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The impact of changes in radiographic sarcopenia on overall survival in older adults undergoing different treatment pathways for pancreatic cancer

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ABSTRACT

Objective: Sarcopenia is associated with poor outcomes in patients undergoing surgery for pancreatic ductal adenocarcinoma (PDAC). However, few studies have assessed changes in sarcopenia during multimodality therapy or its effect on overall survival (OS).
Methods: Computed tomography (CT) total psoas area index (TPAI) and weighted average Hounsfield units (HU) were measured at each treatment interval in patients with resectable PDAC. Four cohorts were compared: 1. Neoadjuvant chemotherapy plus surgery plus adjuvant chemotherapy ("NSA"; n = 20); 2. surgery plus adjuvant chemotherapy ("SA"; n = 20); 3. neoadjuvant chemotherapy with intent to perform surgery ("Chemotherapy"; n = 24); and 4. treated with palliative intent ("Palliative"; n = 21).
Results: Fifty-nine deaths were identified. Median OS was 15.7 months (95% Confidence Interval (CI) 12.7–20.2). Patients who underwent surgery had a higher OS ($p < 0.001$), with the SA group having a longer OS than the NSA group. Cox regression models identified baseline TPAI (Hazard Ratio (HR) = 0.82; $p = 0.04$), but not psoas HU, as a significant predictor of OS. The mean decrease in TPAI following neoadjuvant chemotherapy was 0.6 cm2/m2 ($p < 0.001$; 95% CI −0.8–−0.3) and the mean decrease in HU was 2.7 ($p = 0.04$, 95% CI −5.4–−0.1). For patients who underwent surgery (NSA and SA cohorts), a decrease in TPAI was associated with worse OS (HR 0.52; $p = 0.05$). In contrast, decreased HU was associated with worse OS in patients who did not undergo surgery (HR 0.93; $p = 0.01$).
Conclusions: In patients who received neoadjuvant chemotherapy, there was a significant decrease in TPAI and HU during treatment. Prospective studies are warranted to assess the impact of TPAI loss and HU changes on clinical outcomes to better individualize treatment pathways based on a patient's fitness.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fifth most commonly diagnosed cancer in adults, and it is projected to become the second leading cause of cancer death by the year 2030 [1]. Pancreatectomy, with or without chemotherapy, remains the only potentially curative treatment; however, surgery and chemotherapy are associated with marked morbidity which can have a significant impact on a patient's quality of life as well as their fitness for additional treatment, potentially affecting long-term survival [2–4]. Therefore, special consideration should be given to pre-operative risk stratification for treatment toxicities in patients with pancreatic cancer to assist clinicians and patients in making difficult decisions regarding selection of an appropriate treatment pathway.

One approach to risk-stratification for patients with potentially resectable cancer is the evaluation of *sarcopenia*, a loss of muscle mass and strength [5–11], which can be reliably measured by computed tomography (CT) imaging that is routinely obtained prior to, and during the course of, treatment. Pre-operative evaluation of radiographic sarcopenia (RS) has been defined by measuring the cross-sectional area and density of the right and left psoas muscle at the third lumbar vertebral level (L3), and has predicted perioperative morbidity and overall survival (OS) in patients undergoing surgery for pancreatic ductal

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adenocarcinoma [12]. The *changes* in sarcopenia that occur over the course of a patient's treatment, and whether such changes are associated with important clinical outcomes has not previously been reported in patients undergoing surgery, although studies in patients receiving palliative chemotherapy suggest such changes may be prognostic [13]. With increasing use of neoadjuvant chemotherapy for PDAC in vulnerable older adults, it is possible that preoperative therapy, while theoretically decreasing tumor burden, could also deplete a patient's body mass and increase the risk of surgical intervention. Assessment of RS has the potential to allow clinicians to individualize treatment related decisions based on body composition changes associated with specific treatments. Patients identified as high risk due to substantial muscle loss could choose to forego surgery and/or chemotherapy, and its associated risk of serious morbidity. Similarly, targeted interventions such as prehabilitation [14,15] could be used to reverse body composition changes to prevent subsequent treatment associated morbidity.

In this study, we investigated the relationship between treatment modalities and changes in RS measures over the course of treatments in patients with pancreatic cancer, including combinations that included surgery, chemotherapy, both or neither. We hypothesized that patients undergoing multimodality therapy with neoadjuvant chemotherapy would have significant decreases in RS measures. With muscle mass and strength being a potentially "exhaustible resource" – a resource patients depend on to tolerate cancer therapies to prevent toxicity and improve survival – a significant loss of psoas area or density (i.e. sarcopenia) may negatively impact OS, due either to underlying vulnerability to treatment or subsequent morbidity limiting further cancer-directed treatment.

2. Methods

2.1. Patient Selection and Clinical Outcomes

Patients with pancreatic ductal adenocarcinoma who underwent neoadjuvant chemotherapy at the University of Chicago Medical Center between January 2000 and December 2014 were retrospectively identified from our institutional cancer registry database. To ensure the accuracy and consistency of the data, we restricted our analysis only to patients who completed all of their neoadjuvant chemotherapy and had their imaging studies performed at our medical center. We excluded any patients that lacked non-contrast abdominal CT scans because prior studies have shown that iodinated intravenous contrast can alter the reproducibility of body muscle Hounsfield units (HU) values [16]. Patient groups were matched by cancer stage, demographics, and comorbidity burden, and they were then selected based on either having undergone surgery without neoadjuvant therapy as well as a palliative care control group to create the final 4 cohorts ($n = 85$; Fig. 1 B). During the period of our study, use of neoadjuvant chemotherapy at our institution was based upon "resectability". Patients with "borderline resectable" pancreatic cancer (defined as tumor involvement of the superior mesenteric vein or portal vein) underwent neoadjuvant chemotherapy, while patients with easily resectable disease underwent surgery first.

Date of death or date of last contact was obtained for all patients from the medical record, Social Security Death Index or obituaries, and OS was defined as time from pathologic diagnosis to death from any cause. Pre-therapy comorbidities (diabetes, coronary artery disease, and renal failure), clinical markers (CA19–9, albumin), and performance status as defined by the Eastern Cooperative Oncology Group (ECOG) [18] were obtained to clinically characterize patients. The study was approved by the institutional review board (IRB) at the University of Chicago.

2.2. Imaging Analysis for Radiographic Sarcopenia

RS was measured by trained personnel at the L3 levels on all available non-contrast computed tomography (CT) scans: pre-treatment, post-neoadjuvant, post-operative, and after completion of all treatment. Total psoas muscle cross-sectional area index (TPAI) as well as attenuation in HU were measured as estimates of psoas volume and density, respectively. Standardized calculations for determining the TPAI and weighted average psoas HU have been published elsewhere [17].

2.3. Statistical Analysis

Demographic and disease characteristics, along with sarcopenia measures, were summarized using frequency count and percentages for categorical variables and median with interquartile ranges (25%–75%) for continuous variables. Comparisons across groups were made using chi-squared tests and analysis of variance (ANOVA) or Kruskal-Wallis tests, as appropriate. The correlation between the two sarcopenia measures, TPAI and HU at L3, was assessed using a Pearson correlation coefficient. Kaplan-Meier curves were generated and survival compared across groups using the Prentice-Wilcoxon test. In survival analyses, those who were lost to follow-up were censored at the date of last contact. In order to test the impact of the baseline RS measures and other covariates on OS, univariate Cox regression models were fit. Covariates which had a $p < 0.10$ on univariate analysis were included in a multivariate analysis. Age and gender, as known predictors of survival, were included in all multivariate models, irrespective of their significance in the univariate analysis. To determine whether the association between RS and OS varied by treatment group, RS interactions were tested and dropped from the final model if not statistically significant ($p < 0.05$). Analyses looking at the association between changes in sarcopenia and survival used time from last sarcopenia measure to death from any cause ($n = 42$ patients, 28 deaths). Due to the small number of events, multivariate analysis could not be performed and thus exploratory, univariate analyses were performed. Analyses were performed using Stata Version 14 (StataCorp., College Station, TX).

3. Results

3.1. Demographics and Clinical Information

We identified 292 patients that were diagnosed with PDAC at our institution from 2000 to 2014 (Fig. 1A). Eighty-five patients met all of the aforementioned inclusion criteria. Four separate cohorts based on treatment patterns over time were generated: 1) Neoadjuvant chemotherapy plus surgery plus adjuvant chemotherapy ("NSA"; $n = 20$), 2) surgery plus adjuvant chemotherapy ("SA"; $n = 20$); 3) neoadjuvant chemotherapy with intent to perform surgery ("Chemotherapy"; $n = 24$); and 4) treated with palliative intent ("Palliative"; $n = 21$) (Fig. 1B).

Patient demographics and pre-treatment characteristics are depicted in Table 1. The median patient age was 67 years (59–75 years), 41% were male, and the median body mass index (BMI) was 26.9 kg/m^2 (21.9–30.0 kg/m^2). The median biomarker CA19–9 value at diagnosis was 105 U/mL (29–486 U/mL). Forty-three percent of patients had an ECOG performance status (PS) of 0, 33% had a PS of 1, and 24% had a PS of 2 or greater. The median albumin at diagnosis was 3.9 mg/dL (3.5–4.2 mg/dL). Although there were statistically significant differences in PS and albumin (Table 1), this was due to the Palliative group, and there were no differences in PS (f-statistic $= 0.78$, $p = 0.46$) or albumin (f-statistic $= 0.53$, $p = 0.59$) when comparing the three groups treated with curative intent (NSA, SA and Chemotherapy groups). Pre-treatment median psoas TPAI was 5.0 cm^2/m^2 (3.9–6.2 cm^2/m^2) and weighted average HU were 43.2 (36.7–50.1 HU). Psoas weighted average HU and TPAI were not significantly correlated with each other ($r = 0.14$, $p = 0.21$).

3.2. Univariate Analyses

On univariate analysis, age ($p < 0.001$), ECOG PS ($p < 0.001$), albumin at diagnosis ($p = 0.007$), psoas weighted average HU ($p < 0.001$),

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