A clinically applicable muscular index predicts long-term survival in resectable pancreatic cancer

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Background. *The relationship between myopenia, nutritional status, and long-term oncologic outcomes remains poorly characterized in patients with clinically resectable pancreatic cancer. We sought to reliably quantify prognostic indicators of preoperative cachexia in a manner applicable to any clinical setting.*
Methods. *Preoperative computed tomographies were available electronically and suitable for analysis in 73 of 82 consecutive patients with pancreatic cancer undergoing pancreatoduodenectomy between November 2010 and February 2014. The psoas index was computed from the cross-sectional area of the psoas muscles normalized to vertebral body area at the third lumbar vertebra. Correlation and proportional hazards analyses were performed to identify relationships between muscularity, preoperative nutritional markers, clinicopathologic parameters, and long-term survival.*
Results. *The psoas index correlated strongly with preoperative hemoglobin and albumin levels (*$P = .001$ *and .014, respectively) identifying a pattern of preoperative frailty. High psoas index and the albumin and hemoglobin levels were associated with improved long-term survival (hazard ratio 0.014,* $P < .001$*; hazard ratio 0.43,* $P < .001$*; and hazard ratio = 0.80,* $P = .014$*); however, on multivariate analysis, the psoas index proved to be the only independent predictor of survival (hazard ratio 0.021;* $P = .003$*). Rapid decreases in the psoas index during neoadjuvant chemotherapy were associated with poor postoperative outcomes, as were decreases in the psoas index during the postoperative period.*
Conclusion. *The data indicate that the psoas index, a calculation derived from a clinically mandated, preoperative computed tomography, is a statistically powerful and easily calculated predictor of survival in pancreatic cancer when compared to tumor grade and stage as well as previously validated nutritional parameters. (Surgery 2017;161:930-8.)*

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Pancreatic cancer (PC) is the fourth leading cause of cancer death in the United States and by 2030 is projected to be second only to lung cancer.[1] Local approaches to curative therapy encounter high recurrence rates, indicative of the systemic nature of early stage disease.[2] Therefore, it is not surprising that patients with clinically resectable disease demonstrate highly variable long-term outcomes. Patients predisposed to poor outcomes after resection, however, remain indistinguishable clinically from long-term survivors in the preoperative setting.[3-5] The morbidity and recovery time associated with pancreatic operation underscores the need for better clinical tools to recognize those patients at greatest risk for early disease progression postoperatively.

To this effect, a large body of literature has focused on preoperative risk assessment in surgical patients. Poor nutritional status emerges consistently as a powerful predictor of poor outcomes, particularly in cancer-based investigations.[6-10] In addition to a compromised ability to convalesce from operative trauma, this phenomenon also appears to reflect an association between poor

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enteral intake (anorexia) and an advanced oncologic disease state. Physiologically, this anorexia combined with concurrent abnormal metabolic/catabolic state results in cachexia, characterized by profound muscular atrophy.[11,12]

Classically, preoperative hemoglobin and albumin have been associated with advanced states of cachexia as well as poor perioperative outcomes.[13-15] The evolutionary pressure to conserve serum levels of these factors for essential processes in times of physiologic stress led us to hypothesize that localized muscle wasting may serve as a more reliable indicator of a cachectic state, ie, sarcopenia. Further, early clinical recognition of muscle wasting in patients with PC may convey vital clinical and prognostic information prior to initiating therapy.[16,17] Estimates of sarcopenia from radiologic data, however, mandate the use of expensive, densitometric software and correction factors derived empirically for sex and body surface area, thereby hindering widespread clinical use.

To address this, we provide proof of principle for a quick calculation to simplify radiologic estimates of sarcopenia, thereby establishing a measure that is performed easily and interpreted by the clinician in the preoperative setting. Indeed, we show that the psoas index, defined as the ratio of the psoas area to vertebral body area measured from the clinically mandated computed tomography (CT), is a statistically powerful predictor of survival superior to tumor grade and lymphatic stage as well as previously validated preoperative biomarkers. These data indicate that the careful quantification of muscularity may have a role in the clinical staging of clinically resectable PC.

METHODS

Patient population. A prospectively maintained, institutional review board–approved clinical database at the University of Florida was used to identify all consecutive patients with PC who underwent pancreatoduodenectomy (PD) between November 2010 and February 2014. Of the 82 patients identified, 73 had preoperative CT available electronically and suitable for analysis. The time frame facilitated a minimum postoperative follow-up of 6 months to ensure that early and late complications as well as oncologic outcomes were evaluable.

Preoperative data collected included patient age, sex, body mass index, Charlson comorbidity status, completion of gemcitabine-based neoadjuvant chemotherapy regimens, and serum hemoglobin and albumin levels. Postoperative pathologic data obtained included lymph node ratio, defined as the number of lymph nodes positive for malignancy divided by the total number of evaluated lymph nodes, tumor grade, tumor size, and margin status. Postoperative complications were graded according to the Clavien-Dindo index,[18] and pancreatic fistulas were categorized using the definition of a pancreatic fistula by the International Study Group of Pancreatic Fistula (ISGPF).[19]

CT analysis. Images were stored and analyzed using the Philips iSite Enterprise System (Philips, Eindhoven, the Netherlands). As depicted in Fig 1, *A*, psoas muscles were outlined manually at the level of the inferior portion of the third lumbar vertebra (L3) with both transverse processes in view, as described previously.[20-25] The L3 vertebral body was outlined in a similar manner and the cross-sectional area computed automatically by the iSite software. The psoas index was defined as the average psoas cross-sectional area divided by the area of the L3 vertebral body.

Statistical analysis. All statistical analyses were performed using the SPSS version 22.0 statistical software package (IBM SPSS statistics for Windows; IBM Corp, Armonk, NY) and GraphPad Prism version 5.02 (GraphPad Software, San Diego, CA). Continuous variables were analyzed using the independent samples t test to compare 2 groups or 1-way analysis of variance to compare groups of ≥ 3. Kaplan-Meier survival curves were generated using dichomotized continuous variables at median values and evaluated using the log-rank (or Mantel-Cox) test. Median values were used as cutoffs for dichotomization only in Kaplan-Meier analyses to generate consistently equal groups of patients for each variable. Univariate analysis was performed using a Cox proportional hazards model. All variables significant ($P < .05$) on univariate analysis were included in multivariate Cox regression. Receiver operating characteristic (ROC) curves were generated using GraphPad Prism. Sensitivity and specificity for each variable to predict death within one year of PD was evaluated in the cohort of 68 patients with at least one year of clinical follow-up. ROC curves were plotted against lines of identity, and the area under the curve (AUC) was calculated. Post hoc power calculations were performed to determine statistical robustness using G*Power version 3.9.1.2 as described previously setting α to 0.05.[26,27]

RESULTS

Low psoas index correlates with older age, preoperative anemia, and hypoalbuminemia. Of the 82 consecutive patients undergoing PD for PC,