Adjuvant EBRT improves survival in patients with lymph-node-negative pancreatic cancer

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Though the role of radiation therapy in the adjuvant treatment of pancreatic cancer remains controversial, a recent large retrospective study indicates that radiation is associated with improved survival.

The role of adjuvant external-beam radiotherapy (EBRT) for the treatment of pancreatic adenocarcinoma remains controversial. A randomised trial by the Gastrointestinal Study Group demonstrated a survival benefit with the addition of chemoradiotherapy to surgery, and a randomised trial by the European Organisation for Research and Treatment of Cancer also showed a trend towards improved survival with adjuvant chemoradiotherapy.[1,2] On the other hand, a randomised trial by the European Study Group for Pancreatic Cancer (ESPAC), which comprised four adjuvant treatment arms (observation, chemotherapy alone, radiotherapy with concurrent chemotherapy, and radiotherapy with concurrent chemotherapy followed by maintenance chemotherapy),[3] revealed that the survival of patients who received radiotherapy (with or without maintenance chemotherapy) was inferior to that of patients who did not receive radiotherapy. The authors of this report concluded that radiotherapy had deleterious effects on survival.

The reasons for the decrease in survival in patients receiving radiotherapy on the ESPAC trial remain unclear. Radiation was not reported to increase treatment-related mortality, but late radiation toxicity is difficult to report accurately because it can be difficult to differentiate from symptoms of a progressive tumour, and patients may be lost to follow-up. The ESPAC trial did not describe radiation field size and technique, and central review of radiation plans was not required. The Radiation Therapy Oncology Group (RTOG) has reported that a major deviation from the protocol-defined radiation therapy plan was associated with inferior survival for patients with pancreatic cancer enrolled on the RTOG 97-04 trial, suggesting that radiation technique is important.[4]

The current study based on the SEER registry by Artinyan et al. (see opposite) demonstrates that the addition of radiotherapy to surgery in patients with T1–3N0M0 pancreatic adenocarcinoma is associated with improved survival. Limitations of the SEER registry include its retrospective nature and lack of information regarding surgical-margin status and the use of chemotherapy. In addition, it is not possible to determine any bias in the

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selection of patients for radiotherapy. For example, patients who do not have major health problems could be more likely to receive radiation, thereby biasing survival rates in favour of patients who receive radiation. Alternatively, patients who have high-risk features not assessed in the SEER study may be more likely to receive radiation, biasing results against radiation.

Given the limitations of the SEER registry, the results of this study do not answer the question of whether the addition of radiotherapy to chemotherapy improves survival.

The study does, however, suggest that, at a minimum, radiation is not detrimental to survival, as suggested by the ESPAC study.

In the current study, improvement in survival with radiotherapy was observed regardless of T stage on multivariate analysis, although improvement in survival was limited to patients with T3 disease on univariate analysis. Using the SEER registry data, Hazard and co-authors did not detect a survival benefit of radiotherapy and surgery in patients with T1–2N0M0.[5]

It is possible that T3 disease is associated with a higher probability of margin positivity, and the benefits of radiotherapy are, therefore, greater. It is also possible that patients with T1–2N0 disease who receive radiotherapy are more likely to have high-risk features, thereby limiting the potential survival benefit of radiotherapy.

In summary, this study indicates that adjuvant radiotherapy is an acceptable treatment for pancreatic adenocarcinoma that warrants continued investigation; only a randomised trial can determine whether or not the use of radiotherapy improves survival.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

Synopsis

Avo Artinyan, Minia Hellan, Pablo Mojica-Manosa et al. (2008) **Improved survival with adjuvant external-beam radiation therapy in lymph node-negative pancreatic cancer: a United States population-based assessment.** *Cancer 112:34–42*

Background. The prognosis for patients with lymph-node negative (N0) pancreatic cancer is very poor, with low survival rates after curative resection. Adjuvant treatment regimens consisting of chemotherapy, radiotherapy or a combination of both have been used to improve survival; however, the role of adjuvant radiation therapy is unclear.

Objective. To assess the benefit of adjuvant external-beam radiation therapy (EBRT) in patients with locally confined lymph-node-negative pancreatic cancer.

Design and intervention. This study used the Surveillance, Epidemiology and End Results (SEER) registry to identify patients who had undergone surgery for histologically confirmed, node-negative, invasive pancreatic cancer during the period 1988–2003. Patients whose tumours were excised or who had extensive pancreatic and multiorgan resections were included. Patients who had undergone biopsies, exploratory surgeries or lymph-node dissections alone and patients with no lymph nodes were excluded. A total of 1,930 patients were included in the analysis. Kaplan–Meier analysis was used to compare the survival rates of patients who received EBRT with those of patients who did not. Multivariate Cox regression analysis was used to determine the prognostic significance of adjuvant EBRT.

Outcome measures. The primary end point was overall survival (OS). The administration of adjuvant EBRT was the main prognostic factor of interest.

Results. The median OS for the whole study population was 17 months. Patients who received adjuvant EBRT had significantly better survival than patients who did not (median OS 20 months vs 15 months; $P<0.001$). Univariate regression analysis revealed that adjuvant EBRT was significantly associated with survival (hazard ratio [HR] 0.75, 95% CI 0.67–0.84; $P<0.001$). Age at diagnosis, and tumour location, grade and classification were all associated with survival. Multivariate analysis revealed that EBRT was associated with an approximately 30% reduction in the risk of death (HR 0.72, 95% CI 0.63–0.82; $P<0.001$). With each year of increasing age there was an approximate 1% increase in the risk of death (HR 1.01, 95% CI 1.004–1.016; $P<0.001$). Kaplan–Meier survival curves showed that after the exclusion of patients with less than 3 months survival, there was no difference in OS between patients who did and patients who did not receive adjuvant EBRT (median 20 months vs 19 months; $P=0.14$); however, multivariate analysis showed that adjuvant EBRT was an independent predictor of improved OS (HR 0.87, 95% CI 0.75–1.00; $P=0.044$).

Conclusion. Adjuvant EBRT provided a survival benefit to patients with operable, node-negative pancreatic cancer and should be considered as adjuvant treatment in this group of patients.

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