Original Article

Palliative radiotherapy in pancreatic cancer: a retrospective study of 100 cases and regional patterns of practice

Alvin Ka Nok Liu[1]^, Shilo Lefresne[2,3]

[1]Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [2]Department of Surgery, University of British Columbia, Vancouver, British Columbia, Canada; [3]Department of Radiation Oncology, BC Cancer, Vancouver, British Columbia, Canada

Contributions: (I) Conception and design: Both authors; (II) Administrative support: S Lefresne; (III) Provision of study materials or patients: S Lefresne; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Shilo Lefresne, MD, FRCPC. Radiation Oncologist, Department of Surgery, University of British Columbia, 2775 Laurel Street, Vancouver, British Columbia V5Z 1M9, Canada; Department of Radiation Oncology, BC Cancer, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4E6, Canada. Email: SLefresne@bccancer.bc.ca.

Background: Pancreatic cancer is often incurable and can be associated with significant pain and abdominal symptoms. This study aims to characterize the symptomatic burden of patients with pancreatic cancer receiving palliative radiotherapy and the corresponding symptomatic and radiographic responses.

Methods: Patients with pancreatic adenocarcinoma referred to BC Cancer for palliative radiation from 2006 to 2013 were retrospectively reviewed. Logistic regression and Cox proportional hazards model were used to evaluate variables predictive of symptomatic response and survival respectively.

Results: One hundred patients were identified. The majority had good performance status (Eastern Cooperative Oncology Group score 0–1, 82%), received only one line of chemotherapy (91%), and presented with pain (84%). The most common radiotherapy prescription was 30 Gy in 10 fractions (22%). Pain improved in 69%, early satiety and bloating improved in 59%, and hemostasis was achieved in 73% of cases. Treatment toxicity occurred in 47% of cases and were predominantly grade 1–2 with 1 case of grade 3 toxicity. Median survival was 5.1 months. Tumor size, radiotherapy dose, and concurrent chemotherapy were not predictive of symptomatic response nor prolonged survival.

Conclusions: In the largest cohort to date evaluating palliative radiotherapy in pancreatic adenocarcinoma, radiation was efficacious in improving pain and gastrointestinal bleeding and was generally well-tolerated. Additional studies on the efficacy and optimal prescriptions for palliative radiotherapy are necessary in this population.

Keywords: Pancreatic cancer; palliation; radiotherapy (RT)

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Introduction

Pancreatic cancer is the seventh leading cause of cancer deaths world-wide and is projected to rise to be the second by 2030 (1,2). Due to a lack of symptoms until advanced disease, most patients with pancreatic cancer will have developed tumor extension into critical structures or metastases precluding curative resection by time of diagnosis (3). The prognosis is poor, and patients often experience pain, early satiety and nausea, gastric outlet obstruction, and obstructive jaundice, from local

^ ORCID: 0000-0002-5111-3713.

progression resulting in significant deterioration in quality of life (4,5). To date, most literature on radiotherapy (RT) in pancreatic cancer has focused on the neoadjuvant and adjuvant settings with few studies guiding its role in providing symptomatic palliation (6-9).

While the LAP07 trial demonstrated no benefit in overall survival for chemoradiotherapy compared to chemotherapy alone, local control rates were more than 10% greater in the RT treated group (8). This finding suggests that RT could have an important role in delaying or palliating symptoms associated with local progression. Due to the morbidity associated with local progression, this is an important topic of investigation (10,11). Four contemporary studies totaling 135 patients have demonstrated pain relief with palliative RT (12-15), but the role of RT in improving symptoms of early satiety, abdominal bloating, and life-threatening bleeding remains unexplored (16).

The aims of this provincial, population-based study are to further characterize the symptom burden in patients with unresectable pancreatic cancer referred for RT, describe RT patterns of practice, and assess radiographic and symptomatic response to treatment. Secondarily, factors associated with response to treatment and survival will also be assessed. Due to the lack of guidelines in this setting, our primary hypothesis is that most patients referred for palliative RT will have advanced disease (poor performance status, progression after more than one line of systemic therapy, high symptom burden) and that the RT prescriptions will be highly varied. Our secondary hypothesis is that RT will be associated with a modest improvement in symptoms and well tolerated with minimal acute toxicity. We present this article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1417/rc).

Highlight box

Key findings

- Following conventional radiotherapy, over two-thirds of patients saw improvements in pain and gastrointestinal bleeding and over half of patients saw improvements in early satiety and abdominal bloating.
- Treatment toxicity occurred in approximately half of cases and were predominantly grade 1–2.
- Tumor size, radiotherapy dose, and concurrent chemotherapy were not predictive of symptomatic response nor prolonged survival.

What is known and what is new?

- Prospective trials have demonstrated that chemoradiotherapy improves local control compared to chemotherapy alone in locally advanced pancreatic cancer.
- In the largest study looking at palliative radiotherapy in pancreatic cancer, we observed that radiotherapy was effective at improving pain, symptoms of early satiety and bloating, and achieving hemostasis.

What is the implication, and what should change now?

- The shortest course of palliative radiotherapy to achieve symptom control may be effective and well-tolerated for managing common and life-threatening complications of pancreatic cancer.
- Additional prospective palliative studies are necessary to corroborate the findings of our study.

Methods

Data abstraction

The provincial cancer database was used to identify patients with pancreatic adenocarcinoma referred to BC Cancer, an institution comprised of 5 regional cancer centres, for palliative RT from January 2006 and December 2013. Palliative RT was defined as RT delivered to the pancreas without adjuvant, neoadjuvant, or curative intent. Patients who were previously treated with curative resections and had palliative RT following a local recurrence were included. Patients who had received stereotactic ablative RT were excluded.

Medical records were retrospectively reviewed through the Cancer Agency Information Systems database for patient demographics, presenting symptoms, reason for referral to radiation oncology, performance status, pre-treatment carbohydrate antigen 19.9 (CA19.9) levels, prior operative interventions, chemotherapy and RT details, and response to treatment. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the joint Research Ethics Board of University of British Columbia and BC Cancer (No. H17-01636). A waiver of consent was approved by the ethics board owing to the minimal risk posed by the study and the infeasibility of obtaining consent in a retrospective manner.

Statistical analysis

Patient and treatment characteristics were summarized via descriptive statistics. Radiologic responses of target lesions were assessed with the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Clinical response was categorized as complete response (CR), partial response

(PR), or no response for complete resolution of symptoms and cessation of analgesics, reduction in symptoms, or no change or worsening symptoms, respectively. Toxicity was assessed by reviewing oncologist treatment and follow up notes and graded by study investigators according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4. A logistic regression was performed to determine predictors of symptomatic response, which was dichotomized as no response in any of the evaluated symptoms *vs.* CR or PR in any of the evaluated symptoms.

The Kaplan-Meier method was used to assess survival measured from the date of the first fraction of palliative RT. Factors hypothesized to be associated with clinical response were selected a priori for univariable analysis via a log-rank test. Variables significantly associated with survival ($P<0.05$) were analyzed in a multivariable Cox proportional hazards model. Statistical analysis was performed using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Demographics

One hundred patients received palliative RT for their pancreatic cancer at our institution over the 8-year study period and are summarized in *Table 1*. At time of radiation oncology consultation, most patients presented with good performance status (Eastern Cooperative Oncology Group score 0–1, 82%) and were symptomatic with pain (84%), abdominal bloating/early satiety (40%), and bleeding (15%). Of those on analgesics, 17% were on a combination of non-opioid analgesics and weak opioids such as codeine, hydrocodone, and tramadol, while 76% were on strong opioids such as morphine, hydromorphone, oxycodone, and fentanyl. Only a third of patients had metastatic disease. The majority had prior chemotherapy (54%), which predominantly consisted of gemcitabine-based regimens (93%). A minority of patients (9%) had more than one line of therapy prior to referral for RT. Nineteen patients had prior partial pancreatectomies or Whipple's while fourteen patients had bypass surgeries such as gastrojejunostomies.

Radiotherapy

RT details are described in *Table 2*. Most treatments were delivered via 3D conformal techniques (57%). The regimens typically consisted of 10 or fewer fractions (58%) with the most common prescriptions being 30 Gy in 10 fractions (22%) and 20 Gy in 5 fractions (19%). RT was stopped prior to completion in 15 cases due to toxicity (7%), a decline in performance status (4%), patient declining further treatment (2%), metastatic progression (1%), and death (1%).

Treatment response and toxicity

Symptomatic response to treatment was recorded in 79 cases. Median time to post-treatment assessment of symptomatic response was 28.5 days (range, 0–125 days) following completion of RT. Of these 79 cases, 75 had pain, 39 had bloating or early satiety, and 11 had gastrointestinal (GI) bleeding (*Figure 1*). Most cases had PR or CR to treatment for one or more of the presenting symptoms (75%). Palliation for bleeding was associated with the highest response rate (73% CR). Pain improved in 69% (CR + PR) of cases and a majority (59% CR + PR) of patients had an improvement in bloating and early satiety. Symptomatic response to treatment was not correlated with age, performance status, tumor size, RT dose, or concurrent chemotherapy (all $P\geq0.05$). Post-treatment imaging was available in 52 cases for assessment of radiographic response. Almost one-third of patients experienced local progression. Median time to post-treatment imaging was 47.5 days (range, 1–678 days).

Treatment related toxicity was reported in 47 cases. Grade 1–2 toxicity was reported for nausea (30%), fatigue (16%), diarrhea (15%), and bloating (6%). One patient developed grade 3 diarrhea consisting of 22 bowel movements per day. The patient was hospitalized and eventually improved on a combination of sandostatin, opioids, loperamide, and diphenoxylate/atropine. One patient with pre-existing melena experienced a massive GI bleed following RT, and this was deemed to be due to refractory bleeding rather than RT toxicity.

Survival

All patients died during the study period. The median post-RT survival was 5.1 months [95% confidence interval (CI): 4.5–6.9 months; *Figure 2*]. Three-, 6- and 12-month survival was 71% (95% CI: 63–81%), 42% (95% CI: 33–53%), and 21% (95% CI: 13–29%), respectively. On univariable analysis, absence of distant metastases, lower pre-treatment CA19.9 levels, higher RT dose, and receiving concurrent chemotherapy were associated with prolonged survival

Table 1 Baseline demographics and pre-treatment characteristics (n=100)

Pre-treatment characteristics	Number of cases
Age at diagnosis (years), median [range]	64 [42–94]
Sex	
Male	62
ECOG performance score[†]	
0–1	82
≥2	15
Regional cancer centre	
Vancouver	35
Vancouver Island	30
Surrey	18
Abbotsford	15
Southern-Interior	2
Tumor size prior to radiotherapy (cm)[‡], median [range]	3.8 [1.1–9.0]
CA19.9 prior to radiotherapy[§], median [25th, 75th quartiles]	137.0 [18.5, 868.5]
Prior chemotherapy	
None	46
Number of lines, median [range]	1 [1–3]
Number of cycles, median [IQR]	4.5 [5]
Chemotherapy regimen	
Gemcitabine ± cisplatin	50
Weekly 5-fluorouracil	9
FOLFOX or FOLFIRINOX	4
Other	3
Prior surgical intervention	
None	70
Resection	19
Bypass	14
Presenting symptoms	
Asymptomatic	7
Pain	84
Satiety or bloating	40
Bleeding	15
Analgesics in patients with pain[¶]	
None	7
Non-opioids only	5
Weak opioid	11
Strong opioid	50
Prior biliary stent	43
Prior celiac plexus block	16
Primary indication for radiotherapy	
Local control	31
Pain	48
Gastrointestinal bleeding	12
Early satiety and abdominal bloating	4
Obstruction	4
Dysphagia	1
Distant metastases[††]	
None	67
Liver	23
Lung	11
Omental or peritoneal	4

Unknown: [†], 3 patients; [‡], 15 patients; [§], 7 patients; [¶], 11 patients. [††], total exceeds 100 as some patients had distant metastases to multiple sites. ECOG, Eastern Cooperative Oncology Group; CA19.9, carbohydrate antigen 19.9; IQR, interquartile range; FOLFOX, folinic acid, 5-fluorouracil, oxaliplatin; FOLFIRINOX, folinic acid, 5-fluorouracil, irinotecan, oxaliplatin.

(*Table 3*, all P<0.05). Age, sex, performance score, and tumor size were not significantly associated with survival and were excluded from the multivariable analysis. Only presence of distant metastases was significantly associated with survival [hazard ratio (HR) 2.37, 95% CI: 1.40–4.01, P=0.001] on multivariable analysis.

Discussion

This large, population-based, multi-centre retrospective study suggests that moderate doses of conventional RT offer a palliative benefit for patients with incurable

Table 2 Radiation treatment details (n=100)

Variables	Number of cases
Techniques	
Parallel opposed pair	39
3D conformal	57
IMRT or VMAT	4
Dose delivered	
Median [IQR] (Gy)	30 [30]
20 Gy in 5 fractions	19
30 Gy in 10 fractions	22
40 Gy in 15–20 fractions	5
45–55 Gy in 20–30 fractions	31
Treatment stopped	15
Concurrent chemotherapy	24
Chemotherapy post-radiotherapy	42

3D, three-dimensional; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; IQR, interquartile range.

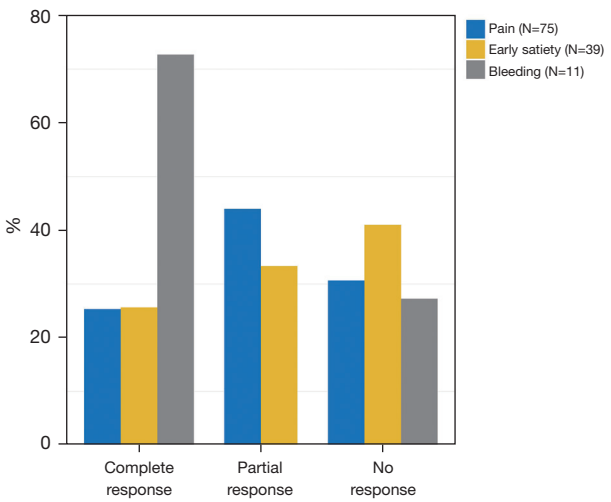

Figure 1 Symptomatic and radiographic response following palliative radiotherapy.

pancreatic cancer experiencing pain, early satiety and bleeding. Contrary to our hypothesis, despite a lack of treatment guidelines for palliative RT in this setting, most of the patients referred for a RT opinion at our institution had good performance status, only moderate sized tumors, and had only received one line of chemotherapy. This may

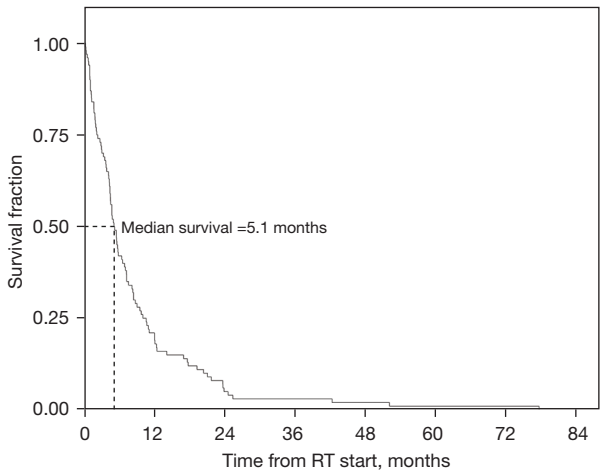

Figure 2 Survival curve following RT. RT, radiotherapy.

reflect our institutional practice of early referral to radiation oncology, which represents a departure from prior studies where RT utilization was limited (17). The secondary hypothesis regarding response to treatment and toxicity was supported, but it is important to exercise caution in interpreting these results given the retrospective nature of this study.

Our pain response rate of 69% agrees well with both prospective and retrospective studies in this area, which range from 57% to 94% (12-15,18). RT prescriptions for these studies varied as well but most commonly included 24 Gy/3 delivered weekly (10) and 30 Gy in 10 fractions (11,12). While RT response to GI bleeding have not been assessed in other pancreatic cancer studies, our high palliation rate for GI bleeding is similar to that of studies in gastric cancers (19,20). In these studies, subjective relief from bleeding and objective stability in hemoglobin following a course of palliative radiation of ≥30 Gy in 10 fractions had response rates of 73% (19) to 91% (20). While there was noted clinical effectiveness of RT in cessation of GI bleeding, the lack of hemoglobin levels, transfusion data, and assessment of response durability necessitates further studies to solidify its use in GI bleeding for pancreatic cancer.

Reported treatment toxicities were lower in our study compared to previous studies. Grade 1–2 nausea was documented in 30% of our cases compared to 22–58% and fatigue in 16% compared to 23% in Wolny-Rokicka *et al.* and 48% in Su *et al.* (14,18). This low rate of toxicity is likely due to under-reporting secondary to the retrospective nature of our study. However, it may also reflect differences

Table 3 Predictors of survival in pancreatic cancer patients following palliative radiotherapy

Variables	N	Univariable P	Multivariable	
			Hazard ratio (95% CI)	P
Age			–	–
<65 years	52	0.9		
≥65 years	48			
Sex			–	–
Male	62			
Female	38	0.9		
ECOG score				
0–1	60			
≥2	37	0.2		
Tumor size			–	–
<40 mm	58			
≥40 mm	39	0.6		
Distant metastases				
No	63		Reference group	
Yes	30	<1e–7	2.37 (1.40, 4.01)	0.001
Pre-radiotherapy CA19.9				
<137 kU/L	41		Reference group	
≥137 kU/L	52	0.007	1.44 (0.91, 2.28)	0.120
Radiotherapy dose				
<30 Gy	52		Reference group	
≥30 Gy	41	<1e–4	0.80 (0.46, 1.38)	0.417
Concurrent chemotherapy				
No	71		Reference group	
Yes	22	1e–5	0.52 (0.27, 1.01)	0.055

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; CA19.9, carbohydrate antigen 19.9.

in RT technique and advances in prophylactics for radiation-induced nausea and vomiting such as ondansetron and dexamethasone (21,22).

The primary reason for referral in one-third of cases was to prevent local progression. Among the evaluable cases, 73% of irradiated tumors were radiographically stable at approximately 6 weeks post-treatment. This is in line with results from a prospective study in 12 patients, which found a local control rate of 83.3% 4 weeks following palliative radiation delivered in 30 Gy in 10 fractions (13). By comparison, the LAP07 trial identified a 68% locoregional control rate at 4 months with chemoradiotherapy compared to 54% in the chemotherapy alone arm (8). Our study cannot provide a reliable estimate of local control post-palliative RT due to lack of consistent follow up imaging and short follow up duration; however, our data considered in the context of the LAP07 data leads us to hypothesize that there may be a role for conventional palliative RT to prevent the symptoms associated with local progression for a period of time.

The median survival following RT of 5.1 months was comparable to other studies evaluating palliative

RT in pancreatic cancer (3.5 to 7.5 months) (12-15,18). The study with the shortest survival had the highest proportion of patients with metastatic disease (62%) (10) while the study with the longest survival had no cases with metastatic disease (11). Similarly, in our study, the presence of distant metastases was a poor prognostic factor in both univariable and multivariable analysis. RT dose and concurrent chemotherapy were not associated with prolonged survival in the multivariable analysis. Wong *et al.* likewise found no increase in survival or local control in patients receiving 50.4 *vs.* 30 Gy of palliative RT in locally advanced pancreatic cancer patients receiving concurrent 5-fluorouracil (5-FU) chemotherapy (23). Rather, the higher RT dose group experienced more hospitalizations from grade 3 toxicities—29% *vs.* 12% (23). While these findings suggest that protracted courses of RT are not beneficial for this population, future prospective study exploring RT prescriptions such as 30 Gy in 10 fractions, 20 Gy in 5 fractions or 24 Gy in 3 fractions are important. Given the short life expectancy of this population, the fewest number of fractions that achieve the goal of palliation would be ideal.

As hypothesized, in our study, there was variability in RT prescriptions, modalities, and delivery with or without chemotherapy. None of these factors nor markers of disease severity were predictive of symptomatic response. Taken altogether, the uncertain survival and palliative benefit of increased RT doses with the variability in prescriptions underscore the need for additional prospective studies to establish standardized RT prescriptions with proven benefit.

The findings of this study should be considered in the context of its strengths and limitations. For example, BC Cancer is the sole provider of RT for the province, therefore referral bias in this sample is limited. In addition to some of the limitations related to the retrospective nature of the study described above, constraints from available documentation prevented comprehensive quality of life evaluations and assessment of treatment response durability. Another limitation is that the majority of patients in this cohort were treated more than 10 years ago. A more current review would likely identify that the majority of patients were treated with more conformal RT techniques. While this difference may be associated with decreased acute toxicity, the efficacy of treatment is unlikely to be different. The findings of this study are still relevant to today's population as the management of incurable pancreatic cancer has not significantly changed from a systemic therapy or supportive care point of view. Despite these limitations, this study is the largest to evaluate the palliative benefit of conventional RT in this population to date and provided a first look at palliative RT in GI bleeding from pancreatic cancer.

Conclusions

This study complements prior literature and suggests that palliative RT can be an effective tool for the management of common and life-threatening complications of pancreatic cancer such as pain and GI bleeding. Given the short life-expectancy of patients referred for RT, short courses may be preferable to decrease toxicity and avoid active oncologic treatment near end of life. The toxicity profile seems acceptable, but prophylactic dexamethasone and ondansetron is recommended prior to each treatment. Further prospective palliative RT studies with patient reported outcomes would be of considerable value for this vulnerable population.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1417/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1417/dss

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1417/coif). SL has received research funding and honoraria from AstraZeneca. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was

conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the joint Research Ethics Board of University of British Columbia and BC Cancer (No. H17-01636). A waiver of consent was approved by the ethics board owing to the minimal risk posed by the study and the infeasibility of obtaining consent in a retrospective manner.

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