ORIGINAL ARTICLE

Trends in the use of pre-operative radiation for adenocarcinoma of the pancreas in the United States

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Abstract

Background: The benefit and timing of radiation therapy (RT) for patients undergoing a resection for pancreatic adenocarcinoma remains unclear. This study identifies trends in the use of radiation over a 10-year period and factors associated with the use of pre-operative radiation, in particular.

Methods: The Surveillance, Epidemiology and End Results registry was used to identify patients aged ≥18 years with pancreatic adenocarcinoma who underwent a surgical resection between 2000 and 2010. Logistic regression was used to identify time trends and factors associated with the use of pre-operative radiation.

Results: The overall use of radiation decreased with time among the 8474 patients who met the inclusion criteria. However, the use of pre-operative radiation increased from 1.8% to 3.9% ($P \leq 0.05$). Factors significantly associated with receipt of pre-operative radiation were younger age, treatment in more recent years and having an advanced T-stage tumour. The 5-year hazard of death was significantly less for those who received pre-operative radiation versus surgery alone [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.55–0.74] and for those who received post-operative radiation versus surgery alone (HR 0.69, 95% CI 0.65–0.73).

Discussion: The use of pre-operative radiation significantly increased during the study period. However, the overall use of pre-operative radiation therapy remains low in spite of the potential benefits.

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Introduction

A number of studies have investigated the outcomes associated with the use of post-operative adjuvant radiation therapy (RT) for the treatment of pancreatic adenocarcinoma. The findings of these studies have been largely inconsistent with some showing a significant survival benefit with the use of chemoradiation[1–4] and others showing only a non-significant trend towards an increase in survival.[5–7] Complicating the picture further, the European Study Group for Pancreatic Cancer Trial 1 (ESPAC-1) results suggested that post-operative chemoradiation may even have a deleterious effect on survival.[8] This uncertainty regarding the benefits of post-operative chemoradiation is reflected in the National Comprehensive Cancer Network (NCCN) guidelines for post-operative adjuvant treatment of pancreatic adenocarcinoma. After surgical resection, the NCCN guidelines recommend enrolment in a clinical trial of post-operative adjuvant therapy. If a clinical trial is not an option, the NCCN guidelines recommend either chemoradiation or chemotherapy alone as appropriate post-operative adjuvant therapy.[9]

While the utility of post-operative radiation has been questioned, several single-institutional studies have reported the outcomes and potential benefits of pre-operative chemoradiation.[10–14] Current NCCN guidelines recommend pre-operative adjuvant therapy as an appropriate option for those with borderline resectable disease and acknowledge that many NCCN member institutions now prefer this approach for

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borderline resectable patients. For patients with resectable disease, the panel recommends these patients enrol in a clinical trial when pursuing pre-operative adjuvant therapy as opposed to a surgery first approach.[9] Currently, there are few data on the frequency and trends of the use of pre-operative RT in the United States or the predictive factors related to receipt of pre-operative radiation therapy. This study evaluated trends in the use of radiation in the pre- and post-operative setting, and sought to identify demographic, patient and tumour predictors that play a role in clinical decision-making. In addition, potential differences in survival were assessed between those patients who received RT (either pre- or post-operative) versus those who underwent surgery alone.

Methodology

Data

The Surveillance Epidemiology and End Results (SEER) programme database was used to examine trends in the use of pre- and post-operative RT for patients who underwent a resection for the treatment of pancreatic adenocarcinoma between 2000 and 2010. The SEER cancer registries provide population-based cancer surveillance for 18 areas that represent approximately 28% of the United States.[15] SEER collects patient demographic and tumour characteristics, including age at diagnosis, race, primary tumour site, tumour laterality, histology type, tumour stage, tumour grade, diagnostic confirmation, type of surgery, the use of radiation therapy, vital status and the cause of death.

Patients

The study was limited to include only patients aged 18 years and older diagnosed with microscopically confirmed pancreatic adenocarcinoma and who had undergone a surgical resection between 2000 and 2010. The analysis excluded patients with non-adenocarcinoma pancreatic cancer, those with multiple primary malignancies in a lifetime and those patients diagnosed while in a nursing home, by autopsy, or on a death certificate. Owing to the concern that registries with very few patients receiving pre-operative RT could skew the analysis, registries were excluded that reported fewer than 10 patients treated with pre-operative RT over the 10-year analytic period. Twelve registries were included, and the six excluded registries comprised Hawaii, New Mexico, Rural Georgia, San Francisco – Oakland, San Jose – Monterey and the Alaska Native Tumor Registry.

Three treatment categories were created: surgery without radiation, pre-operative radiation then surgery and surgery followed by post-operative radiation. Surgical codes included a partial pancreatectomy, NOS (SEER surgical code 30), local or partial pancreatectomy and duodenectomy (without distal/partial gastrectomy and with partial gastrectomy (Whipple); 35–37), a total pancreatectomy (40), a total pancreatectomy with subtotal gastrectomy/duodenectomy (60), an extended pancreatoduodenectomy (70) and a pancreatectomy, NOS (80).

Statistical analysis

Unadjusted treatment patterns were compared over the 10-year study period using the Cochrane–Armitage test for trend. Logistic regression was used to identify time trends, demographics and patient factors associated with the use of pre-operative radiation therapy. All regression models included the patients' age, race, gender, year of diagnosis, tumour size, T-stage, tumour grade, the number of lymph nodes examined, lymph node status, treatment type and registry.

The Kaplan–Meier method and Cox's proportional hazards models were employed to determine the 5-year relative hazard of death based on the treatment received. This model included the patients' age, race, gender, year of diagnosis, tumour size, T-stage, tumour grade, number of lymph nodes examined, lymph node status, treatment type and registry.

All statistical analysis was completed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA). This study was exempt from review by the Human Subjects Committee of the University of Minnesota's Institutional Review Board because it used a de-identified data source.

Results

Description of the population

From 2000 to 2010, 8474 patients were identified who underwent a resection for pancreatic adenocarcinoma. Demographic, pathological and treatment details are provided in Table 1.

Changes in treatment patterns over time

Overall, the use of RT for pancreatic adenocarcinoma significantly decreased in the United States from 2000 to 2010 (45.9% to 32.6%, $P \leq 0.05$). However, the use of pre-operative RT modestly but significantly increased from 1.8% to 3.9% ($P \leq 0.05$). The use of surgery without radiation increased significantly ($P \leq 0.05$) from 54.1% (2000) to 67.4% (2010). At the same time, the use of post-operative radiation significantly decreased over time from 44.1% in 2000 to 28.7% in 2010 ($P \leq 0.05$). Thus, the overall decrease in the use of RT is largely due to a decrease in the use of post-operative RT (Fig. 1).

Factors associated with pre-operative RT

Younger patient age and diagnosis and treatment in more recent years were significantly associated with receipt of pre-operative radiation (Table 2). Significant geographical differences in the use of pre-operative radiation were observed but without obvious broad geographical patterns. Tumour factors that were significantly associated with an increase in pre-operative RT were missing or unknown tumour grade and advanced T stage (Table 2). Finally, there was a significant association between receiving pre-operative RT and positive lymph node status at the time of surgery (Table 2) suggesting that patients with higher stage cancers identified clinically are more likely to get pre-operative therapy. The number of lymph nodes evaluated was not significantly associated with the use of pre-operative radiation.