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Original Contribution

# Measured residual tumor cellularity correlates with survival in neoadjuvant treated pancreatic ductal adenocarcinomas

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## 1. Introduction

Pancreatic cancer is the 3rd most common cause of cancer related death in the United States. The 5-year survival rate is only 8% because the majority of patients present with advanced stage disease [1]. The only potentially curative option for therapy is surgical resection with negative margins. However, only approximately 15% of patients have a resectable tumor at the time of presentation [2]. Neoadjuvant therapy has been increasingly used, especially in patients with borderline resectable pancreatic tumors [3-7]. Neoadjuvant therapy may provide some benefit for patients with borderline resectable tumors, but its value in patients with resectable pancreatic cancer remains unclear [8]. Studies have shown a lower incidence of positive surgical resection margins and reduced lymph node involvement after neoadjuvant therapy [9]. Neoadjuvant therapy causes distinctive cytomorphologic changes in tumor cells, increased stromal fibrosis, and decreased neoplastic cellularity [10].

Several systems to grade tumor regression for pancreatic ductal adenocarcinomas (PDACs) resected after neoadjuvant therapy have been described. The most frequently used systems are: the Evans system [11], College of American Pathologists (CAP) system [12], and the MD Anderson system [13]. These grading systems are primarily based on the ratio of residual neoplastic cells to stroma within resected tumors. Unfortunately, the CAP and Evans systems use numeric grading schemes which are inverted with respect to one another. In the CAP system, a low grade indicates a good treatment response, whereas in the Evans system it indicates a poor response.

Studies evaluating the relationship of tumor regression grades to patient survival have shown conflicting results. Breslin et al. demonstrated no significant relationship between the Evans grade and patient survival [6]. White et al. showed a significant difference in overall survival between Evans grade I tumors and grouped Evans grade II through IV tumors [14]. Chuong et al. also showed a significant difference in overall and progression free survival between patients with Evans grade I tumors and grouped patients with Evans grades IIa through IV tumors. They also found that the CAP system had no significant relationship with overall or progression free survival [15]. Chatterjee et al. showed that patients with no viable residual tumor cells have better disease-free survival than those with viable residual tumor cells. However, they did not find significant differences in survival between patients with CAP grades 2 and 3 or Evans grades I, IIa, or IIb tumors. The study by Chatterjee et al. demonstrated that patients with tumors having $< 5\%$ viable residual tumor (which they designated HTRG 1) had significantly better disease-free survival and overall survival than patients with tumors having $\geq 5\%$ viable residual tumor (which they designated HTRG 2) [13]. More recently, the same group applied the same tumor regression grading system (MD Anderson System) to another cohort of 167 patients and showed that the HTRG 0 (no residual tumor cells) and HTRG 1 groups had significantly longer disease-free survival and overall survival than the HTRG 2 group [16]. Reproducibility is an issue as the cut off of 5% viable residual tumor was determined based upon visual estimation by surgical pathologists, not by objective measurement.

In light of these promising but inconsistent findings, multiple groups have noted significant difficulties in the practical application of tumor regression systems. First, some of the systems are based on the percentage of residual tumor cells present in relation to the original tumor cellularity. This is based upon an assumption that the cellularity of the pretreated tumor is known, which is rarely the case. Second, some of the systems define grades by precise cellularity cutoffs. Yet, all studies have been based on subjective, visual estimates of tumor cellularity and no study to date has objectively measured the cellularity of post neoadjuvant therapy pancreatic cancers. Third, some of the systems rely on determination of the viability of neoplastic cells based on histomorphology, another subjective assessment which has been challenged [17-19]. Due to this subjectivity, a recent study by Kalimuthu et al. showed that the interobserver reproducibility of the three most common grading systems is low [20].

The aim of the current study was to assess the prognostic significance of residual neoplastic cellularity in tumors resected after neoadjuvant therapy. We measured residual tumor cellularity using a more objective and reproducible measurement approach than has been reported in other studies. We also evaluate the previously described tumor regression grading systems in our patient cohort and assess their

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prognostic value and relationship with residual neoplastic cellularity. We assessed tumor neoplastic cellularity in patients who underwent pancreas resection without prior neoadjuvant therapy (naïve tumors) to provide a baseline for comparison.

## 2. Materials and methods

### 2.1. Patient selection and follow-up

This is a retrospective study of 91 patients who underwent pancreaticoduodenectomy or distal pancreatectomy for pancreatic ductal adenocarcinoma (PDAC) between 2009 and 2015 at Froedtert and the Medical College of Wisconsin, Milwaukee, WI. 76 of the patients received neoadjuvant therapy prior to resection and 15 had resection without neoadjuvant therapy. Of the patients who underwent neoadjuvant therapy, 46 had neoadjuvant chemoradiation and 30 had neoadjuvant chemotherapy alone. 40 of the patients with neoadjuvant chemoradiation were treated with gemcitabine for 6 weeks and radiation. The remaining six patients were treated with a six-week course of capecitabine and radiation. Follow-up and clinical information were obtained from patient medical records.

### 2.2. Tumor stage and regression grading

Hematoxylin and eosin stained slides from the cases were reviewed by D.R. and K.O. Each case was assigned CAP and Evans grades, and the originally assigned CAP grade was also recorded (when available). The CAP and Evans grades were assigned per the criteria in Table 1 [11,12]. American Joint Committee on Cancer (AJCC) 7th edition was used for T, N, and M staging [21]. For tumor size, gross measurement was used.

### 2.3. Measurement of residual tumor cellularity

The tumor slides for each case were reviewed and slides with representative cellularity were selected for each case by two pathologists (DR and KO). If a tumor had uniform cellularity, a single representative slide was selected for measurement. If a tumor had variable cellularity, slides to represent each different area were selected. The selected slides were scanned using a digital scanning system (NanoZoomer 2.0, Hamamatsu Photonics, Hamamatsu City, Japan). The tumor bed was defined as the area of fibrosis without residual non-neoplastic pancreatic structures including acini, ducts, or islet cells. The tumor bed and each individual focus of neoplastic cells (single cells, groups of cells, or glands) were outlined manually and areas were measured using NanoZoomer software (Fig. 1). The total area of neoplastic cells was calculated by adding the area of each group of neoplastic cells (or single cells). The lumina of dilated neoplastic glands were not included in total neoplastic cell area. The neoplastic cellularity was calculated as follows: total area of neoplastic cells ($mm^2$)/area of tumor bed ($mm^2$) × 100%.

### 2.4. Statistical analysis

Frequencies and medians with interquartile ranges (25th to 75th percentiles) are presented for categorical and continuous variables, respectively. Patient and tumor characteristics for patients treated with and without neoadjuvant therapy were compared using Wilcoxon rank-sum and Fisher's exact tests as appropriate. Neoplastic cellularity distributions were compared across tumor regression grades using Kruskal-Wallis test with Dunn's test for paired comparisons with Benjamini-Hochberg adjustment for multiplicity, after a significant global test. Kaplan-Meier survival curves were constructed for the entire sample and by cellularity level and were compared using log-rank test. The association between residual tumor cellularity and survival was also evaluated using univariate and multivariate Cox proportional hazards models. Interrater reliability was tested using the kappa statistic. Analysis was performed using Stata 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

## 3. Results

### 3.1. Clinical and gross data

Patient clinical information and tumor characteristics are summarized in Table 2. The gender distribution was 44 (48.4%) females and 47 (51.6%) males. The median age was 65.5 years (range, 43–87 years). Most patients had stage pT3 (70%) or pT2 (21%) tumors. Lymph node positivity was demonstrated in 49.5% of patients (pN1), while 50.5% of patients had negative lymph nodes (pN0). The median gross tumor size in patients with no neoadjuvant therapy was 3.7 (3–4) cm in greatest dimension and in patients with neoadjuvant therapy it was 3.0 (2–4) cm in greatest dimension ($p = 0.036$).

### 3.2. Tumor regression grading and histologic evaluation

The distribution of CAP grades among the 76 patients treated with neoadjuvant therapy was as follows: grade 0–0 patients (0%), grade 1–4 patients (5.3%), grade 2–26 patients (34.2%), and grade 3–46 patients (60.5%). The same patients were also graded by the Evans system as follows: grade I - 2 patients (2.6%), Evans grade IIa - 44 patients (57.9%), Evans grade IIb - 26 patients (34.2%), Evans grade III - 4 patients (5.3%) (Table 3). The originally assigned CAP tumor regression grade from the pathology report was available for 50 cases. Concordance of CAP grades between the original report and re-examination for this study was 72% ($\kappa = 0.49$, moderate agreement).

### 3.3. Cellularity of pancreatic cancers with neoadjuvant and without neoadjuvant therapy

The neoplastic cellularity of naïve tumors was 12.7 (8.2–30.7) % ($n = 15$) and 3.9 (1.7–7.9) % ($n = 76$) for tumors with neoadjuvant therapy. The residual tumor cellularity was significantly lower in patients who received neoadjuvant therapy ($p = 3.1 \times 10^{-6}$). The mean median neoplastic cellularity for tumors with CAP grades 1, 2, and 3 was: 0.4 (0.1–0.8) %, 1.5 (0.3–3.6) %, and 5.9 (3.9–11.2) %, respectively ($p < 0.001$). Despite the significant differences in cellularity distributions among the CAP regression grade groups, there was marked overlap in the range of cellularity among CAP grade groups as

**Table 1**
Evans and CAP tumor regression grading system criteria.

| Evans system | | CAP system | |
|---|---|---|---|
| Grade | Criteria | Grade | Criteria |
| 1 | < 10% tumor cell destruction | 0 | No viable cancer cells |
| 2a | Destruction of 10–50% of tumor cells | 1 | Single cells or rare small groups of cancer cells |
| 2b | Destruction of 51–90% of tumor cells | 2 | Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells |
| 3 | < 10% viable appearing tumor cells present | 3 | Extensive residual cancer with no evident tumor regression |
| 4 | No viable tumor cells present | | |

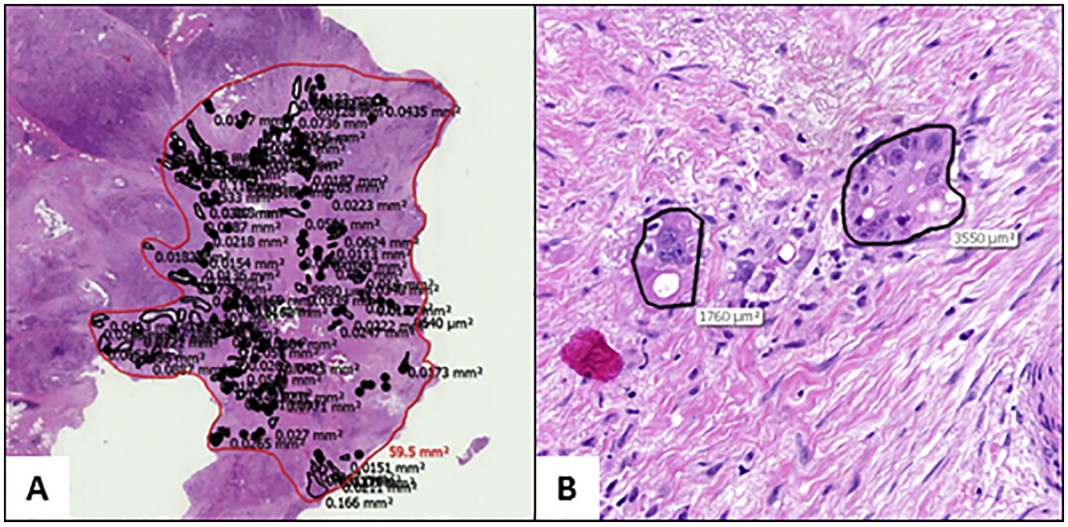


**Fig. 1.** Measurement of residual tumor cellularity.
A) Low power photograph showing tumor bed outlined in red. B) High-power photograph showing each group of tumor cells outlined in black.

**Table 2**
Patient and tumor characteristics for patients treated with and without neoadjuvant therapy N = 91.

| | Neoadjuvant | No neoadjuvant | Total | p-Value | Test |
|---|---|---|---|---|---|
| | N = 76 | N = 15 | N = 91 | | |
| Sex | | | | | |
| F | 40 (53%) | 4 (27%) | 44 (48%) | 0.091 | Fisher's exact |
| M | 36 (47%) | 11 (73%) | 47 (52%) | | |
| Age at diagnosis | 65.4 (58.4–70.4) | 66.6 (61.9–70.4) | 65.5 (59.8–70.4) | 0.65 | Wilcoxon rank-sum |
| T stage | | | | | |
| 1 | 7 (9%) | 0 (0%) | 7 (8%) | 0.76 | Fisher's exact |
| 2 | 16 (21%) | 3 (20%) | 19 (21%) | | |
| 3 | 52 (68%) | 12 (80%) | 64 (70%) | | |
| 4 | 1 (1%) | 0 (0%) | 1 (1%) | | |
| N stage | | | | | |
| No | 39 (51%) | 7 (47%) | 46 (51%) | 0.78 | Fisher's exact |
| Yes | 37 (49%) | 8 (53%) | 45 (49%) | | |

Data are presented as median (IQR) for continuous measures, and n (%) for categorical measures.

**Table 3**
Evans and CAP tumor regression grades for tumors with neoadjuvant therapy.

| | N | Measured cellularity | | | | | p-Value[a] |
|---|---|---|---|---|---|---|---|
| | | Median | 25th perc. | 75th perc. | Min | Max | |
| Evans grade | | | | | | | |
| I | 2 | 22.9 | 17.2 | 28.6 | 17.2 | 28.6 | < 0.001 |
| IIa | 44 | 5.7 | 3.8 | 9.8 | 0.3 | 41.9 | |
| IIb | 26 | 1.5 | 0.3 | 3.6 | 0.2 | 10.5 | |
| III | 4 | 0.4 | 0.1 | 0.8 | 0 | 1.1 | |
| NA | 15 | 12.7 | 8.2 | 30.7 | 2.4 | 52 | |
| Total | 91 | 4.9 | 2.1 | 10.3 | 0 | 52 | |
| CAP grade | | | | | | | |
| 1 | 4 | 0.4 | 0.1 | 0.8 | 0 | 1.1 | < 0.001 |
| 2 | 26 | 1.5 | 0.3 | 3.6 | 0.2 | 10.5 | |
| 3 | 46 | 5.9 | 3.9 | 11.2 | 0.3 | 41.9 | |
| NA | 15 | 12.7 | 8.2 | 30.7 | 2.4 | 52 | |
| Total | 91 | 4.9 | 2.1 | 10.3 | 0 | 52 | |

Note: All pairwise comparisons are statistically significant at 0.05 level using Benjamini-Hochberg adjustment for multiplicity.
[a] Kruskal-Wallis test.

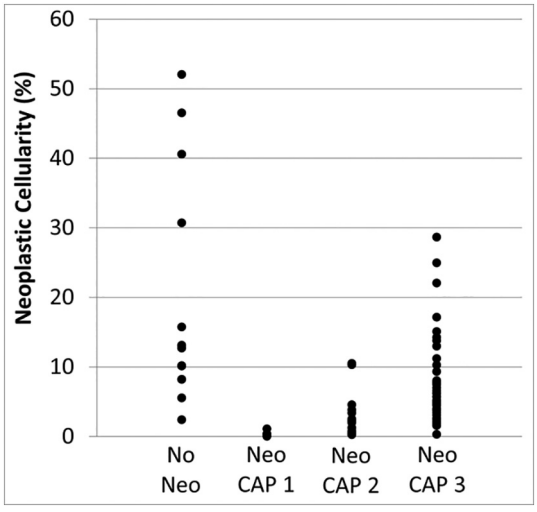


**Fig. 2.** Cellularity of tumors with no neoadjuvant therapy (No Neo) and with neoadjuvant therapy (Neo), separated by CAP tumor regression grade.

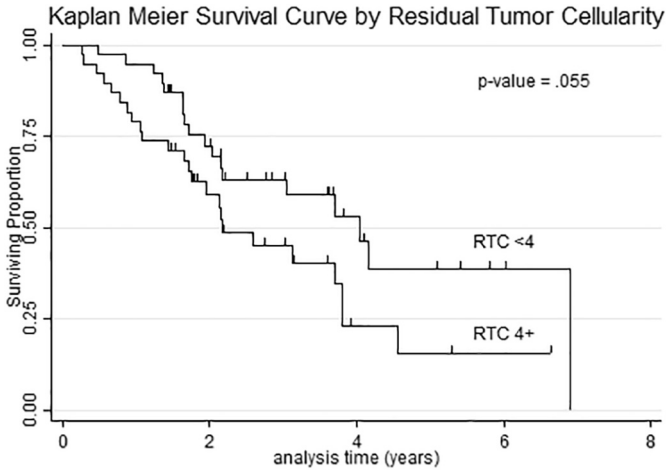


**Fig. 3.** Overall survival of patients with neoadjuvant treatment, based on residual tumor cellularity.

well as between neoadjuvant treated and non-neoadjuvant groups (Table 3, Fig. 2). Notably, the treatment naïve tumor group showed the widest range of tumor cellularity.

### *3.4. Tumor cellularity and patient survival among patients treated with neoadjuvant therapy*

Neoadjuvant tumors with a measured neoplastic cellularity of < 4% (n = 38, 50% of patients) had longer overall survival than those with a cellularity of 4 or > 4% (n = 38, 50% of patients, p = 0.055 by log-rank test) (Fig. 3). In the overall patient cohort, the CAP and Evans grades did not significantly correlate with overall survival (p = 0.608 and p = 0.798, respectively, Fig. 4). In the group of patients without neoadjuvant therapy, only one patient had a tumor neoplastic cellularity < 4%, therefore a similar survival analysis was not possible due to the limited sample size.

The estimated adjusted hazard ratio for patients with neoplastic cellularity ≥4% was nearly double (HR = 1.95, 1.01 to 3.77, p = 0.046–3.37) that of patients with residual tumor cellularity < 4% and this was adjusted for tumor stage (Table 4).

At the time of resection, 39 (51%) patients had no lymph node metastases and 37 (49%) had lymph node metastases. In lymph node positive patients, the CAP grade was associated with survival (p = 0.037) while Evans grade was not (p = 0.107). In lymph node negative patients, neither the CAP or Evans grades correlated with overall survival (p = 0.65 and 0.65, respectively). Lymph node positive patients with residual tumor cellularity of < 4% had significantly longer overall survival than those with residual tumor cellularity ≥4% (p = 0.020) (Fig. 5). However, in lymph node negative patients, survival did not significantly differ between patients with residual tumor cellularity of < 4% and those with neoplastic cellularity ≥4%, (p = 0.53).

## 4. Discussion

Several independent factors including lymph node status, resection margin status, and tumor size have prognostic significance in patients with surgically resected pancreatic cancer [2,22,23]. Multiple tumor regression grading systems have also been developed to describe tumor response to neoadjuvant therapy and to predict patient prognosis [11-13]. These tumor regression grading systems are largely based on the subjective evaluation of the relative amount of neoplastic cells and stroma after treatment [18]. However, development of tumor regression grading systems for PDAC has been a challenge because many naïve PDACs have low cellularity due to the dense desmoplastic stromal

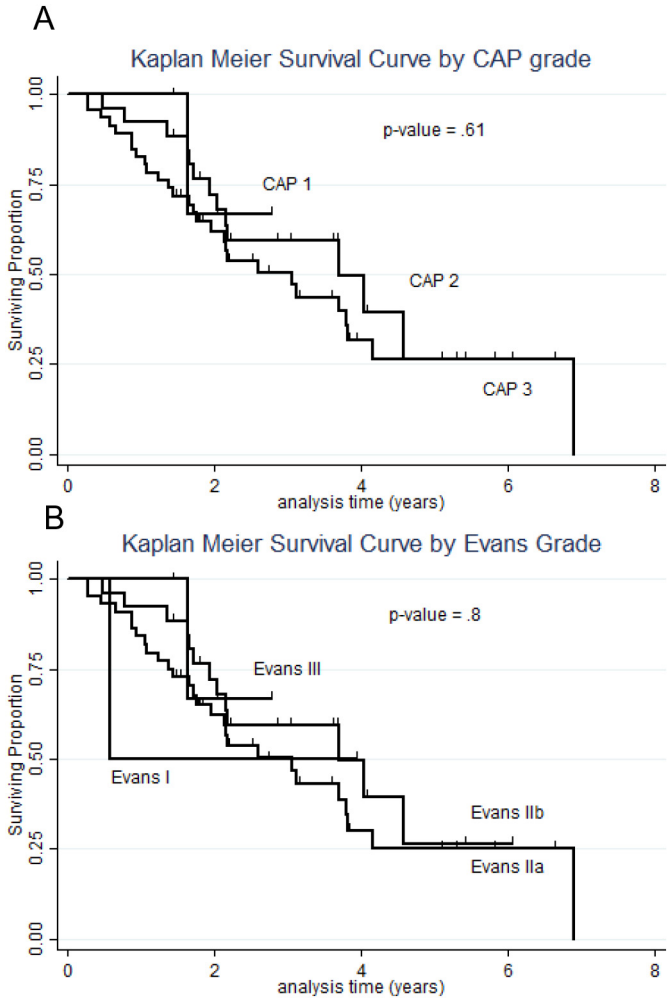


**Fig. 4.** Overall survival of patients with neoadjuvant treatment, based on CAP (A) and Evans classification (B).

reaction that is the hallmark of PDAC. Therefore, tumor regression grading systems which consider more than residual tumor cellularity alone have been developed. The Evans system takes cell viability into account and the CAP system considers the distribution of cells as single cells or rare small groups. Unfortunately, these findings are subjective and the reproducibility of these grading systems is low [17]. Furthermore, studies evaluating the prognostic significance of these systems have yielded conflicting results [6,13-16]. Recently, the MD Anderson group proposed a tumor regression grading system based entirely on residual tumor cellularity. This grading system correlates with disease free survival and overall survival [13,16]. However, the studies validating this system were based on visual estimation of whether a tumor has more or < 5% cellularity. In this study, we sought to evaluate the relationship between residual neoplastic cellularity and prognosis more objectively by using slide imaging software.

We show that tumors resected after neoadjuvant therapy have significantly smaller gross tumor size and lower measured neoplastic cellularity compared to treatment naïve PDACs. Neoadjuvant therapy was also associated with other morphologic changes which have been previously described [10]; hyperchromatic, pyknotic nuclei with irregular nuclear contours and more voluminous, vacuolated and densely eosinophilic cytoplasm. In cases with minimal residual tumor cells, it can be challenging to identify the rare atypical single cells embedded in dense fibrous stroma. The stroma also changes and typically becomes more prominent with increased fibrosis.

Intense desmoplastic stromal reaction is also a hallmark of

**Table 4**
Results of univariate and multivariate cox regression models for overall survival.

| | Number of patients who died/total number of patients | Univariate models | | Adjusted models | |
|---|---|---|---|---|---|
| | | Hazard ratio (95% confidence interval) | p-Value | Hazard ratio (95% confidence interval) | p-Value |
| TSR | | | | | |
| < 4 | 18/38 | 1.000 | | 1.000 | |
| 4+ | 24/38 | 1.827 [0.991,3.369] | 0.054 | 1.954 [1.012,3.772] | 0.046 |
| T stage | | | | | |
| I–II | 13/23 | 1.000 | | 1.000 | |
| III–IV | 29/53 | 1.024 [0.540,1.940] | 0.943 | 1.268 [0.627,2.562] | 0.509 |
| N stage | | | | | |
| No | 22/39 | 1.000 | | | |
| Yes | 20/37 | 1.148 [0.623,2.114] | 0.659 | | |
| PNI | | | | | |
| N | 17/28 | 1.000 | | | |
| Y | 25/48 | 1.081 [0.579,2.021] | 0.806 | | |
| LVI | | | | | |
| N | 34/62 | 1.000 | | | |
| Y | 8/14 | 1.082 [0.517,2.264] | 0.835 | | |
| *N* | | 76 | | 76 | |

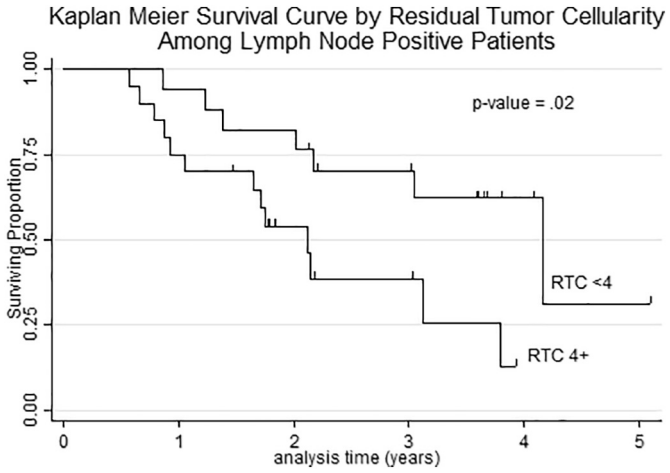


**Fig. 5.** Overall survival of lymph node positive patients with neoadjuvant treatment, based on residual tumor cellularity.

treatment naïve PDAC. Because of this, many naïve pancreatic cancers have low cellularity from the beginning and therefore low residual tumor cellularity itself may not necessarily indicate good treatment response. To evaluate the range of cellularity in treatment naïve PDAC we measured the tumor cellularity of 15 PDACs that were resected without prior neoadjuvant therapy. These naïve pancreatic cancers had a wide range of neoplastic cellularities (2.4 to 52.1%). This range was quite wide and should be kept in mind when assessing treatment response. Since pancreatic cancers are typically diagnosed by fine needle aspiration cytology, pre-treatment tumor cellularity is almost always unknown; therefore it is difficult to determine how much the tumor cellularity decreases after treatment.

Similar to treatment naïve PDAC, neoadjuvant treated carcinomas which were classified in CAP grades 2 and 3 also show a wide range of tumor cellularity (Fig. 2). This indicates that other than recognizing the extreme of single cells or rare small groups of residual cancer cells, estimation of tumor cellularity is highly subjective and unreliable. Kalimuthu et al. recently supported this finding by demonstrating poor concordance among four gastrointestinal pathologists using three major regression grading systems. Unanimous grading agreement was reached in only one of 14 cases included in their study [20].

In order to evaluate the relationship between tumor regression and patient outcome, we performed survival analysis on our entire cohort of neoadjuvant treated patients and stratified the patients based on CAP grade, Evans grade, and our current approach, measured residual neoplastic cellularity. We found that the CAP and Evans grades did not significantly correlate with survival, whereas measured residual tumor cellularity did significantly correlate with overall survival. Our analysis indicated that the best fit for the data was to group patients into two cohorts, those with tumors having 4% or greater neoplastic cellularity and those with < 4% neoplastic cellularity. This cutoff point also represents the median tumor cellularity of neoadjuvant treated tumors in our study and is near the 5% cutoff point used in the MD Anderson System [13,16]. Patients with tumors having a measured neoplastic cellularity of < 4% had on average longer survival than those with a measured cellularity of ≥4% ($p = 0.055$ by log-rank test). This survival difference was strongest among patients with lymph node positive disease ($p = 0.020$) and it was weak among patients without lymph node involvement ($p = 0.53$). Multivariate Cox regression model also showed that higher residual tumor cellularity (4+% vs < 4%) was associated with estimated 95% increase in risk of death ($p = 0.046$), although the confidence interval was wide due to the relatively small sample size. These findings support the use of residual tumor cellularity as a potential prognostic indicator in tumor regression grading systems.

The finding that characteristics of the primary tumor are more important in patients with lymph node metastasis was unexpected. Further investigation and validation of this finding in a different patient cohort is needed. A possible explanation for this finding is that patients with local disease are more likely to have a complete tumor resection, while patients with metastatic disease are more likely to have residual tumor (in other metastatic sites) after surgery, in which case the characteristics and treatment responsiveness of the residual tumor may have a greater impact on survival.

We acknowledge that the approach to measuring tumor cellularity used in our study is likely too labor intensive for routine use in practice, however our findings support the validity of tumor regression grading systems that are based entirely on measured residual neoplastic cellularity. After accounting for cellularity, none of the other tumor-related characteristics, such as T stage, Evans or CAP grade scores were statistically associated with survival in our models. Additionally, we acknowledge that the selection of representative slides for measurement introduced some level of subjectivity into our methods. However, when quantitative measurements are performed on large tumor resections it is usually impractical or impossible to evaluate the entire specimen and some selection must occur whether at the time of grossing or microscopic quantitation.

In conclusion, we show that there is significant variation in the tumor cellularity of treatment naive pancreatic cancers. This suggests that measurements of tumor cellularity after treatment to assess treatment response should be used with caution. Furthermore, we introduce an objective quantitative approach to measuring neoplastic cellularity that might correlate the best with overall survival after adjuvant therapy. The findings particularly support the use of cellularity-based tumor regression grading system, should be replicated in other cohorts. Finally, we found that the characteristics of the primary tumor are more important when lymph node metastases are present, a finding that will require further investigation.

## Conflicts of interest

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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