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Original article

Sarcopenia and survival in patients undergoing pancreatic resection[★]

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ABSTRACT

Background: Recent studies have suggested that lean core muscle area may predict outcomes from major abdominal surgeries. Pancreatic resections have been independently analyzed less frequently.

Methods: Pancreatic resections from 2005 to 2012 were reviewed. Sarcopenia was defined as the lowest tertile for lean psoas muscle area (LPMA). Preoperative risk factors, including comorbidities, albumin, weight loss, age and gender, were analyzed with a primary endpoint of overall survival. Secondary endpoints included complications, discharge destination and readmission.

Results: The study sample of 270 patients had complications in 42% of patients, with 26% developing serious complication. The majority (80%) were discharged home, and 1.9% died in the peri-operative period. The mean length of follow up was 31.2 months (range 0–94), and 37% required at least one readmission. LPMA was predictive of discharge destination for females (p = 0.038). Sarcopenia was predictive of readmission in males, compared to subjects in the second LPMA tertile (HR 0.3; 95% CI: 0.1 –0.9). In all male subjects, including a subset with adenocarcinoma, patients with sarcopenia were more likely to die than males in the highest LPMA tertile (HR: 2.6; 95% CI: 1.4–4.8 and HR: 2.4; 95% CI: 1.2–4.9, respectively). In all patients with pancreatic ductal adenocarcinoma, transfusion (HR: 1.9; 95% CI: 1.2–3.4) and positive margins (HR: 2.0; 95% CI: 1.2–3.3) were the only factors predictive of overall survival. Conclusions: Sarcopenia appears to be a predictor of overall survival in male patients undergoing pancreatic resections, but not specifically for patients with pancreatic ductal adenocarcinoma. As prospective data in future studies are identified, sarcopenia may become a useful tool in predicting outcomes.

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Introduction

Pancreatic resections have traditionally been associated with high rates of morbidity and mortality, particularly when performed for oncologic purposes [1,2]. Various factors have been identified contributing to these complications, including pancreatic gland

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texture [3], need for blood transfusions [4], sarcopenia [5] and surgeon volume [6]. Differences in surgical techniques, such as the method of pancreatic anastomosis, have been proposed to minimize complications [7,8], but often the patient and/or tumor factors are unable to be modified. While patient selection is critical to any elective surgery, oncologic necessity and urgency does not always allow for complete optimization.

Many patients undergoing pancreatic resection have suffered weight loss from a variety of causes. These include cancer cachexia syndrome or chronic malnutrition from ongoing pancreatitis [9–12]. Changes in body composition may reflect sarcopenia (decreased muscle mass), cancer cachexia (a syndrome consisting

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of both muscle and adipose loss, weight loss, and anorexia), or chronic anorexia (as in chronic pancreatitis or other illness). Recently, several studies have demonstrated that sarcopenia may be predictive of worse outcomes in patients undergoing major abdominal surgeries [13—16]. Similarly, cachexia has been shown to be associated with poor outcomes [17,18]. A recent systematic review assessed the impact of sarcopenia on survival in patients with pancreatic ductal adenoma and concluded that further studies are needed [19]. Few studies to date have examined the specific relationship between muscle mass and density to surgical outcomes in patients undergoing pancreatic resections but seem to suggest a predictive value for the presence of sarcopenia [5,20].

We sought to identify the effect of sarcopenia on post-operative outcomes for all patients undergoing pancreatic resections and to compare this value to established preoperative predictive variables. The primary end-point was median survival. Secondary end-points included peri-operative complications, post-hospital discharge destination, and readmission rates. We further sought to clarify any outcome differences secondary to sarcopenia attributed to adenocarcinoma from other etiologies.

Methods

We reviewed all adult (age > 18 years) patients who underwent a pancreatic resection at a University affiliated, community based institution from July 1, 2005 to December 31, 2012 by a single, high volume pancreas surgeon. Presenting details included recent weight loss greater than 10%, initial body mass index (BMI), and albumin levels. Surgical details, as well as the postoperative course were recorded. Comorbidities were classified according to the Charlson Comorbidity Index (CCI) [21], and complications were noted according to the Clavien—Dindo (CD) [22] classification. Pancreatic fistulas were recorded according to the International Pancreatic Fistula Study Group (IPFSG) [23]. All data were collected in a retrospective manner after receiving appropriate approval by the Institutional Review Board.

Patients were included in this study if they underwent a pancreatectomy including proximal (pancreatico-duodenectomy), distal, central or total. Patients were excluded if they were deemed to not be operative candidates (based on radiographic imaging of the tumor or from co-morbidities/performance status that caused a prohibitively high risk for surgery). Patients were also excluded if they were not able to undergo a resection (receiving an exploration only or palliative bypass instead of resection due to extensive tumor involvement or intra-operative discovery of metastatic disease).

Clinical variables, including surgical intensive care unit (ICU) length of stay (LOS), discharge destination, and readmission criteria were managed according to each patient's medical necessity. In general, patients undergoing a pancreatico-duodenectomy were admitted to the ICU post-operatively, whereas patients undergoing a distal pancreatectomy were not, unless a specific need arose. The necessity of remaining in the ICU was discussed daily by the operating surgeon and the intensivists who participated in the patient's care. Discharge destination was decided on by a multidisciplinary team including the surgeon, physical therapists, social workers, and the patient/family members. Readmission criteria were determined according to the independent factors involved for each patient. Readmissions to outside hospitals were not able to be captured; therefore the readmission rate reflects those patients who returned or were transferred to the primary institution.

Final pathology reports were used to classify the tumors. These were then grouped into pancreatic ductal adenocarcinoma, any adenocarcinoma (including periampullary, duodenal, and distal cholangiocarcinoma as well as pancreatic ductal adenocarcinoma), or other.

Skeletal muscle mass was identified according to preoperative computed tomography (CT). The cross sectional area of the psoas muscle was measured bilaterally at the level of the fourth lumbar vertebrae. Hounsfield units were used to correct for the density of the muscle. The mean lean psoas muscle area (LPMA) was calculated for each patient according to the formula given by Miller et al. [24]. LPMA data were not able to be collected in patients whose outside images were not loaded onto the hospital computer system or whose preoperative imaging consisted of magnetic resonance imaging only.

LPMA was defined into tertiles and treated as a categorical variable. Sarcopenia was defined as the lowest tertile for LPMA. Tertiles were calculated for all patients, as well as for female subjects alone and for male subjects alone. Summary statistics were calculated. Quantitative data are expressed as the mean \pm SD, while nominal data are expressed as a percentage. LPMA values for males and females were compared using the two-tailed t-test. Comparisons between tertiles for the nominal variables of CD status, discharge destination, and readmission within six months were evaluated using the χ^2 test.

These same three dependent variables were analyzed using logistic regression, using LPMA tertiles, transfusion (intraoperative RBC), any adenocarcinoma, preoperative albumin concentration < 3.5 g/dL, estimated blood loss > 300 mL, preoperative weight loss greater than 10%, CD status of III or IV, BMI > 35, age \geq 65 years, CCI \geq 3, and distal vs. Whipple/total as the independent variables.

Kaplan-Meier curves were constructed, using survival of all patients, or for all patients with pancreatic ductal adenocarcinoma, as the dependent variables and LPMA tertiles as the independent variables. Cox proportional hazards analyses were performed, using either survival of all patients, all patients with adenocarcinoma, or all patients with pancreatic ductal adenocarcinoma, as the dependent variables. For the first two analyses, the same independent variables described above for the logistic regression analyses were used. In addition, positive margin status was also tested as an independent variable for the analysis of adenocarcinoma patients. For the hazards analysis of patients with pancreatic ductal adenocarcinoma, the independent variables used were LPMA tertiles, transfusion (intraoperative RBC), preoperative concentration < 3.5 g/dL, estimated blood loss > 300 mL, CD status of III or IV, age \geq 65 years, and positive margin status. Statistics were performed using IBM SPSS Statistics 22.0 (Armonk, NY). A p < 0.05 was considered statistically significant.

Results

A total of 270 patients met the inclusion criteria. Females and males were analyzed separately given the inherent difference in LPMA ($1337\pm350~{\rm cm}^2~{\rm vs.}~2154\pm549~{\rm cm}^2$, respectively, p < 0.001). LPMA was then divided within each gender into tertiles. Data regarding LPMA was complete for 122 (96.8%) females and 138 (95.8%) males. Pathology included pancreatic ductal adenocarcinoma (N = 107, 39.6%), pancreatitis (N = 42, 15.6%), neuroendocrine (N = 31, 11.5%), ampullary adenocarcinoma (N = 29, 10.7%), intraductal papillary mucinous neoplasm or mucinous cystic neoplasm only (N = 31, 11.5%), distal cholangiocarcinoma (N = 8, 3.0%), and other tumors including lymphoma, metastatic disease, gastrointestinal stromal tumor, solid pseudopapillary neoplasm, and sarcoma (N = 22, 8.1%).

Pre-, intra- and post-operative details are shown in Table 1. Preoperative values showed there were slightly more males than females, with an average age greater than 60 years. The most

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