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ORIGINAL ARTICLE

The association of adjuvant therapy with survival at the population level following pancreatic adenocarcinoma resection

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Abstract

Background: Using a retrospective observational cohort approach, the overall survival (OS) following curative-intent resection of pancreatic adenocarcinoma (PC) was defined at the population level according to adjuvant treatment, and predictors of OS were identified.

Methods: Patients undergoing resection of PC in the province of Ontario between 2005 and 2010 were identified using the provincial cancer registry, and linked to databases that include all treatments received and outcomes experienced in the province. Pathology reports were abstracted for staging and margin status. Patients were identified as having received chemotherapy (CT), chemoradiation therapy (CRT), or no adjuvant treatment (NAT). Kaplan–Meier survival analysis of patients surviving $\geq$6 months was performed, and predictors of OS identified by log-rank test. Cox multivariable analysis was used to define independent predictors of OS.

Results: Among the 473 patients undergoing PC resection, the median survival was 17.8 months; for the 397 who survived $\geq$6 months following surgery, the 5-year OS for the CT, CRT, and NAT groups was 21%, 16%, and 17%, respectively (p = 0.584). Lymph node-negative patients demonstrated improved OS associated with chemotherapy on multivariable analysis (HR = 2.20, 95% CI = 1.25–3.83 for NAT vs. CT).

Conclusions: Following PC resection, only patients with negative lymph nodes demonstrated improved OS associated with adjuvant chemotherapy.

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Previous Presentation of Material: Portions of this study have been previously presented at the Americas Hepato-Pancreato-Biliary Association Conference in March 2015 in Miami, the Applied Research in Cancer Control Conference in June 2015 in Montreal, and the Canadian Surgical Forum Conference in September 2015 in Quebec City. There are no accompanying submission or publication requirements.

Introduction

Pancreatic adenocarcinoma (PC) is projected to become the 2nd leading cause of cancer mortality within the next decade.[1] Only 15–20% of patients are candidates for surgical resection, which remains the sole potentially curative treatment.[2] Following surgery, most patients experience recurrence and succumb to their disease.[3,4] Despite progress in surgical and perioperative management, as well as adjuvant treatment with chemotherapy and/

or radiation therapy, long-term survival following pancreatectomy for cancer is still poor, with recent series reporting median disease-specific survival of 29 months,[5] median overall survival (OS) of 27 months,[6] and 5-year OS rates of 23%.[7] Furthermore, these values represent actuarial survival estimated using Kaplan–Meier methods; actual 5-year survival following PC resection has been reported to be between 12 and 18%.[4,8]

Based on the results of several randomized controlled trials, the use of adjuvant treatment is currently recommended following surgery; however, controversy persists regarding the effectiveness of adjuvant chemotherapy (CT) and chemoradiation therapy (CRT) in improving survival.[9–12] Additionally, it is not known if the benefits of adjuvant treatment demonstrated in the highly regulated setting of a randomized trial translate into improvements when applied to a real-world population of patients.[13] The purpose of this study was to define OS following curative-intent resection of PC at the population level in order to assess the real-world outcomes of adjuvant CT and CRT on survival, as well as to identify other clinicopathologic and sociodemographic predictors of OS.

Methods

Using the Ontario Cancer Registry (OCR), patients diagnosed with PC in the province of Ontario between January 2005 and 2010 were identified using ICD9 anatomic location codes for pancreas plus ICD-O morphology codes and linked to administrative databases at the Institute for Clinical Evaluative Sciences (ICES). These datasets were linked using unique encoded identifiers and analyzed at ICES. These databases included the Canadian Institute for Health Information (CIHI), the National Ambulatory Care Reporting System (NACRS), the Ontario Health Insurance Plan (OHIP), the Registered Persons Database (RPDB), and the Cancer Care Ontario Activity Level Reporting (ALR) database. These methods have previously been described for cancers originating in other organs.[14–16]

Pathology reports of resection specimens were obtained from the OCR and linked using identification numbers. Pathology reports were abstracted using the 2013 College of American Pathologists protocol,[17] and validated by independent abstraction of approximately 15% of the reports.

Patients undergoing pancreaticoduodenectomy or distal pancreatectomy were identified for inclusion in the cohort. Patients were excluded using the following criteria: age <18 years; diagnosis of not adenocarcinoma; diagnosis of any other cancer within the preceding 5 years; receipt of neoadjuvant therapy; and receipt of radiation alone as this was considered palliative. Patients dying within 6 months of undergoing surgery were also excluded from analysis, as they were likely not well enough to be considered for adjuvant treatment.

Patients were defined as having received adjuvant CT or CRT based upon physician billing codes (OHIP) for chemotherapy infusion or radiation treatment planning within 120 days of surgery. OHIP records all physician claims in Ontario for all patients treated for pancreatic cancer. Those patients who had at least two chemotherapy codes separated by at least one week were classified as "Chemotherapy (CT)," and those who also had radiation codes within 12 weeks of adjuvant chemotherapy were classified as "Chemoradiation (CRT)." Patients who did not have any codes for chemotherapy in the first 120 days following surgery, and those who received less than one week of chemotherapy, were designated "No Adjuvant Treatment (NAT)." The use of OHIP codes to define receipt of adjuvant therapy has been described previously.[14,18] Adjuvant therapy definitions based on OHIP codes were compared to patient medication usage records (ALR), which demonstrated >90% concordance. The timing and sequence of all OHIP and ALR codes were reviewed for each individual patient by one of the authors (DJK) to ensure accurate classification.

Baseline demographic characteristics were recorded, including age, gender, comorbidity (Adjusted Clinical Group System score, used with permission of producers), rurality status and median income quintile.[19] Receipt of treatment at one of 10 provincially-designated hepatopancreatobiliary centres was also recorded. Histopathologic and operative characteristics were obtained from pathology reports, including type of resection, T, N, and M stages, tumor grade, lymphovascular invasion, perineural invasion, microscopic tumor extension, margin status, and lymph node positivity ratio. Using this data, hybrid variables were generated: socioeconomic status (based on rurality and median income quintile); and nodal status (based on LN positivity ratio and number of LNs examined). Postoperative complications were identified using a combination of physician claims data, cross-referenced with discharge summaries, to generate a score based on the Clavien–Dindo classification of surgical complications,[20] according to the most severe complication experienced during the 30-day postoperative period. Overall survival was defined using death certificates (RPDB).

Descriptive analysis of baseline characteristics of the cohort was performed, with patients stratified by adjuvant treatment group. Landmark Kaplan–Meier OS analysis excluding patients dying within 6 months of surgery (early postoperative demise) was performed, with data censored on March 31, 2012. Univariate and multivariable Cox proportional hazards regression analysis were performed, with inspection of the log–log graph used to check the proportional hazards assumption. Multivariable modeling was performed using backwards elimination with a cutoff p-value of 0.1, with the primary variable of interest identified *a priori* (adjuvant therapy) forced into the multivariable model. A p-value of 0.05 was considered significant. All tests were 2-tailed, and performed using SAS Enterprise Guide 6.1 (Cary, North Carolina). Research ethics board approval for this study was obtained from the appropriate institutional review committees. In accordance with institutional policies, cell sizes containing <6 individuals were suppressed.