Long-term survival in patients with pancreatic ductal adenocarcinoma

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Background. *Long-term survival (LTS) is uncommon for patients with pancreatic ductal adenocarcinoma (PDAC). We sought to identify factors that predict 10-year, LTS after resection of PDAC.*
Methods. *We identified all patients with PDAC who underwent resection at UCLA after 1990 and included all patients eligible for observed LTS (1/1/1990–12/31/2004). An independent pathologist reconfirmed the diagnosis of PDAC in patients with LTS. Logistic regression was used to predict LTS on the basis of patient and tumor characteristics.*
Results. *Of 173 included patients, 53% were male, median age at diagnosis was 66 years, and median survival was 23 months. The rate of observed LTS was 12.1% (*n = *21). Age, sex, number of lymph nodes evaluated, margin status, lymphovascular invasion, and adjuvant chemotherapy and radiation were not associated with LTS. The following were associated with LTS on bivariate analysis: low AJCC stage (Ia, Ib, IIa) (*P = *.034), negative lymph node status (*P = *.034), low grade (well-, moderately-differentiated) (*P = *.001), and absence of perineural invasion (*P = *.019). Only low grade (odds ratio 7.17,* P = *.012) and absent perineural invasion (odds ratio 3.28,* P = *.036) were independently associated with increased odds of LTS. Our multivariate model demonstrated good discriminatory power for LTS, as indicated by a* c*-statistic of 0.7856.*
Conclusion. *Absence of perineural invasion and low tumor grade were associated with greater likelihood of LTS. Understanding the tumor biology of LTS may provide critical insight into a disease that is typically marked by aggressive behavior and limited survival. (Surgery 2016;159:1520-7.)*

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The incidence of pancreatic cancer is increasing, but the prognosis for the majority of patients remains strikingly poor. Overall 5-year survival for all patients with pancreatic ductal adenocarcinoma (PDAC) is approximately 7.1%.[1,2] By 2030, researchers project that pancreatic cancer will become the second-leading cause of cancer related death in the United States after lung cancer, surpassing colorectal, breast, and prostate cancer.[3] In 2015, it is estimated there will be 48,960 new cases and 40,560 deaths attributable to pancreatic cancer in the United States—indicative of near-universal lethality. Of these pancreatic cancers, approximately 96% will be PDAC.[2]

Curative resection is attempted in the small subset of patients that present with localized disease; however, the overall 5-year survival rate for these patients remains no greater than 26%.[2] Furthermore, unlike other solid malignancies for which 5-year survival rates often are equivocated with "cure" rates, patients who survive 5 years after PDAC resection continue to be at high risk for recurrence and disease-related mortality.[4-6] Extended or long-term survival (LTS) after PDAC resection has been reported in a number of retrospective series and has been defined variously as survival greater than 5 or 10 years, depending on the study. In many of these series, however, a histopathologic diagnosis of PDAC was not confirmed by a re-review of the pathology in a sizeable number of patients purported to achieve LTS. Many patients were instead found to harbor

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adenocarcinoma of various subtypes that are less aggressive than PDAC, and some were found not to harbor malignancy at all.[7-9] This finding has led some experts to question whether LTS—let alone a cure—truly exists for patients with PDAC.[10]

The factors that impact prognosis in PDAC are well described. Small primary tumor size, negative operative margins, absence of lymph node metastasis, a favorable lymph node ratio, and adjuvant chemotherapy and radiation are among the most notable.[11-14] More recently, the marked impact of tumor grade on prognosis also has been recognized.[11, 15] There are data to suggest, however, that the group of patients that ultimately achieve LTS after PDAC resection do not reliably meet the aforementioned criteria for ideal prognosis; many may have advanced stage or other markers of poor prognosis.[16, 17] It appears that our understanding of the tumor biology of patients with LTS after PDAC resection is therefore lacking. We undertook the present study for the following reasons: to provide an accurate, observed rate of LTS after resection of pathologically confirmed PDAC at our institution and to perform a dedicated analysis to formally identify predictors of LTS.

METHODS

Patient population and definition of LTS. With approval from the institutional review board from the University of California Los Angeles, we identified all patients who had operative resection of PDAC at our institution after January 1, 1990. Patients diagnosed after December 31, 2004 were excluded such that all patients in the study population were eligible for the outcome of interest—10-year survival, or LTS—at the time of analysis. Patients who were found to have unresectable PDAC at the time of operative exploration were excluded.

We considered a patient to have achieved LTS only if the following criteria were strictly met: confirmed overall survival for 10 years or more from the time of diagnosis and a confirmed pathologic diagnosis of PDAC. We defined overall survival time as the length of time between the date of diagnosis and the date of death or last known contact. To ensure a conservative estimation of LTS, we presumed all patients lost to follow-up before achieving 10-year survival to be dead at the date of last known contact ($n = 24$). For all patients who appeared to achieve LTS, an independent pathologist (D.D.) re-reviewed the pathology specimen to confirm a true diagnosis of PDAC. We excluded cases in which there was a discrepancy between the original pathologic diagnosis and the subsequent re-review ($n = 2$). In 1 case, the specimen contained no residual tumor as a result of treatment effect and was therefore not confirmed by re-review. This case was included, however, on the basis of 2 consecutive preoperative biopsies—including an open surgical biopsy—that concordantly demonstrated PDAC.

Covariates. We collected the following demographic and clinical variables: age, sex, type of operation, American Joint Committee on Cancer (AJCC) stage, and receipt of adjuvant chemotherapy and radiation. Pathologic data collected include, tumor size, margin status (negative = R0, positive = R1, R2), number of lymph nodes evaluated, tumor grade, and the presence or absence of both perineural and lymphovascular invasion. At our institution margin status is defined as positive only when tumor is definitively present at the surgical margin, not whenever tumor is within 1 mm of the surgical margin. For analysis, we included the following as categorical variables: age (<50, 50–70, >70), AJCC stage ("low stage" = Ia, Ib, IIa; "high stage" = IIb, III, IV), number of lymph nodes evaluated (≤ 12, >12—according to international consensus),[18] tumor grade ("low grade" = well-differentiated, moderately-differentiated; "high grade" = poorly-differentiated).

Statistics. We compared patients with and without LTS on the basis of age, sex, AJCC stage, lymph node status, number of lymph nodes evaluated, tumor grade, margin status, perineural invasion, and lymphovascular invasion by using chi-square tests. We tested the association between perineural invasion and lymph node status in a similar fashion. We then performed multivariate logistic regression to predict LTS, controlling for these covariates. Lymph node status was not included in the regression because of collinearity with AJCC stage, of which it is an integral component. Adjuvant chemotherapy and radiation also were omitted from the multivariate regression, for the following reasons. Missing data regarding adjuvant therapy (primarily as a result of patients receiving adjuvant therapy at an outside institution) would have excluded a large number of patients from the regression. Furthermore, adjuvant chemotherapy with or without radiation has become standard practice at our institution and is recommended almost uniformly. Because most patients for whom information regarding adjuvant therapy was available did in fact receive adjuvant therapy, we believed its inclusion into the model might introduce a degree of selection bias.