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## Tumor Size Differences Between Preoperative Endoscopic Ultrasound and Postoperative Pathology for Neoadjuvant-Treated Pancreatic Ductal Adenocarcinoma Predict Patient Outcome

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Supplementary Material

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## Abstract

**BACKGROUND & AIMS:** The assessment of therapeutic response after neoadjuvant treatment and pancreatectomy for pancreatic ductal adenocarcinoma (PDAC) has been an ongoing challenge. Several limitations have been encountered when employing current grading systems for residual tumor. Considering endoscopic ultrasound (EUS) represents a sensitive imaging technique for PDAC, differences in tumor size between preoperative EUS and postoperative pathology after neoadjuvant therapy were hypothesized to represent an improved marker of treatment response.

**METHODS:** For 340 treatment-naïve and 365 neoadjuvant-treated PDACs, EUS and pathologic findings were analyzed and correlated with patient overall survival (OS). A separate group of 200 neoadjuvant-treated PDACs served as a validation cohort for further analysis.

**RESULTS:** Among treatment-naïve PDACs, there was a moderate concordance between EUS imaging and postoperative pathology for tumor size ( $r = 0.726$ ,  $P < .001$ ) and AJCC 8<sup>th</sup> edition T-stage ( $r = 0.586$ ,  $P < .001$ ). In the setting of neoadjuvant therapy, a decrease in T-stage correlated with improved 3-year OS rates (50% vs 31%,  $P < .001$ ). Through recursive partitioning, a cutoff of 47% tumor size reduction was also found to be associated with improved OS (67% vs 32%,  $P < .001$ ). Improved OS using a 47% threshold was validated using a separate cohort of neoadjuvant-treated PDACs (72% vs 36%,  $P < .001$ ). By multivariate analysis, a reduction in tumor size by 47% was an independent prognostic factor for improved OS ( $P = .007$ ).

**CONCLUSIONS:** The difference in tumor size between preoperative EUS imaging and postoperative pathology among neoadjuvant-treated PDAC patients is an important prognostic indicator and may guide subsequent chemotherapeutic management.

## Keywords

Pancreas; Prognosis; Cancer; Diagnosis; Survival; Size; Stage; Treatment

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer deaths in the United States and is associated with a dismal 5-year survival rate of only 9%.<sup>1</sup> Currently, combined surgical intervention and adjuvant therapy offer potential for cure. However, only 10%–20% of patients have resectable disease at the time of diagnosis. In addition, nearly half of all patients undergoing curative-intent pancreatectomy fail to complete systemic treatment because of postoperative complications.<sup>2</sup> This has led to an increased emphasis on the use of neoadjuvant therapy as a strategy to treat PDAC patients. Neoadjuvant therapy has multiple potential benefits including treatment of occult micrometastases, better compliance with chemotherapy, increased margin-negative resection rates, downstaging of nodal disease, and improved patient operability and performance status to receive adjuvant treatment.<sup>3–6</sup> The assessment of responsiveness to chemotherapy can also aid in deciding a subsequent adjuvant treatment regimen. Nevertheless, determining therapeutic response after neoadjuvant treatment and pancreatectomy for PDAC has been an ongoing challenge.

In the past decade, several studies have attempted to define an optimal method of posttreatment evaluation. The fundamental premise has been to identify objective markers of response that correlate with an improvement in overall survival (OS). For example, an estimation of tumor burden from pretreatment and posttreatment abdominal imaging scans has been examined. However, the major obstacle with abdominal imaging such as multidetector computed tomography (MDCT) scans is the inability to accurately measure the size of PDAC.<sup>7,8</sup> Furthermore, the diagnostic performance of MDCT is reported to be reduced after neoadjuvant therapy.<sup>9</sup> Radiographic response data also correlate poorly with OS. In contrast, a reduction in serum tumor markers such as carbohydrate antigen 19-9 (CA19-9) has demonstrated significant promise. We have previously reported that a reduction in CA19-9 by 85% after neoadjuvant therapy is associated with 2-fold increase in patient survival.<sup>10</sup> The limitations of serum CA19-9 are its elevation in benign pancreatobiliary diseases, such as cholangitis, obstructive jaundice, and pancreatitis, and normal levels in up to 10% of PDAC patients who are Lewis antigen negative.<sup>11</sup> Finally, grading of pathologic treatment response by histologic examination is often considered subjective because the amount of tumor present before neoadjuvant therapy is uncertain.<sup>12</sup> Thus, alternative indicators of neoadjuvant response are required to determine the effectiveness of treatment after surgery.

Endoscopic ultrasound (EUS) is one of the most sensitive imaging modalities of the pancreas and is considered to be more accurate than MDCT in the detection of PDAC and staging of local disease.<sup>13–16</sup> In addition, combined with fine-needle aspiration (FNA), pancreatic EUS-FNA can obtain tissue samples for pathologic examination to confirm the presence of PDAC. Considering the high sensitivity of EUS in detecting PDAC, we hypothesized that tumor size measurements, specifically the greatest dimension, that are based on EUS findings closely approximated those obtained by pathology on treatment-naïve postsurgical specimens, and that determining the difference in tumor size between

preoperative EUS and postoperative pathology after neoadjuvant therapy may represent an improved method of evaluating treatment response. Therefore, the aims of this study were to (1) ascertain the concordance of unidimensional tumor size between preoperative EUS imaging and postoperative pathology in treatment-naïve PDAC patients, (2) determine whether tumor size differences between preoperative EUS and postoperative pathology after neoadjuvant therapy correlate with OS, and (3) identify the prognostic significance of changes in tumor size after treatment in conjunction with other clinicopathologic variables.

## Methods

### Study Design and Case Selection

The study design is summarized in Figure 1 and was approved by the Institutional Review Board at the University of Pittsburgh (IRB# STUDY19070069). The study comprised 3 separate patient cohorts (Supplementary Material). First, the surgical pathology archives at the University of Pittsburgh Medical Center (UPMC) were queried for pancreatotomy specimens harboring PDAC between 2006 and 2016. Cases were cross-referenced with clinical, imaging, laboratory, treatment, and follow-up data obtained from patient paper and/or electronic medical records. Patient inclusion criteria included the following: pancreatotomy with curative intent, documentation of presence or absence of preoperative treatment, availability of preoperative EUS reports with corresponding images, postoperative gross pathology reports, availability of all H&E-stained slides for pathologic re-review, and follow-up OS data of at least 3 months. In total, 705 patients with a resected PDAC fulfilled the aforementioned criteria and consisted of 2 patient cohorts, 340 treatment-naïve and 365 neoadjuvant-treated PDAC patients. For validation purposes, a separate cohort of PDAC patients was queried from the UPMC surgical pathology archives between 2017 and 2019. Inclusion criteria were the same as those mentioned previously; however, treatment-naïve patients were excluded. Of note, in the 2-year timeframe, >90% of resected PDAC patients at UPMC received neoadjuvant therapy. This separate validation cohort consisted of 200 neoadjuvant-treated PDAC patients.

Individual patient medical records were reviewed to confirm that a pancreatic mass was identified by EUS (Figure 1A and B), a concurrent FNA was performed, and a diagnosis of PDAC was rendered by pathologic evaluation. The largest tumor dimension by EUS was recorded and designated as preoperative tumor size within this study. Both EUS images and reports were evaluated by at least 2 gastroenterologists. For postoperative pathologic specimens, gross pathology reports and corresponding H&E-stained slides were reviewed by at least 2 pathologists to document several pathologic features including the largest unidimensional tumor size. Of note, the UPMC Department of Pathology evaluates pancreatotomy specimens by using a standardized approach. Briefly, for specimens with a grossly identifiable mass (Figure 1C), macroscopic tumor size and other gross pathologic findings are correlated with histologic sections taken for microscopic assessment (Figure 1D and E). However, for cases with no grossly identifiable mass, the entire pancreatotomy specimen is systematically submitted for microscopic examination. Particular attention is made to carefully map sections taken of the pancreas such that the tumor size can be measured using corresponding H&E-stained slides. For PDAC cases that consist of a

single microscopic focus of adenocarcinoma, the largest linear dimension of the tumor is measured from an H&E-stained slide. If the tumor consists of multiple microscopic foci (multifocal distribution), the largest linear dimension that is involved by adenocarcinoma to include intervening fibrotic stroma and/or uninvolved tissue is used as tumor size.<sup>17</sup> This measurement excludes associated fibrosis/desmoplasia beyond the neoplastic cells.

In addition to tumor size, each pancreatectomy specimen was evaluated for tumor location, involvement of resection margins, lymphovascular invasion, perineural invasion, and regional lymph node metastases. Pathologic primary tumor classification (T-stage) and positive resection margins were determined according to the 8th edition of the American Joint Committee on Cancer (AJCC) Staging Manual.<sup>18</sup> Demographic data; tumor anatomic type (resectability criteria) based on a multidisciplinary consensus conference/clinic as per Society of Surgical Oncology/Society for Surgery of the Alimentary Tract/Americas Hepato-Pancreato-Biliary Association guidelines; serum CA19-9 levels with total bilirubin; chemotherapeutic regimens; and OS were extracted from the patient's medical record.<sup>19</sup> Serum CA19-9 levels were excluded from assessment if pretreatment serum CA19-9 was normal (<37 IU/mL) or if total bilirubin was elevated (>2 mg/dL) because hyperbilirubinemia may falsely elevate serum CA19-9.<sup>20</sup>

### Statistical Analysis

Chi-squared analysis or Fisher exact tests were used to compare categorical data, and Mann-Whitney *U* test was used to compare continuous variables. Tumor size and T-stage correlation between preoperative EUS imaging and postoperative pathology was calculated by Pearson correlation. Survival curves were constructed by using the Kaplan-Meier method, and differences between groups were evaluated by the log-rank test. OS was calculated from the date of surgery to the date of death and censored at the date of last follow-up. The prognostic significance of clinical and pathologic characteristics was determined by using univariate Cox regression analysis. Multivariate analyses of significant risk factors by univariate analysis were performed by using Cox proportional hazard regression to identify independent risk factors for OS. To determine the significance of confounding variables, multiple Cox proportional hazard regression models were evaluated by inclusion of non-confounding and confounding variables (Supplementary Table 2). All statistical analyses were performed by using the SPSS Statistical software, version 26 (IBM, Armonk, NY), and statistical significance was defined as *P* value <.05.

## Results

### Concordance Analysis of Unidimensional Tumor Size Between Preoperative Endoscopic Ultrasound Imaging and Postoperative Pathology

To determine the degree of concordance between preoperative EUS tumor size and postoperative pathologic tumor size, a cohort of 340 treatment-naive PDAC patients who underwent surgical resection with curative intent was evaluated (Table 1, Supplementary Material). EUS imaging revealed a tumor that measured 0.7–8.7 cm in greatest dimension (mean, 2.9 cm; median, 2.7 cm). In comparison, postoperative pathologic tumor size ranged from 1.0 to 13.0 cm (mean, 3.3 cm; median, 3.0 cm) and significantly correlated with

EUS tumor size ( $r = 0.726$ ,  $P < .001$ ) (Figure 2). However, pathologic tumor size was larger by a median of 0.4 cm when compared with EUS imaging for the same patient. Overall, 241 tumors (71%) were larger on the basis of pathology than EUS. The difference between these 2 measurements was 0.5 cm for 170 cases (50%), 1.0 cm for 244 cases (72%), and 1.5 cm for 290 cases (85%). Of note, there was no difference in tumor size for 29 cases (9%). On the basis of the AJCC 8th edition T-staging system, which is dependent on tumor size, the Pearson correlation coefficient between EUS T-staging and pathologic T-staging was 0.586 ( $P < .001$ ). A similar analysis was performed for MDCT but demonstrated a weaker correlation than EUS (Supplementary Figure 1). As expected, no correlation between preoperative EUS/MDCT and postoperative pathology was observed for 365 neoadjuvant-treated PDAC patients.

### Survival Analysis Based on Unidimensional Tumor Size Differences Between Preoperative Endoscopic Ultrasound Imaging and Postoperative Pathology After Neoadjuvant Treatment

Among the 365 PDAC patients who received neoadjuvant therapy, the AJCC pathologic T-staging system was prognostically significant for OS ( $P < .001$ ) (Figure 3A). Excluding 5 ypT0 patients as no deaths were reported during follow-up, the OS rates for ypT1, ypT2, and ypT3 patients at 3 years and 5 years were 46% and 31%, 38% and 16%, and 26% and 12%, respectively ( $P < .001$ ). Pretreatment and posttreatment serum CA19-9 levels were available for 232 patients (64%), and 78 patients (21%) had 85% decrease in serum CA19-9. The 3-year and 5-year OS rates for patients with 85% CA19-9 reduction were 55% and 32%, respectively, as compared with 29% and 16%, respectively, for patients with <85% CA19-9 reduction ( $P < .001$ ) (Figure 3B).

On the basis of a comparison of preoperative EUS and postoperative pathology, 114 tumors (31%) decreased, 194 tumors (53%) remained unchanged, and 57 tumors (16%) increased in T-stage. The OS rates at 3 years and 5 years for patients that decreased, remained unchanged, and increased in T-staging after treatment were 50% and 31%, 37% and 19%, and 34% and 16%, respectively ( $P = .003$ ). When combining patients with tumors that remained unchanged or increased T-stage after neoadjuvant therapy, a decrease in T-stage was associated with improved 3-year (50% vs 33%) and 5-year OS rates (31% vs 18%,  $P < .001$ ) (Figure 3C). Recursive partitioning was used to determine an optimal threshold for tumor size reduction (Supplementary Table 1). In this analysis, a cutoff of 47% was identified, and within the neoadjuvant cohort, 64 patients (18%) had a PDAC that decreased in size by 47%. Overall survival rates for patients with tumors that shrunk by 47% were 67% and 47% at 3 years and 5 years as compared with 32% and 16%, respectively, for patients with tumors that shrunk by <47%, remained the same size, or increased in size ( $P < .001$ ) (Figure 3D).

To validate the association between improved OS and either decreased T-stage or tumor size reduction by 47% after neoadjuvant therapy, a separate cohort of 200 neoadjuvant-treated PDAC patients was analyzed (Supplementary Material). Although patient follow-up for this validation cohort was insufficient to calculate 5-year OS rates, 3-year OS rates were longer for patients who experienced a decrease in T-stage after neoadjuvant therapy as compared



with patients whose tumors remained unchanged or increased in T-staging (66% vs 35%,  $P=.009$ ). Similarly, a reduction in tumor size by 47% after neoadjuvant therapy was associated with improved patient 3-year OS as compared with patients with tumors that shrunk by <47%, remained the same size, or increased in size (72% vs 36%,  $P<.001$ ) (Supplementary Figure 2).

### **Clinicopathologic Features and Prognostic Significance of Differences in Unidimensional Tumor Size Between Preoperative Endoscopic Ultrasound Imaging and Postoperative Pathology After Neoadjuvant Treatment**

By combining both neoadjuvant cohorts, a decrease in T-stage and tumor size reduction by 47% after neoadjuvant therapy were identified in 179 (32%) and 109 (19%) PDAC patients, respectively (Table 2). Statistically, patients with tumors that decreased in T-stage or shrunk by 47% were more likely to have received a 5-fluorouracil–based regimen and exhibit lower mean posttreatment serum CA19-9 levels ( $P<.05$ ). Upon pathologic examination, they were found to harbor neoplasms that were smaller in size, lower T-stage, lower histologic grade, less frequent perineural and lymphovascular invasion, lower N-stage, and less often with positive margins ( $P<.001$ ). Of note, a 47% decrease correlated with 85% serum CA19-9 response to neoadjuvant treatment ( $P=.014$ ).

Cox regression analysis for OS with respect to various clinicopathologic features is summarized in Table 3. By univariate analysis, shorter OS was associated with age, postoperative pathologic tumor size, ypT3 stage, poor/undifferentiated histologic grade, perineural and lymphovascular invasion, metastasis in 4 regional lymph nodes (ypN2), and positive resection margin(s) ( $P<.01$ ). In comparison, longer OS was associated with 85% CA19-9 response, decreased postoperative T-stage, 47% tumor size reduction, and receipt of adjuvant therapy ( $P<.01$ ). Multivariate analysis was used to determine the prognostic significance of decreased T-stage and 47% shrinkage in tumor size after neoadjuvant therapy and included patient age, poor/undifferentiated histologic grade, perineural invasion, lymphovascular invasion, ypN2, positive margin(s), 85% CA19-9 response, and adjuvant treatment status. A reduction in tumor size by 47% was an independent prognostic factor for improved OS ( $P=.007$ ), whereas a change in T-stage was not ( $P=.418$ ) (Supplementary Table 2).

## **Discussion**

Updated guidelines from the National Comprehensive Cancer Network (NCCN) not only suggest neoadjuvant therapy for borderline resectable PDAC patients but also emphasize the consideration for neoadjuvant therapy in patients with resectable PDAC.<sup>21</sup> Among resectable PDAC patients, barriers to complete neoadjuvant therapy are limited and include low patient compliance in accepting neoadjuvant therapy and an adverse drug reaction to neoadjuvant therapy. In addition, the NCCN guidelines recommend that patients who received neoadjuvant therapy should consider adjuvant treatment after pancreatectomy. As per the NCCN, “adjuvant treatment options are dependent on the response to neoadjuvant therapy and other clinical considerations.” Thus, determining the responsiveness of PDAC to neoadjuvant therapy can potentially aid in deciding whether the patient should continue

with a similar or different adjuvant treatment regimen. Herein we found neoadjuvant downstaging of the primary PDAC based on a decrease in tumor size between preoperative EUS imaging and postoperative pathology correlated with improved patient OS. Through recursive partitioning, a tumor size reduction of 47% or greater was established as an optimal cutoff for median OS. This 47% threshold was further validated in a separate cohort of neoadjuvant-treated PDAC patients and identified to be an independent prognostic indicator for improved OS.

There are many advantages to using differences in tumor size as a marker of neoadjuvant response. The standardized approach to the preoperative and postoperative evaluation of PDAC is to report tumor size along the long axis of the neoplasm. In addition, the recently revised AJCC 8th edition T-staging system for the prognostic classification of pancreatic exocrine neoplasms is based on the greatest dimension of the tumor.<sup>18</sup> Moreover, the general method of assessing tumor burden for solid neoplasms after therapy, especially for oncologic clinical trials, has been Response Evaluation Criteria in Solid Tumors (RECIST).<sup>22,23</sup> The basic principle of RECIST is to determine the change in a measurable primary tumor using a transaxial image such as those obtained by MDCT. However, RECIST assumes that tumors are spherical objects. As shown by Rezai et al<sup>24</sup> and Welsh et al,<sup>25</sup> PDAC is not spherical in shape, and as a result, RECIST may significantly overestimate tumor burden. Katz et al<sup>9</sup> applied RECIST criteria to MDCT images from 129 borderline resectable PDAC patients who received neoadjuvant therapy. The authors concluded that RECIST response did not associate with median OS and appeared to be of little clinical value. In comparison, high-resolution images by EUS are reported to be superior to MDCT in the detection of PDAC.<sup>26</sup> Within a prospective, observational cohort study of 80 patients with proven PDAC, the sensitivity of EUS and MDCT for detecting a pancreatic mass was 98% and 86%, respectively.<sup>27</sup> Furthermore, for tumors  $\geq 2.0$  cm, the sensitivity of MDCT is reported to decrease to between 68% and 77%, whereas the sensitivity of EUS remains at  $>95\%$ .<sup>28</sup> Although previous studies have not evaluated the accuracy of EUS in measuring tumor size, our findings demonstrate that the discrepancy between EUS and pathology was limited to  $\leq 1.0$  cm for most cases. Upon applying these measurements to the AJCC T-staging classification system, the Pearson correlation coefficient yielded a moderate association between preoperative EUS imaging and postoperative pathology for treatment-naïve PDAC patients. In comparison, a weaker correlation was observed between MDCT and postoperative pathology. Hence, within this study, tumor size measurements based on EUS imaging rather than MDCT were used as a baseline to gauge neoadjuvant response.

Grading of response to treatment by using unidimensional differences in tumor size alone also has its disadvantages. PDAC is tridimensional and ill-defined and has irregular margins. Alternatively, volumetric and functional imaging studies have been proposed as methods of assessing treatment response. However, the preoperative volumetric quantification of tumor size can be difficult and time-consuming and is not widely available.<sup>24,29</sup> Functional imaging studies, such as fluorodeoxyglucose positron emission tomographic techniques, can exhibit false-negative and false-positive results.<sup>30</sup> For example, hyperglycemia and inflammation of the pancreatic gland itself can lead to reduced fluorodeoxyglucose uptake through competitive inhibition.<sup>31,32</sup> False-negative cases may also occur in colloid



carcinomas because of tissue hypocellularity and in necrotic neoplasms. In contrast, PDACs in proximity to areas of high physiological uptake such as the ampulla can lead to erroneous measurements.<sup>31</sup>

In addition, changes in tumor size do not account for reported pathologic features associated with treatment response, such as loss of tumor cells with retention of desmoplastic stroma, acellular mucin pools, and necrosis.<sup>33</sup> However, the histologic distinction between desmoplasia and fibrosis as a result of obstructive chronic pancreatitis can be problematic. Similar difficulties exist in determining whether the presence of acellular mucin pools is indicative of treatment response or extrusion from an associated intraductal precursor neoplasm, such as an intraductal papillary mucinous neoplasm or pancreatic intraepithelial neoplasia. It should also be noted that current histologic grading schemes for treated PDAC are subjective for percentage of tumor destruction, residual viable tumor cells, and radiation-induced fibrosis and regressive changes.<sup>12,34–37</sup> Moreover, applying these pathologic systems has not consistently demonstrated statistical significance with respect to OS.<sup>38</sup>

It is worth noting that there are several limitations to our study. Although it represents one of the largest series of neoadjuvant-treated PDAC to be prognostically analyzed for markers of therapeutic response, our study is retrospective in design and may suffer from surgical selection bias. In addition, not all patients were treated with the same neoadjuvant regimen or protocol, and no standardized approach was used to determine operability. Similarly, this study did not control for adjuvant therapy. The treatment of PDAC represents a formidable challenge, and a uniform method of management for all patients or at least a significant subset of patients has yet to be defined. Nevertheless, patients seen at our institution are routinely evaluated within a pancreatic cancer-focused clinic, and therapeutic decisions are based on a multidisciplinary approach to consider opinions from several specialties that include gastroenterology, radiology, oncology, radiation oncology, surgery, pathology, and others.<sup>39</sup> Another issue with our study is the inherent operator dependence of EUS imaging and interobserver variability of pathologic evaluation.<sup>40</sup> To minimize the subjectivity of using both modalities, it would be ideal to use a single assay to determine differences in tumor size before and after treatment. However, repeat EUS imaging is not typically performed once a diagnosis of PDAC has been rendered, and to our knowledge, a comprehensive study evaluating the role of EUS imaging after neoadjuvant therapy has not been reported. Preoperative pathologic evaluation would certainly be the gold standard; however, this is not technically feasible. Therefore, a comparison of preoperative EUS imaging and postoperative pathology currently represents a widely available and generalizable option to assess therapeutic response among neoadjuvant-treated PDAC patients.

In summary, our study demonstrates that changes in unidimensional tumor size can be a useful marker in predicting patient OS after neoadjuvant therapy and pancreatectomy. Through recursive partitioning, an optimal cutoff of 47% tumor size reduction achieved the greatest difference in median OS and was validated in a separate cohort of neoadjuvant-treated PDAC patients. In addition, a decrease in tumor size by 47% after treatment correlated with several favorable prognostic findings, such as 85% serum CA19-9 response, and was an independent prognostic indicator for improved OS. Although

additional studies are required, incorporating preoperative EUS and postoperative pathologic tumor size measurements into the standard evaluation of neoadjuvant-treated PDAC patients may guide subsequent management in the adjuvant setting.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Abbreviations used in this paper:

<b>AJCC</b>	American Joint Committee on Cancer
<b>CA19-9</b>	carbohydrate 19-9
<b>EUS</b>	endoscopic ultrasound
<b>FNA</b>	fine-needle aspiration
<b>MDCT</b>	multidetector computed tomography
<b>NCCN</b>	National Comprehensive Cancer Network
<b>OS</b>	overall survival
<b>PDAC</b>	pancreatic ductal adenocarcinoma
<b>UPMC</b>	University of Pittsburgh Medical Center

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## What You Need to Know

### Background

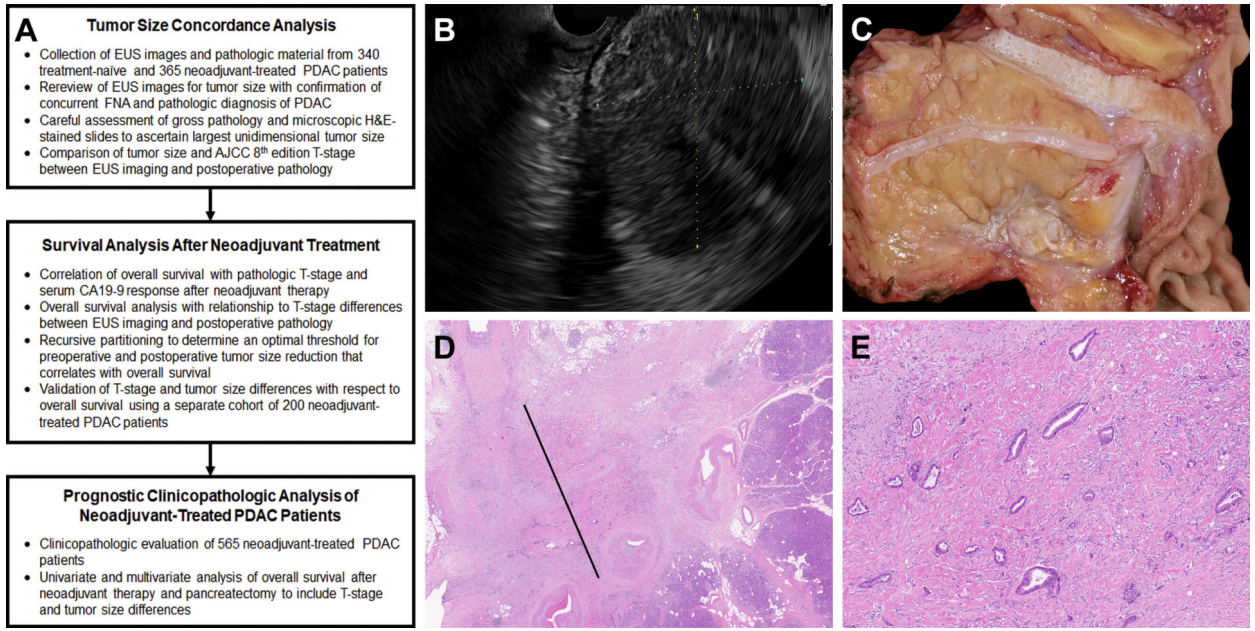
The assessment of treatment response after neoadjuvant therapy and pancreatectomy for PDAC can be a useful indicator for prognosis and further management. However, several limitations to current grading systems necessitate the identification of additional markers of response.

### Findings

Through systematic analysis of preoperative EUS imaging and postoperative pathologic specimens of 565 neoadjuvant-treated PDAC patients, tumor size reduction of 47% correlated with improved overall survival and was an independent, positive prognostic factor.

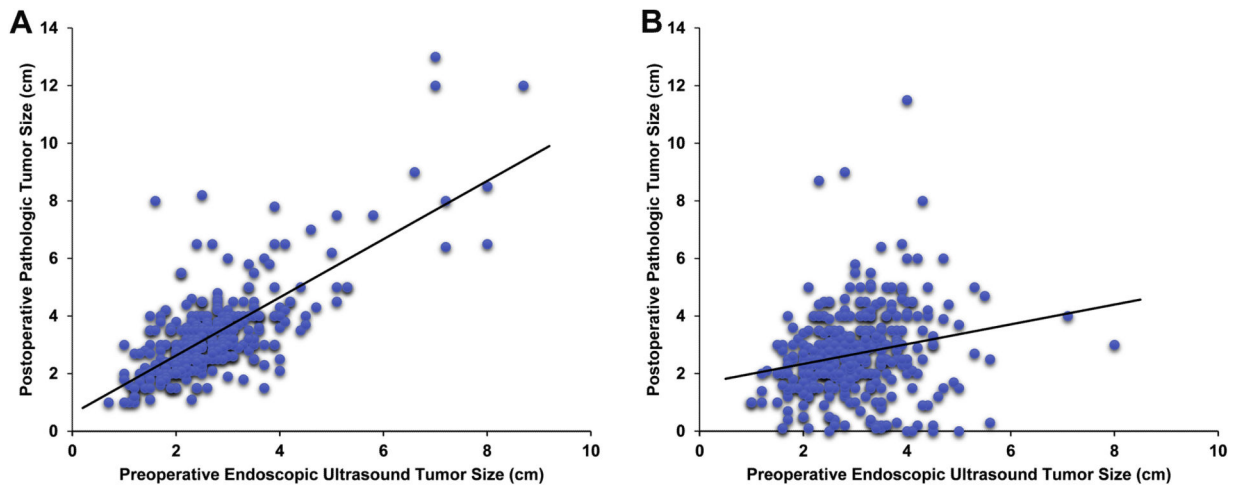
### Implications for patient care

Incorporating tumor size differences between preoperative EUS and postoperative pathology into the standard evaluation of PDAC after neoadjuvant therapy and pancreatectomy can potentially improve the prognostic stratification and adjuvant treatment of patients.



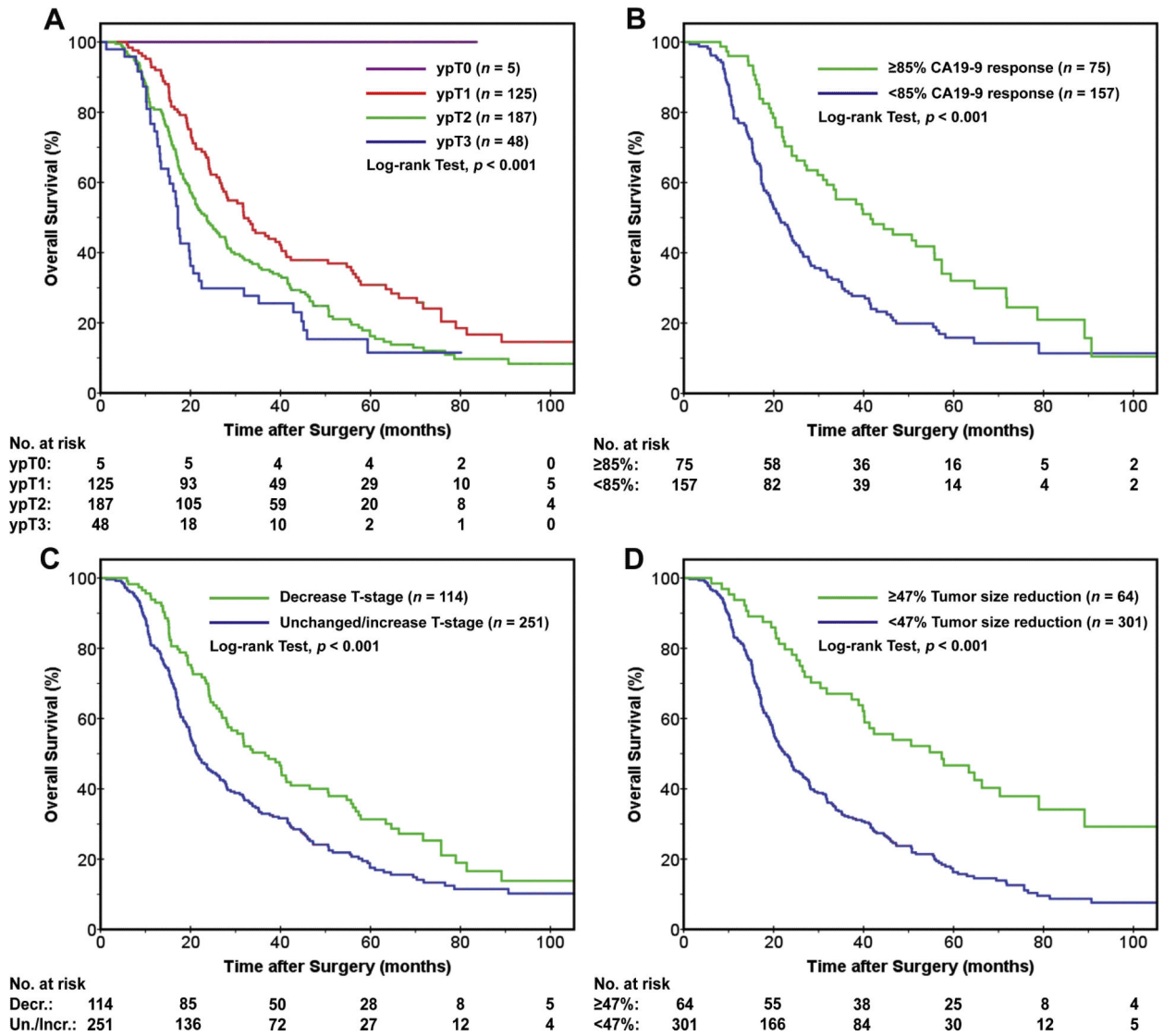
**Figure 1.** Summary of study design (A) and methodology used to evaluate 905 pancreatic ductal adenocarcinoma (PDAC) patients. (B) Within this example, a 54-year-old woman presented with a 2.6-cm pancreatic ductal adenocarcinoma by endoscopic ultrasound (EUS). (C and D) After neoadjuvant FOLFIRINOX and pancreatectomy, the adenocarcinoma grossly measured 1.2 cm; however, microscopically it measured 0.3 cm in greatest dimension. AJCC, American Joint Committee on Cancer; CA19-9, carbohydrate 19-9; FNA, fine-needle aspiration.





**Figure 2.**

Tumor size concordance analysis between preoperative EUS imaging and postoperative pathology. (A) Among 340 treatment-naive PDACs, the Pearson correlation between preoperative EUS imaging and postoperative pathology was 0.726 ( $P < .001$ ). (B) For 365 neoadjuvant-treated PDACs, the association between EUS imaging and pathology was weaker ( $r = 0.214$ ,  $P < .001$ ). *Solid line* indicates linear regression relationship. EUS, endoscopic ultrasound; PDAC, pancreatic ductal adenocarcinoma.



**Figure 3.** Kaplan-Meier curves comparing OS for 365 PDAC patients after neoadjuvant treatment and pancreatectomy. Consistent with prior studies, (A) pathologic T-stage (American Joint Committee on Cancer 8th edition) and (B) 85% serum CA19-9 response (n = 232) were statistically significant ( $P < .001$ ). (C) Similarly, evaluation of preoperative EUS imaging and postoperative pathology revealed a decrease in T-stage was associated with improved OS as compared with a T-stage that remained unchanged or increased ( $P < .001$ ). (D) OS for patients with tumors that shrunk by  $\geq 47\%$  in tumor size was improved as compared with patients with tumors that shrunk by  $< 47\%$ , remained the same size, or increased in size ( $P < .001$ ). CA19-9, carbohydrate 19-9.

**Table 1.** Clinicopathologic Features of 340 Treatment-Naive and 365 Neoadjuvant-Treated PDAC Patients

Patient/tumor characteristics	Treatment-naive cohort (n = 340, 48%, n (%))	Neoadjuvant treated cohort (n = 365, 52%, n (%))	P value
Gender			
Female	167 (49)	185 (51)	.706
Male	173 (51)	180 (49)	
Median age (range), y	70.5 (21–90)	65.0 (34–89)	<.001
Location			
Head/neck/uncinate	248 (73)	276 (76)	.438
Body/tail	92 (27)	89 (24)	
EUS median tumor size (range), cm	2.5 (0.7–8.7)	2.9 (1.0–8.0)	<.001
Primary tumor (cT), by EUS			
cT1	85 (25)	50 (14)	.001
cT2	228 (67)	276 (76)	
cT3	27 (8)	39 (11)	
Pathologic median tumor size (range), cm	3.0 (1.0–13.0)	2.5 (0–11.5)	<.001
Primary tumor (pT), by pathology			
(y)pT0	0 (0)	5 (1)	<.001
(y)pT1	53 (15)	125 (34)	
(y)pT2	230 (68)	187 (51)	
(y)pT3	57 (17)	48 (14)	
Histologic grade			
Well/moderately differentiated	240 (71)	273 (75)	.236
Poorly differentiated/undifferentiated	100 (29)	92 (25)	
Perineural invasion	307 (90)	288 (79)	<.001
Lymphovascular invasion	249 (73)	244 (67)	.071
Regional node (pN), by pathology			
(y)pN0	110 (32)	136 (37)	.061
(y)pN1	117 (34)	137 (38)	
(y)pN2	113 (34)	92 (25)	
Positive margin(s)	129 (38)	135 (37)	.816

EUS, endoscopic ultrasound; PDAC, pancreatic ductal adenocarcinoma.

**Table 2.** Clinicopathologic Features of 565 Neoadjuvant-Treated PDAC Patients With Respect to Changes in T-Stage and Tumor Size

Patient/tumor characteristics	Unchanged/increased T-stage (n = 386, 68%), n (%)	Decreased T-stage (n = 179, 32%), n (%)	P value	<47% Tumor size reduction (n = 456, 81%), n (%)	47% Tumor size reduction (n = 109, 19%), n (%)	P value
Gender						
Female	186 (48)	93 (52)	.417	221 (48)	58 (53)	.395
Male	200 (52)	86 (48)		235 (52)	51 (47)	
Mean age (range), y	65.1 (35–85)	64.3 (34–85)	.534	65.4 (35–85)	62.5 (34–85)	.006
Location						
Head/neck/uncinate	287 (74)	150 (84)	.013	350 (77)	87 (80)	.527
Body/tail	99 (26)	29 (16)		106 (23)	22 (20)	
EUS mean tumor size (range), cm	2.7 (1.0–5.5)	3.2 (2.1–8.0)	<.001	2.8 (1.0–7.1)	3.3 (1.4–8.0)	<.001
Primary tumor (cT), by EUS						
cT1	88 (23)	0 (0)	<.001	74 (16)	14 (13)	<.001
cT2	282 (73)	144 (80)		354 (78)	72 (66)	
cT3	16(4)	35 (20)		28 (6)	23 (21)	
Neoadjuvant chemotherapy <sup>a</sup>						
Gemcitabine-based	265 (69)	103 (58)	.022	310 (68)	58 (53)	.008
5-Fluorouracil based	104 (27)	69 (39)		126 (28)	47 (43)	
Both	17(4)	7(3)		20 (4)	4(4)	
Combined neoadjuvant chemoradiation	57 (15)	21 (12)	.361	63 (14)	15 (14)	1.000
85% CA19-9 response <sup>b</sup>	55 (29)	38 (40)	.084	68 (29)	25 (48)	.014
Mean pathologic tumor size (range), cm	3.1 (0.1–11.5)	1.4 (0.0–4.0)	<.001	2.9 (0.8–11.5)	0.9 (0.0–4.0)	<.001
Primary tumor (pT), by pathology						
ypT0	0(0)	8(4)	<.001	0(0)	8(7)	<.001
ypT1	58 (15)	154 (86)		116 (26)	96 (88)	
ypT2	259 (67)	17(10)		271 (59)	5(5)	
ypT3	69 (18)	0(0)		69 (15)	0(0)	
Histologic grade						
Well/moderately differentiated	288 (75)	151 (84)	.009	347 (76)	92 (84)	.073
Poorly differentiated/undifferentiated	98 (25)	28 (16)		109 (24)	17(16)	

Patient/tumor characteristics	Unchanged/increased T-stage (n = 386, 68%), n (%)	Decreased T-stage (n = 179, 32%), n (%)	P value	<47% Tumor size reduction (n = 456, 81%), n (%)	47% Tumor size reduction (n = 109, 19%), n (%)	P value
Perineural invasion	343 (89)	117 (65)	<.001	409 (90)	51 (47)	<.001
Lymphovascular invasion	291 (75)	89 (50)	<.001	336 (74)	44 (40)	<.001
Regional node (pN), by pathology						
ypN0	114 (30)	96 (54)	<.001	142 (31)	68 (62)	<.001
ypN1	152 (39)	57 (32)		176 (39)	33 (30)	
ypN2	120 (31)	26 (14)		138 (30)	8(7)	
Positive margin(s)	182 (47)	55 (31)	<.001	211 (46)	26 (24)	<.001
Received adjuvant therapy <sup>b</sup>	264 (69)	115 (65)	.329	313 (70)	66 (61)	.107

CA19-9, carbohydrate antigen 19-9; EUS, endoscopic ultrasound; PDAC, pancreatic ductal adenocarcinoma.

<sup>a</sup>Based on 557 patients (99%) with available adjuvant therapy data.

<sup>b</sup>Based on 284 patients (50%) with available pretreatment and posttreatment CA19-9 serum levels.

**Table 3.** Univariate and Multivariate Cox Regression Analysis of Overall Survival for 565 Neoadjuvant-Treated PDAC Patients

Patient/tumor characteristics	Univariate analysis			Multivariate analysis model 1			Multivariate analysis model 2		
	Hazard ratio (95% CI)	P value		Hazard ratio (95% CI)	P value		Hazard ratio (95% CI)	P value	
Gender, female (ref) vs male	1.136 (0.924–1.396)	.225							
Age, y	1.016 (1.005–1.027)	.003		1.007 (0.995–1.020)	.264		1.005 (0.992–1.018)	.455	
Location, body/tail (ref) vs head/neck/uncinate	1.209 (0.942–1.552)	.136							
EUS tumor size, cm	0.941 (0.842–1.052)	.287							
EUS T-stage, cT1/cT2 (ref) vs cT3	0.675 (0.451–1.010)	.056							
Neoadjuvant treatment, <sup>a</sup> Gem-based (ref) vs 5-FU based	0.797 (0.627–1.013)	.064							
Pathologic tumor size, cm	1.229 (1.155–1.309)	<.001							
Pathologic T-stage, ypT0/ypT1/ypT2 (ref) vs ypT3	1.633 (1.168–2.285)	.004							
Histologic grade, well/moderate (ref) vs poor/undiff	1.943 (1.541–2.451)	<.001		1.645 (1.216–2.225)	.001		1.668 (1.232–2.257)	.001	
Perineural invasion, absence (ref) vs presence	2.238 (1.661–3.015)	<.001		1.790 (1.197–2.678)	.005		1.530 (1.013–2.310)	.043	
Lymphovascular invasion, absence (ref) vs presence	1.747 (1.383–2.207)	<.001		1.134 (0.796–1.617)	.486		1.101 (0.774–1.567)	.591	
Lymph node metastasis, ypN0/ypN1 (ref) vs ypN2	1.764 (1.409–2.207)	<.001		1.637 (1.212–2.212)	.001		1.661 (1.231–2.242)	.001	
Resection margin(s), negative (ref) vs positive	1.704 (1.385–2.097)	<.001		1.414 (1.069–1.871)	.015		1.482 (1.119–1.964)	.006	
CA19-9 response, <sup>b</sup> <85% (ref) vs 85%	0.560 (0.412–0.762)	<.001		0.630 (0.460–0.864)	.004		0.639 (0.466–0.876)	.005	
T-stage, unchanged/increase (ref) vs decrease	0.625 (0.496–0.789)	<.001		0.882 (0.651–1.195)	.418				
Decrease in tumor size, <47% (ref) vs 47%	0.385 (0.280–0.529)	<.001					0.554 (0.359–0.853)	.007	
Adjuvant therapy, <sup>c</sup> did not receive (ref) vs did not receive	0.575 (0.461–0.716)	<.001		0.397 (0.296–0.532)	<.001		0.410 (0.305–0.549)	<.001	

5-FU, 5-fluorouracil; CI, confidence interval; EUS, endoscopic ultrasound; Gem, gemcitabine; PDAC, pancreatic ductal adenocarcinoma; ref, reference.

<sup>a</sup>Excludes 24 patients (4%) who received both gemcitabine and 5-fluorouracil based neoadjuvant therapy.

<sup>b</sup> Pretreatment and posttreatment serum CA19-9 levels were available for 284 patients (50%).

<sup>c</sup> Adjuvant treatment data were available for 557 patients (99%).