Abstract

The role of radiotherapy in pancreatic cancer is controversial. Its utility in treatment has been investigated in a number of clinical settings, including before and after surgery for operable cancers and in the treatment of locally advanced, inoperable disease. Adjuvant treatment has had mixed results in trials and there is now interest in better selecting patients who may benefit from neoadjuvant treatment. The benefit of radiotherapy continues to be poorly defined, due in part to the large number of differing treatment regimens that have been investigated. This article reviews the current evidence for radiotherapy in pancreatic cancer, with a focus on identifying those patients who are most likely to benefit from radiotherapy treatment. It will also discuss some of the planning considerations.

Adjuvant treatment

Successful surgical resection provides the best potential for a cure of pancreatic cancer, but distant metastatic disease remains the main source of treatment failure. Despite this, local failure occurs commonly following surgical resection and approximately 30% in autopsy series die of predominantly local progression. In the adjuvant setting, the role of radiotherapy is controversial. Early randomised trials have had mixed results.

A possible benefit for radiotherapy in the adjuvant setting was demonstrated initially by a Gastrointestinal Tumour Study Group trial conducted in the 1970s. Patients were randomised to receive adjuvant chemoradiotherapy (n=22) or be observed (n=21) following curative resection. The chemoradiotherapy consisted of two courses of 20Gy in 10 fractions concurrent with bolus 5-FU, with a two week break. There was an increased survival benefit in those undergoing adjuvant treatment of 20 vs 11 months. However, this trial has been criticised for old techniques incorporating low radiotherapy dose and lack of radiotherapy quality control.

An ESPAC-1 trial of 289 randomised post operative patients to receive adjuvant chemoradiotherapy or to undergo observation alone. The radiotherapy was similar to the previous randomised trials. However, the concurrent chemotherapy consisted of infusional 5-FU opposed to bolus administration. The study showed a non-significant improvement in median survival of 24.5 months in the treatment group compared to 19.0 months in the observation arm, p=0.208. Whether the radiation component contributed to the trend towards improved survival is open to conjecture.

The results of these trials are difficult to translate to modern radiotherapy treatments for pancreatic cancer. The above trials have been criticised for utilising older radiotherapy techniques such as two dimensional planning, smaller doses of radiotherapy, treatment breaks and bolus 5-FU as concurrent chemotherapy. Surgical techniques have also improved potentially reducing the risk of local recurrence. A large retrospective series from Johns Hopkins Hospital reviewed patients treated with median doses of 50Gy, three dimensional planning and majority with no treatment breaks. There was a statistically significant median (21.2 months vs 14.4 months), two year (43.9% vs 31.9%) and five year (20.1% vs 15.4%) survival of chemoradiotherapy compared to surgery alone. It can be argued that chemotherapy alone is responsible for this benefit. However in the chemotherapy alone trials local recurrence is still a major issue.

The CONKO-001 trial randomised 368 patients with R0 (negative margins) (>80%) or R1 resection to Gemcitabine
The median disease-free survival was 13.4 months vs 6.9 months favouring the treatment arm, p<0.001. This trial reported local recurrence rates of 34% in the Gemcitabine arm and 41% in the observation arms, suggesting that 30-40% of patients would benefit from further local treatment such as radiotherapy and hence justifying it’s use in many centres, especially in the United States.

The RTOG 9704 trial conducted in North America, where adjuvant radiotherapy is used more often than in other countries had some of the best loco-regional control rates. The study delivered radiotherapy with contemporary doses (50.4Gy) and had good quality control. 5-FU based chemoradiotherapy was sandwiched between either gemcitabine chemotherapy or 5-FU chemotherapy. Locoregional control rates were 25% and 30% respectively. Despite this, over 70% of patients developed distant metastases.

Identifying patients with higher risk of local recurrence

The cohort that would most benefit from adjuvant radiotherapy has not been established. A meta-analysis demonstrated a survival benefit from chemoradiotherapy in patients with positive margins, highlighting the importance of local control, despite pancreatic cancer having a high propensity for metastatic spread. The role of the addition of adjuvant radiotherapy continues to be studied, with a current trial (RTOG 0848) randomising patients to 5-FU based CRT or further CTx alone in patients who have not progressed during induction with Gemcitabine chemotherapy, evaluating end-points of overall and disease-free survival.

There is a growing interest in identification of biomarkers that may differentiate those patients who are more likely to progress locally rather than distantly and therefore benefit from aggressive local treatment. An autopsy study found that positive staining for the intracellular protein DPC4 (or SMAD4) suggested a patient was more likely to recur locally. Only 22% of patients with no metastatic disease at biopsy showed loss of expression of DPC4. Conversely, 73% of patients with extensive metastatic disease demonstrated loss of staining.

Neoadjuvant treatment for maximal local control prior to definitive surgery

Over the last 20 years there has been interest in neoadjuvant chemotherapy and chemoradiotherapy in both resectable and unresectable pancreatic cancer at risk of R1 resection and/or local recurrence. The rationale for neoadjuvant treatment includes early treatment of micrometastatic disease and allowing time for micrometastases to declare themselves prior to undergoing extensive surgery. Neoadjuvant treatment allows for an assessment of tumour responsiveness and can overcome the issue of delayed post-operative treatment due to surgical complications or the need for recovery of adequate performance status.

A phase 2 neoadjuvant trial treated patients with seven weekly gemcitabine infusions (400mg/m2) plus radiotherapy 30Gy/10# over two weeks, with surgery 4-6 weeks after completion of neoadjuvant treatment. Eighty-six patients were enrolled in the study and 74% underwent successful surgery. The other patients were deemed inoperable due to disease progression, decline in performance status or extra pancreatic disease at time of surgery. In the patients who underwent surgery, median survival was 34 months with a 27% five year survival. Importantly, there was only an 11% local recurrence rate.

The French SFRO 97-04 phase II trial of 41 patients combined 5-FU-cisplatin chemotherapy with 50Gy of radiation followed by surgical resection. Sixty-three per cent of patients underwent surgical resection with an 80.7% R0 resection rate. There was a low median follow-up period of only 11 months, however the local recurrence rate was only 4% with 48% one year survival.

Locally advanced disease

A number of studies assessing the benefit of chemoradiotherapy have been conducted in the locally advanced/unresectable population. There is extensive heterogeneity between the studies and results have been mixed. Radiotherapy regimens in this cohort are discussed in detail in this issue of Cancer Forum.

Radiotherapy technique

In this current era, with a paucity of good evidence for radiotherapy in pancreatic cancer, it is imperative that patients are treated with good quality radiotherapy.

Compliance with standardised radiotherapy technique has been shown to improve patient outcomes in the post-operative setting. A secondary analysis of the adjuvant RTOG 9704 trial was undertaken to determine whether deviation from radiotherapy protocols including simulation, image verification, target volume delineation and normal tissue dose constraints influenced survival outcomes. Fifty-one per cent of patients were treated as per protocol and had a median survival of 1.74 years, compared with a median survival of 1.46 years if treated less than per protocol, p=0.0077. Patients were also significantly less likely to recur if they were treated as per protocol, p=0.016.

Volumes can be safely reduced by omitting prophylactic nodal irradiation in the locally advanced setting. A study of 74 patients with locally advanced disease gave 36Gy/15# concurrent with full-dose gemcitabine 1000mg/m2 and treated the gross tumour volume (GTV) + 1cm only. Only 5% failed in the peri-pancreatic nodes justifying the reduction in treatment volumes. The risk of gastrointestinal
toxicity has been found to correlate with planning tumour volume (PTV) with statistically significant lower risk with PTV volumes <260cc.

**New techniques**

Intensity modulated radiotherapy (IMRT) has reduced toxicity rates in radiation treatment of pancreatic cancer. A systematic review comparing with 3D conformal radiotherapy found lower rates of ≥ grade 3 nausea and vomiting (13.4% vs 7.8%, p<0.001 and ≥ grade 3 diarrhoea (11.6% vs 2.0%, p<0.001). There was also a lower incidence of late toxicity in the IMRT arm, predominantly gastrointestinal bleeding or duodenal ulcer (10.6% vs 5.0%, p=0.017). There were no differences in overall or progression-free survival.

Increased dose conformity is being assessed to allow for radiotherapy dose escalation. A phase 1/2 trial of IMRT with breath-hold or 4D-CT to accurately account for organ motion and generate an internal target volume allowed for a dose escalation of 55Gy in 25 fractions with full-dose gemcitabine (1000mg/m2). Dose-limiting toxicity was seen in 24% and deemed to be safe. The treatment was not without its complications however, with cases of duodenal bleed and perforation, and two patients dying of possible treatment related causes.

A retrospective series of patients undergoing five fractionated treatments of 7-10Gy showed similar local control rates (81% at 12 months) with less toxicity. Late grade three toxicity was seen in only four patients (5.3%) and consisted of gastrointestinal bleeding and anorexia requiring nasogastric feeding. This trial demonstrates that more fractionated treatments reduce toxicity, however stereotactic radiotherapy for pancreas cancer remains investigation.

**Conclusion**

It appears there may be a benefit of radiotherapy for a subset of patients with pancreatic cancer, however that group is not well defined from the evidence at this stage and perhaps further evaluation of biomarkers will identify that group. It is evident that poorly delivered radiotherapy in high doses and toxic chemotherapy is harmful to patients, negating any possible benefit of further local treatment.

**References**


**Figure 1**: CT/PET fusion demonstrating IMRT volumes. GTV – light blue, CTV – light green, PTV - red. Organs at risk: liver – purple; stomach – green; kidneys – dark blue; small bowel - orange.

**Figure 2**: Isodose lines for same plan - 95% isodose line in magenta, 100% isodose line in green. Note sculpting of dose around the stomach.

**Stereotactic radiotherapy**

There is growing interest in the use of stereotactic radiotherapy in order to reduce treatment margins and reduce treatment time with higher doses per fraction. A series of 77 patients treated with a single fraction of 25Gy demonstrated a 12-month freedom from local progression rate of 84%. However, there was a 25% rate of grade 2 or greater late toxicity at 12 months consisting of gastric ulceration, duodenal or biliary sticture and one episode of bowel perforation.


