


Application of stereotactic body radiotherapy in advanced pancreatic cancers in Australia

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Abstract

Introduction: The majority of pancreatic cancers present locally advanced and carry a high mortality rate. Treatment is challenging, with mixed data suggesting use of chemotherapy alone or in combination with radiotherapy. The use of radiotherapy has previously been limited due to lack of ability to deliver radiation to the tumour mass without causing significant toxicity to surrounding organs. Stereotactic body radiotherapy (SBRT) allows delivery of higher biologically equivalent dose in a shorter treatment duration. We sought to investigate the safety and application of this technique in our centre. **Method:** We enrolled 27 patients from 2015, identified as locally advanced unresectable with histologically confirmed, non-metastatic, pancreatic adenocarcinoma. All patients had endoscopically inserted fiducial markers and where possible concurrent chemotherapy was administered. Dose schedules ranged from 25 to 42 Gy in 5 or 3 fractions. **Results:** With an overall median follow up of 9 months (range, 3–32.7), the median survival was 11.6 months. Of those alive at 1 year, the local control rate was 67%. Six patients had Grade 3 toxicity, and other six had Grade 2 toxicity. None had Grade 4 or above toxicity. The most common symptom recorded was fatigue. **Conclusion:** SBRT for locally advanced pancreatic cancer is technically complex but feasible in a high volume centre. SBRT is unique, allowing safe delivery of high radiation dose resulting in good local control and decreases treatment time making it an attractive option for patients with unresectable pancreatic cancer.

Introduction

Pancreatic cancer remains one of the most aggressive malignancies and is the fifth most common cause of cancer-related deaths in Australia.¹ The number of new cases in Australia increased from 1206 in 1982 to 2865 in 2013 and is predicted that by 2030, pancreatic cancer will be the second highest cause of cancer mortality. The overall 5 years survival rate for pancreatic cancer is less than 8%, and this rate has not significantly improved in the past 30 years.¹ Complete surgical resection remains the only means of providing long-term control and potential cure.² However, a majority of patients present

late in their disease with up to 85% being unresectable, either from metastatic disease or locally advanced disease, leading to even worse overall survival.³

Currently, the standard treatment for these patients involves chemotherapy alone with conflicting results for the addition of radiation treatment. A more recent trial, LAP07, failed to demonstrate a statistically significant difference in the median survival between chemoradiotherapy compared to chemotherapy alone. However, it showed improvement in local control and the potential quality of life afforded by the addition of radiotherapy through delayed or decreased need for salvage therapy.⁴ In addition, Iacobuzio-Donahue et al.⁵ demonstrated that

up to 30% died from locally obstructive disease with few or no distant metastases. This highlights the potential benefit and importance of local therapy in the management of locally advanced pancreatic cancer.

The use of radiotherapy has been limited in the past due to the lack of ability to deliver the radiation to the pancreatic mass without causing significant toxicity to surrounding organs. Conventional radiotherapy requires approximately 6 weeks of daily treatment, which is significant for what is otherwise a disease with poor prognosis. Stereotactic body radiotherapy (SBRT) is a minimally invasive, innovative treatment option that allows delivery of a higher biologically equivalent dose, in a shorter treatment duration with minimal side effects. We investigated the application and safety of SBRT for locally advanced unresectable pancreatic cancer with the use of endoscopic ultrasound (EUS) inserted fiducials and concurrent chemotherapy.

Methods

Patients and eligibility

This was a pilot prospective feasibility trial and we have data from 27 consecutively treated patients with biopsy proven non-metastatic, locally advanced, unresectable pancreatic cancer at the Royal Adelaide Hospital between July 2015 and December 2017. The patients were deemed inoperable from assessment of a multi-disciplinary team. Typical criteria include solid tumour contact with superior mesenteric artery (SMA) or celiac artery by more than 180°, celiac plexus involvement or unreconstructible superior mesenteric vein (SMV). Patients were included if they were 18 years or older, had Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, with projected life expectancy of at least 6 weeks. Exclusion criteria included prior abdominal radiotherapy, other serious uncontrolled medical conditions or ECOG performance scores of 3 or 4. The study was approved by our institutional ethics committee and before receiving treatment, all patients provided written informed consent.

Treatment planning

Three to four gold fiducial seeds were inserted using preloaded EUS needles outlining the tumour periphery. Computed tomography (CT) planning images were obtained with intravenous contrast, 3 mm slices and multi-detector 4DCT. The patient underwent imaging and radiotherapy in the supine position, with arms up and full body immobilisation using the OmniV SBRT system (Bionix Radiation Therapy, Toledo, OH, USA). Treatment planning utilised fusion of magnetic resonance

imaging (MRI) and/or positron emission tomography (PET) scan to ensure accurate delineation of the target volume. Free breathing technique was used with utilisation of 4DCT and internal target volume (ITV) concept to account for all phases of breathing. The gross tumour volume (GTV) was defined as the tumour based on the fused MRI and/or PET scan. The planning target volume 1 (PTV1) included an expanded uniform 5 mm margin. The planning target volume 2 (PTV2) was a smaller volume where a copy of PTV1 was made, but edited to include area of vessel abutment and boosted to a higher dose.

Radiation dose and delivery

Our initial PTV1 dose prescription was 25 Gy in 5 fractions which was later adapted to 30 Gy in 5 fractions in our protocol. PTV2 was prescribed to 35 Gy and delivered as a simultaneous integrated boost. The prescription isodose encompassed at least 95% of the PTV. Dose constraints for the organs at risk followed the Timmerman guidelines.⁶ Total treatment was 5 fractions delivered at least 48 h apart. Daily on-board imaging was utilised with cone-beam CT matching to fiducials with 0 mm tolerance for couch shifts. Treatment was delivered using flattening filter free linac based volumetric modulated arc radiotherapy (VMAT) technique. Majority of patients received 3 months of neoadjuvant chemotherapy involving Fluorouracil, Leucovorin, Irinotecan and Oxaliplatin (FOLFIRINOX), then concurrent Capecitabine during SBRT.

Follow-up

The patients were examined 1 month after SBRT and every 3 months thereafter by the treating radiation oncologists. At each follow up, clinical examination, CA 19-9, CT scan and toxicity profile were collected. Local control was defined by stable findings on CT scan with absence of local, nodal or distant progression. Acute toxicity was defined as adverse events occurring less than 3 months after SBRT and long term was defined as those occurring after 3 months. Toxicity was graded using the Common Terminology Criteria for Adverse Events v4.03. The local control and length of survival were calculated from the initiation of SBRT to progression or death.

Statistical analysis

Statistical analysis was carried out using R statistical software version 3.4.2 for Windows. The comparisons between arms and subgroups were performed using Chi-square and Fisher's exact test for categorical response

variable and *t*-test for quantitative response variables. Univariate analysis for survival was performed using the Kaplan-Meier method and differences in Kaplan-Meier curves were tested for statistical significance using the log rank test. Cox regression analysis was carried out to

estimate the effect of significant factors on overall survival rate. The optimal Cox regression model was developed using a log-likelihood ratio statistical test to compare several candidate models, including those considering interactions. Once the optimal statistical model was selected, it was used to produce adjusted survival curves for various subgroups of patients.

Table 1. Baseline characteristics (*n* = 27).

	<i>n</i>	%
Median age (range)	74 (56–92)	
ECOG		
0	2	7
1	20	74
2	5	19
Stage		
IB	2	7
IIA	11	41
IIB	2	7
III	11	41
Recurrent	1	4
Median size (cm, range)	3.3 (1.5–6.3)	
Median initial CA 19-9 (U/mL, range)	173 (2–6779)	
Concurrent chemotherapy		
Yes	22	81
No	5	19
Radiation dose		
25 Gy/5 F, 35 Gy SIB	10	37
30 Gy/5 F, 35 Gy SIB	13	48
36 Gy/3 F	3	11
42 Gy/3 F	1	4

F, fractions; SIB, simultaneous integrated boost.

Results

Table 1 lists the patient and treatment characteristics. Of the 27 patients, 10 received 25 Gy in 5 fractions with 35 Gy simultaneous integrated boost to the area of vessel abutment. The initial dose of 25 Gy was used in our protocol to assess the safety and feasibility and once we were confident in treatment planning and delivery, our protocol was developed into 30 Gy with 35 Gy simultaneous integrated boost. All but five patients received concurrent chemotherapy with oral Capecitabine. Three patients were deemed unfit for chemotherapy due to their age (>80 years old) or with significant medical comorbidities. The radiation dose was escalated to 36 Gy in 3 fractions for patients who did not have chemotherapy. One patient had protocol deviation where a higher dose of 42 Gy in 3 fractions was delivered. This patient in particular was young and fit with an isolated nodal recurrence following Whipple’s procedure and adjuvant chemotherapy. This was feasible as the volume was small and away from organs at risk, allowing safe dose escalation.

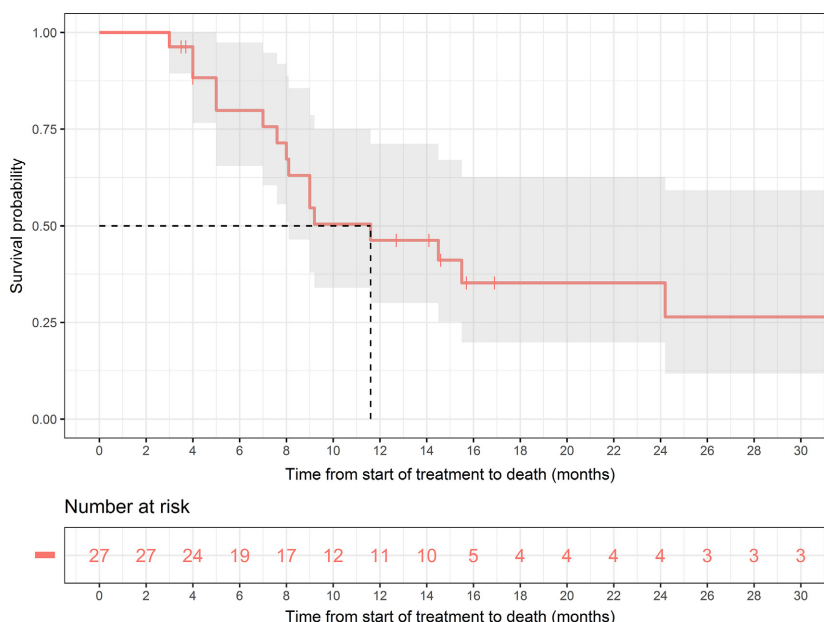


Figure 1. Kaplan-Meier curve of overall survival.

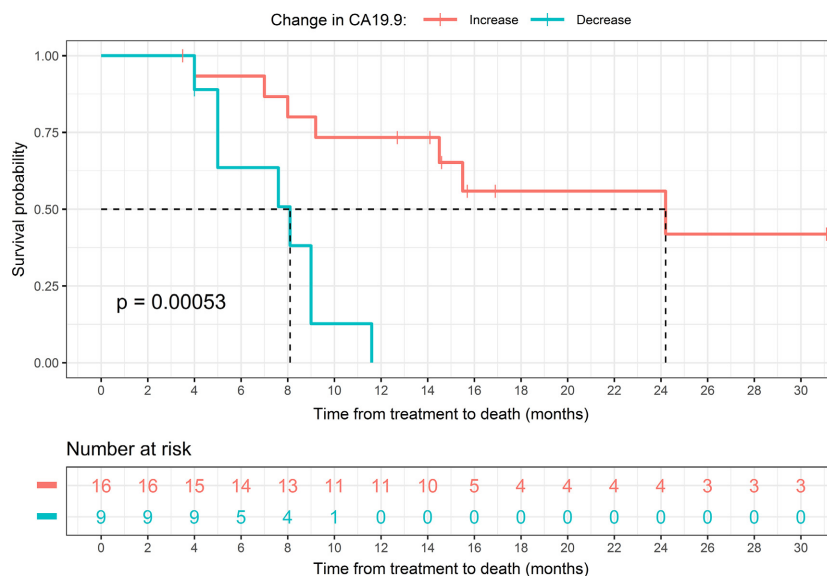


Figure 2. Kaplan-Meier curve of survival with increase and decrease in CA 19-9 with survival.

At median follow up of 9 months (range 3–32.7 months), the median length of overall survival was 11.6 months (Fig. 1). Of the cohort of patients alive at 1 year, the local control rate was 67%. The median CA 19-9 was 173 U/mL. We had two missing data on the post-treatment CA 19-9 values which had to be excluded in our CA 19-9 analysis. Figure 2 demonstrates the relationship between survival and change in CA 19-9. As expected, a decrease in CA 19-9 post-treatment was associated with significant longer survival with a P value

of 0.00053. Of the 27 patients, six were known to have developed distant metastases and 13 achieved initial regression of their local disease (Table 2).

All of our patients had Grade 3 or less acute toxicity with majority having Grade 1 toxicity (33%). Six patients (22%) each experienced Grade 2 and Grade 3 acutotoxicity. These included fatigue, nausea and abdominal pain. Five of the six patients with Grade 3 toxicity received a dose of 25 Gy in 5 fractions with 35 Gy simultaneous integrated boost. The one other patient with grade 3 toxicity received a higher dose without chemotherapy of 36 Gy in 3 fractions. Another six patients experienced no toxicity at all (Table 3). Fatigue was the most common side effect experienced by our cohort, occurring in 13 patients (Table 4). Chemotherapy associated toxicities like diarrhoea and skin toxicities were not seen.

Table 2. Results.

1 year local control	67%
Initial radiological	
Regression	13 (48%)
Stable	6 (22%)
Progression	8 (30%)
Progression	
Metastatic disease	6 (22%)
Overall survival	11.6 months

PFS, progression free survival.

Table 3. Toxicity grade (CTCAE v4.03).

	No. (%)
Grade 0	6 (22)
Grade 1	9 (33)
Grade 2	6 (22)
Grade 3	6 (22)
Grade 4	0 (0)

CTCAE, common terminology criteria for adverse events; No, number.

Discussion

The technological development in the field of radiation, in particular SBRT, has made delivery of radiation

Table 4. Common toxicity type.

	No. (%)
Fatigue	13 (48)
Nausea/vomiting	9 (33)
Pain	6 (22)
Decreased appetite	5 (19)

No, number.

Table 5. Literature summary in pancreatic SBRT.

References	Patients	Dose	1 year local control (%)	MS (months)	Chemo
Koong et al ¹⁰	16 LA	25 Gy × 1	94	8.3	5-FU concurrent
Didolkar et al ¹¹	85 LA/LR	5–10 Gy × 3	92	18.6	Post-SBRT GEM
Polistina et al ¹²	23 LA	10 Gy × 3	50	10.6	6 weeks induction GEM
Mahadevan et al ¹³	39 LA	8–12 Gy × 3	85	20	2c induction GEM
Schellenberg et al ¹⁴	20 LA	25 Gy × 1	94	11.8	1c induction + post-SBRT GEM
Goyal et al ¹⁵	19 LA/LR	20–25 Gy × 1, 8–10 Gy × 3	81	14.4	5-FU or GEM
Lominska et al ¹⁶	28 LA/LR	4–8 Gy × 3–5	86	5.9	5-FU or GEM prior to SBRT
Chuong et al ¹⁷	73 BR/LA	5–10 Gy × 5	81	16.4 BR, 15 LA	3 cycles GTX
Gurka et al ¹⁸	38 BR/LA	5–6 Gy × 5	79	12.3	Post/concurrent- GEM or 5-FU
Moningi et al ¹⁹	88 BR/LA	5–6.6 Gy × 5	61	18.4	Peri-SBRT GEM or 5-FU
Herman et al ²⁰	49 LA	6.5 Gy × 5	78	13.9	Pre-SBRT GEM
Lin et al ²¹	20 LA	7–9 Gy × 5	70	20	Concurrent GEM
Tozzi et al ²²	30 LA/LR	7.5 Gy × 6	77	11	Pre-SBRT GEM based

LA, locally advanced; 5-FU, 5-fluorouracil; LR, locally recurrent; SBRT, stereotactic body radiotherapy; GEM, gemcitabine; MS, median survival; BR, borderline resectable; GTX, gemcitabine, taxotere, xeloda; c, cycle.

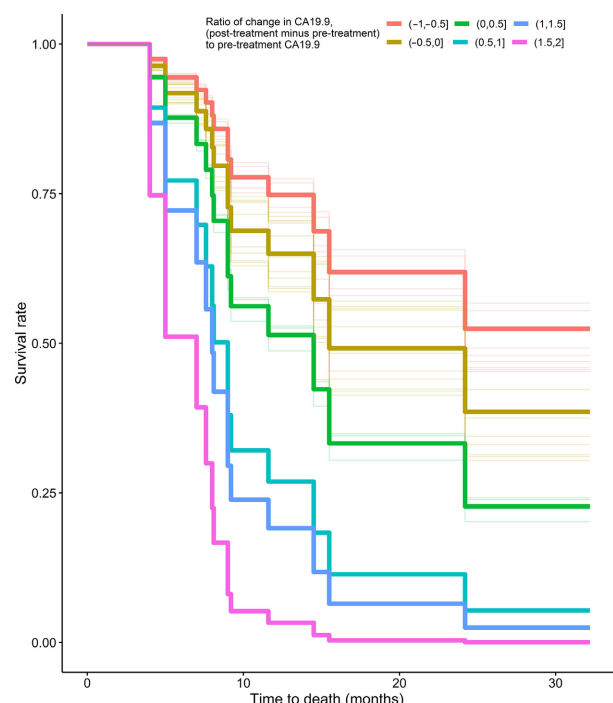


Figure 3. Adjusted survival curves based on magnitude of change in CA 19.9. Group 1 (–1, –0.5) is more than 50% decrease; Group 2 (–0.5, 0) is 0–50% decrease; Group 3 (0, 0.5) is 0–50% increase; Group 4 (0.5, 1) is from 50% to 100% increase; Group 5 (1, 1.5) is 100–150% increase; Group 6 (1.5, 2) is from 150% to 200% increase.

extremely precise allowing sparing of normal organs more efficiently, whilst simultaneously delivering a higher biological dose over a shorter treatment time, thereby improving the therapeutic window.

This is particularly desirable in the treatment of locally advanced pancreatic cancers where obtaining durable local control is important and beneficial, but at the same time, being confronted by the intimate position of the tumour in relation to radiosensitive gastroduodenal structures.

To date, the role of radiotherapy in the treatment paradigm for patients with locally advanced pancreatic cancer has been conflicting. Older trials, including the Gastrointestinal Tumour Study Group (GITSG) 9283 and Eastern Cooperative Oncology Group (ECOG) 4201 demonstrated improved survival with chemoradiotherapy compared to chemotherapy alone. However, this also resulted in significant increased toxicity.^{7,8} In contrast, the French study published in 2008 demonstrated decreased overall survival rates undergoing combined chemoradiotherapy compared to gemcitabine alone.⁹ With the aim to further clarify the uncertainty regarding the role of standard chemoradiotherapy, the phase III LAP07 trial was developed. This evaluated the role of chemoradiotherapy following induction chemotherapy compared to chemotherapy alone. The investigators reported no significant improvement in overall survival. However, the addition of radiation therapy was associated with decreased local progression. Even with this improvement, local control is poor which is consistent with most studies involving conventional three-dimensional conformal radiation therapy. Importantly, poor local control often causes pain and/or obstructive symptoms that negatively affect patient’s quality of life. Iacobuzio-Donahue et al.⁵ demonstrated up to 30% of pancreatic cancer patients died from locally obstructive disease with few or no distant metastases. These findings highlight the potential benefit

and importance of local radiation therapy in the management of locally advanced pancreatic cancer and also the need for further advancement in technique to improve local control.

Non-randomised evidence investigating SBRT in pancreatic cancer has demonstrated very encouraging results with excellent locoregional control rates when compared to standard treatment paradigms. Reported 1 year locoregional control rates ranged from 50% to 94% (Table 5) compared to the 54% local control rate using conventional radiotherapy technique reported by Hammel et al.^{4,10–20} Pooled analysis of 18 SBRT studies published in 2017 reported median overall survival of 17 months (range 5.7–47 months), superior to current patient outcomes with conventional treatments.²³ Our cohort's median overall survival of 11.6 months, and 1 year local control of 67% were within the range of the other SBRT studies outside of Australia.

Furthermore, SBRT is given over a limited number of fractions substantially decreasing the overall treatment time compared to the conventional 5–6 weeks chemoradiotherapy course. This allows fewer interruptions in systemic therapy, which may ultimately improve outcome based on the high rates of distant metastasis seen within this patient population. Additionally, given the poor prognosis of these patients, life expectancy is very short. SBRT is able to minimise patient's time spent undergoing treatment, thereby potentially improving their quality of life.

SBRT regimens have been associated with less incidence of Grade 3 and above acute toxicities compared with conventionally fractionated radiation therapy.^{24–26} However, late gastroduodenal complications with ulcers and bleeding have been seen in earlier studies, especially those with single fraction SBRT at a rate of 10–47%.^{11,27,28} More recent studies using hypofractionated SBRT (3–5 fractions) have shown reduced rates of late gastroduodenal toxicity compared to single fractionated treatment, hence our reasoning behind a 5 fraction regimen.^{17,20,29} Investigators from South Korea have also reported that patients treated over consecutive days experienced higher rates of toxicity suggesting that increasing interfraction interval to greater than 24 h reduced side effects.³⁰ The prescription used in our protocol was 30 Gy in 5 fractions over 2 weeks with a simultaneous integrated boost of 35 Gy to area of vessel abutment. This equated to BED10 of 48 and 59.5 Gy respectively.

The only factor that was found to have a statistical significant effect on survival was the change in CA19-9 values before and after treatment. As expected a decrease indicated longer survival and an increase was related to shorter survival. It is likely that there are further factors that may be of significance which were not detected due to the small number of patients in our study. We further

looked at the magnitude of change in CA19-9 and found that a decrease of 10% from the initial CA19-9 value reduced the monthly hazard rate of death by 9.7% (95% CI: 4–15.7%). Figure 3 illustrates the estimated survival curve for specific group of patients defined by the magnitude of decrease or increase in CA19-9. Further research is needed to validate if indeed the magnitude of change in CA19-9 in pancreatic SBRT is a reliable prognostic predictor.

We acknowledge this paper's limitation on the ability for robust comparisons due to the small patient number and heterogeneity. But with these encouraging preliminary results and the apparent benefits seen, pancreatic SBRT remains an exciting field for further investigation. It must be explored in a randomised setting to validate the use of this novel technique and include studies focusing on organ tolerance, combining systemic and/or immunotherapy, molecular profiling, biochemical prognostic factors and robust quality of life measurements.

Conclusion

Our institute's experience in SBRT for locally advanced unresectable pancreatic cancer has demonstrated promising local control rates which are higher than conventional external beam radiation therapy regimens, with minimal toxicities. In view of these findings, we find this treatment approach a feasible option for selected patients. Our results are in keeping with other centres internationally who have explored the role of SBRT in the management of locally advanced pancreatic cancer. To our knowledge, this is the first published data in the Oceanic region looking into this. Further phase three studies will likely validate the use of SBRT as standard treatment for locally advanced unresectable pancreatic cancer.

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Conflict of Interest

The authors declare no conflict of interest.

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