4.30 ± 4.67 | |
| CAP grade 0 | 8 | 1.36 ± 1.01 | <0.001 | 1.32 ± 1.58 | 0.01 |
| CAP grade 1 | 43 | 1.60 ± 1.23 | | 3.09 ± 5.40 | |
| CAP grade 2 | 195 | 2.22 ± 1.01 | | 3.65 ± 5.09 | |
| CAP grade 3 | 97 | 2.57 ± 0.83 | | 5.35 ± 5.41 | |
| MDA grade 0 | 8 | 1.36 ± 1.01 | <0.001 | 1.32 ± 1.58 | 0.14 |
| MDA grade 1 | 43 | 1.60 ± 1.23 | | 3.09 ± 5.40 | |
| MDA grade 2 | 292 | 2.34 ± 0.97 | | 4.22 ± 5.25 | |

**Table 2.**

Correlations of Radiologic Tumor Stage and Tumor Volume With Clinicopathological Parameters

| | Radiologic tumor stages (RTS) | | | | | RadV Groups | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Variables** | **RTS 0** | **RTS1** | **RTS2** | **RTS3** | ***P* value** | **RadV0** | **RadV1** | **RadV2** | ***P* value** |
| Sex | | | | | | | | | |
| Female | 8 | 60 | 86 | 3 | 0.28 | 8 | 79 | 70 | 0.03 |
| Male | 17 | 67 | 94 | 8 | | 17 | 68 | 101 | |
| Age | | | | | | | | | |
| < 65 | 13 | 61 | 109 | 5 | 0.16 | 13 | 71 | 104 | 0.08 |
| >= 65 | 12 | 66 | 71 | 6 | | 12 | 76 | 67 | |
| ypT8 | | | | | | | | | |
| ypT0 | 2 | 4 | 2 | 0 | <0.001 | 2 | 3 | 3 | <0.001 |
| ypT1 | 20 | 90 | 20 | 0 | | 20 | 83 | 27 | |
| ypT2 | 3 | 32 | 139 | 4 | | 3 | 59 | 116 | |
| ypT3 | 0 | 1 | 19 | 7 | | 0 | 2 | 25 | |
| ypN8 | | | | | | | | | |
| Negative | 16 | 62 | 72 | 7 | 0.12 | 16 | 74 | 67 | 0.08 |
| 1–2 positive LN | 7 | 40 | 73 | 4 | | 7 | 46 | 71 | |
| >2 positive LN | 2 | 25 | 35 | 0 | | 2 | 27 | 33 | |
| Differentiation | | | | | | | | | |
| Well-Mod | 18 | 84 | 111 | 9 | 0.42 | 18 | 98 | 106 | 0.50 |
| Poor | 7 | 43 | 69 | 2 | | 7 | 49 | 65 | |
| CAP response grading | | | | | | | | | |
| Garde 0 | 2 | 4 | 2 | 0 | <0.001 | 2 | 3 | 3 | <0.001 |
| Grade 1 | 11 | 16 | 15 | 1 | | 11 | 19 | 13 | |
| Grade 2 | 10 | 80 | 98 | 7 | | 10 | 95 | 90 | |
| Grade 3 | 2 | 27 | 65 | 3 | | 2 | 30 | 65 | |
| MDA Response Grading | | | | | | | | | |
| Grade 0 | 2 | 4 | 2 | 0 | <0.001 | 2 | 3 | 3 | <0.001 |
| Grade 1 | 11 | 16 | 15 | 1 | | 11 | 19 | 13 | |
| Grade 2 | 12 | 107 | 163 | 10 | | 12 | 125 | 155 | |
| SMA margin | | | | | | | | | |
| Positive or <= 1.0 mm | 3 | 27 | 43 | 4 | 0.04 | 3 | 37 | 37 | 0.007 |
| 1.0 to 5.0 mm | 4 | 40 | 67 | 5 | | 4 | 42 | 70 | |
| > 5.0 mm | 18 | 60 | 70 | 2 | | 18 | 68 | 64 | |
| Recurrence/metastasis | | | | | | | | | |
| No | 13 | 46 | 49 | 2 | 0.049 | 13 | 51 | 46 | 0.04 |
| Yes | 12 | 81 | 129 | 8 | | 12 | 96 | 122 | |

Abbreviations: LN, lymCAP, College of American Pathologists; MDA, MD Anderson Cancer Center, SMA, superior mesenteric artery

**Table 3.**

Post-treatment pathologic tumor size and tumor stage of 25 patients with no radiologically detectable tumor after treatment

| Patient No | Pre-treatment Rectability | Pathologic tumor size (cm) | ypT stage |
|---|---|---|---|
| 1 | potentially resectable | 0.0 | ypT0 |
| 2 | Locally Advanced | 0.0 | ypT0 |
| 3 | potentially resectable | 0.1 | ypT1 |
| 4 | potentially resectable | 0.2 | ypT1 |
| 5 | potentially resectable | 0.2 | ypT1 |
| 6 | potentially resectable | 0.2 | ypT1 |
| 7 | potentially resectable | 0.4 | ypT1 |
| 8 | potentially resectable | 0.5 | ypT1 |
| 9 | potentially resectable | 0.5 | ypT1 |
| 10 | potentially resectable | 0.5 | ypT1 |
| 11 | potentially resectable | 0.5 | ypT1 |
| 12 | potentially resectable | 0.5 | ypT1 |
| 13 | potentially resectable | 0.5 | ypT1 |
| 14 | potentially resectable | 0.6 | ypT1 |
| 15 | potentially resectable | 0.8 | ypT1 |
| 16 | potentially resectable | 0.9 | ypT1 |
| 17 | Borderline resectable | 1.0 | ypT1 |
| 18 | potentially resectable | 1.2 | ypT1 |
| 19 | potentially resectable | 1.5 | ypT1 |
| 20 | Borderline resectable | 1.8 | ypT1 |
| 21 | potentially resectable | 2.0 | ypT1 |
| 22 | potentially resectable | 2.0 | ypT1 |
| 23 | Borderline resectable | 3.0 | ypT2 |
| 24 | potentially resectable | 4.0 | ypT2 |
| 25 | potentially resectable | 4.0 | ypT2 |