Editorial | Palliative Medicine and Palliative Care for Incurable Cancer

Palliative radiotherapy for pancreatic cancer

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Pancreatic cancer is a devastating disease, with 5-year survival rates of 12.5% (1). In the adjuvant setting for resectable tumors, radiation may be utilized in the case of positive margins or other pathologic risk factors for local recurrence; in borderline resectable disease, neoadjuvant radiation can be offered to sterilize surgical resection borders and increase the probability of a margin-negative resection (2,3). Unfortunately, most patients present with unresectable locally advanced or metastatic disease (1). In the locally advanced population, radiation has not consistently prolonged survival (4-6), but can improve local control (7,8). In the metastatic setting, systemic therapy remains the mainstay of treatment (9), but pancreas-directed radiotherapy remains a powerful tool for both palliation and primary tumor control.

Pancreatic cancer may lead to a myriad of symptoms due to its anatomic location. Patients may have pain related to local effects of the tumor, celiac plexus involvement with neuropathic symptoms, mild to life-threatening bleeding from tumor erosion, post-prandial intestinal angina from vasculature encasement, altered stool and urine function from biliary blockage, or abdominal bloating and early satiety from gastric outlet obstruction. This introduces questions to the radiation oncologist in each unique scenario: What is the optimal dose and fractionation? What is the target? What technique of radiation should be used? And how quickly can we return the patient to optimal systemic treatment without causing harm?

In this issue, Liu and Lefresne offer insight to these considerations (10). The authors retrospectively review the provincial cancer database across five regional centers in British Columbia between 2006–2013 for patients receiving palliative radiotherapy to the pancreas. The authors report the largest series to date, including 100 patients with metastatic, recurrent, or locally advanced disease in the study. Patients received a wide variety of radiotherapy prescriptions ranging from 20 Gy in 5 fractions to 45–55 Gy in 20–30 fractions, most often delivered with simple radiotherapy techniques [i.e., two-dimensional (2D) complex and three-dimensional (3D) conformal radiation]. The most common regimens were 30 Gy in 10 fractions (22%) and 20 Gy in 5 fractions (19%). Patients receiving stereotactic body radiotherapy (SBRT) were excluded.

Importantly, the authors list response to palliation for pain in addition to early satiety and bleeding, the latter of which are underrepresented or rarely reported in the literature. Responses to treatment were excellent: 73% of patients had a complete response to palliation for bleeding, 69% had improvement in pain, and 59% had improvement of early satiety. Palliation was safe without significant toxicity; only one patient had a grade 3 event of diarrhea. A significant finding was that symptom response was not correlated with radiotherapy dose.

The study is not without limitations. Most patients were treated over 10 years ago and 50% of the cohort received non-contemporary systemic therapy (i.e., gemcitabine).

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Table 1 Literature summary of palliative radiotherapy for pancreatic cancer

Author and study year	Study design	Radiotherapy intervention	Number of patients	Primary outcome of interest	Efficacy	Toxicity	Target volumes and simulation details
Morganti, 2003, (12)	Prospective, single-arm	30 Gy in 10 fractions	12	Pain	50% of patients did not require analgesics at 4 weeks; mean reduction in consumption of analgesics was 63.1%	33% G1–2 nausea/ vomiting, 8% G2 diarrhea, no G3 events	3-field technique, 9–10 MV photons, CTV = tumor volume with 1.5 cm margin
Wolny-Rokicka, 2016, (13)	Retrospective	6–30 Gy in 1–10 fractions	31	Pain	55% achieved good pain control without need for further analgesics at 4 weeks	19% G2 nausea, 10% G2 vomiting, 10% G1 diarrhea	3DCRT, 20 MV photons, 2- or 3-field technique, CTV = whole pancreas with 1.0 cm margin
Ebrahimi, 2018, (14)	Retrospective	8 Gy in 1 fraction, repeated over 1, 2, or 3 weeks	61	Pain	66% with any pain resolution, 7% with complete response, median 2.5 months relief	51% G1–2 nausea, 21% G1–2 vomiting, 33% pain flare	14% AP/PA, 56% 3DCRT, 30% IMRT. No details regarding targets
Tian, 2018, (15)	Single-arm, prospective	40–42 Gy in 7–10 fractions	31	Pain (BPI) and QoL (FACT-G)	57% with pain improvement at 1 month, 89% with improvement in QoL	52% G2 anorexia, 29% G2 nausea, 1 patient with G3 ileus	SBRT (CyberKnife), GTV = tumor causing symptoms = PTV, Rx to 70–80% IDL
Wang, 2018, (16)	Retrospective	25 Gy in 5 fractions	24	Pain	79% with decreased pain at 2 weeks	29% nausea and vomiting, 13% diarrhea, 21% pain flare	No immobilization, 17% SBRT (CyberKnife), 58% IMRT, 25% 3-field 3DCRT. No details regarding targets
Hammer, 2022, (17)	Prospective, single-arm phase II	25 Gy in 1 fraction	18	Severe, celiac plexus-associated pain	84% with decreased pain at 3 weeks and 22% with complete relief at 6 weeks, significant reduction in MME	11% G1–2 diarrhea, 39% G1–2 fatigue, 22% G1–2 vomiting. No G3+ events	4DCT with abdominal compression and IV contrast, 100% SBRT with 6 MV photons, GTV = anterior-medial aspect aorta at T12–L2
Tello Valverde, 2023, (11)	Prospective, single-arm phase II	8 Gy in 1 fraction, repeated over 1, 2, or 3 weeks	30	Severe pain (BPI), QoL (EORTC-QLQ-C15)	80% with pain reduction ≥2 points, significant improvement in global QoL, significant reduction in MME	34% G1–2 nausea, 23% G1–2 vomiting, 7% G3 nausea, 3% G3 vomiting, 10% G3 pain flare	100% IMRT/VMAT with 6–10 MV photons, no motion management, GTV = tumor with fat infiltration, CTV = GTV + 5 mm, PTV = CTV + 2.0 cm CC and 1.0 AP

Data from Palliative Radiation Oncology 1st Edition (18). G1, grade 1; G2, grade 2; G3, grade 3; CTV, clinical target volume; 3DCRT, three-dimensional conformal radiotherapy; AP, anterior/posterior; PA, posterior/anterior; IMRT, intensity-modulated radiotherapy; BPI, brief pain inventory; QoL, quality of life; FACT-G, Functional Assessment of Cancer Therapy-General; SBRT, stereotactic body radiotherapy; GTV, gross tumor volume; PTV, planning target volume; Rx, prescription; IDL, isodose line; MME, morphine milligram equivalents; 4DCT, four-dimensional computed tomography; IV, intravenous; EORTC-QLQ-C15, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Quality of Life Questionnaire-Core 15; VMAT, volumetric-modulated arc therapy; CC, craniocaudal.

Pain and symptom response was dependent on physician interpretation of the medical record, which may result in bias. Finally, pancreatic cancer symptoms are temporally dynamic; the single timepoint of assessment in the study may underreport data regarding the evolving nature of pain in this disease. Regardless, this remains the most robust report to date and the data will help guide physicians faced with the task of palliating pancreatic tumors.

In line with the findings of this study, the utility of a short-course hypofractionated regimen in this population was also validated in the phase II PAINPANC trial that demonstrated three single fractions of 8 Gy (once weekly) rapidly reduced pain within three weeks and improved global quality of life (11). Patients underwent computed tomography (CT) simulation without contrast or motion management with generous clinical planning margins. Further literature for palliative radiation in pancreatic cancer is summarized in *Table 1* and are in general

agreement with the present article at hand. American Society for Radiation Oncology (ASTRO) guidelines for pancreatic cancer additionally suggest standard regimens of 20 Gy in 5 fractions or 30 Gy in 10 fractions as reasonable approaches for palliation (19).

In this context, when the goals of treatment are purely palliative in a patient with limited life expectancy, our practice is to offer short course hypofractionated regimens that relieve symptoms, assuage patient and family logistical burdens, and minimize time off systemic therapy. Given the vulnerable patient population and guarded median survival (5.1 months in this study), we maximize comfort during simulation and premedicate with low dose anti-emetics or dexamethasone to quell any unanticipated side effects during treatment. Protracted or dose-escalated courses of radiation with or without systemic therapy are reserved for patients with controlled disease and more favorable prognoses where durable local control may significantly impact survival or quality of life (8,20,21).

Unfortunately, despite this promising data, pancreatic cancer does not universally respond to palliation, as evidenced in the approximately 30% of patients without pain response in the study at hand. Further work involving advanced forms of radiotherapy remains to optimize pain response. For example, celiac plexus radiosurgery was recently piloted in a proof-of-concept phase II trial where a single fraction of SBRT resulted in a significant reduction in severe pain for 84% of patients with complete resolution of pain in 22% (17).

Ultimately, our goals as physicians should focus on helping patients live longer, better, or hopefully, both. This study demonstrates that radiation oncologists are armed with a powerful therapeutic tool in the setting of advanced symptomatic pancreatic cancer. Equipped with this knowledge, we can feel confident that we are improving the quality of life and alleviating suffering in a particularly vulnerable population.

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