Review Article

The role of radiotherapy in metastatic pancreatic cancer: a narrative review

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Background and Objective: To describe the current and emerging role of radiotherapy in metastatic pancreatic cancer (MPC), including for palliation of locally invasive primary disease; metastasis-directed therapy in the setting of oligometastatic disease; and for immunomodulation in the setting of immunotherapy.

Methods: A search of the PubMed database was performed using the search terms "metastatic pancreatic cancer", "oligometastatic pancreatic cancer", and "radiotherapy" for articles published between January 1, 1980 to July 30, 2022. Articles were included at the discretion of the authors.

Key Content and Findings: This review provides an updated and comprehensive evaluation of the role of radiotherapy in the context of modern radiotherapy techniques [i.e., stereotactic body radiation therapy (SBRT)], as well as a discussion of key considerations regarding the potential role for radiotherapy to enhance the immune response to immune checkpoint inhibition. While palliative radiotherapy for MPC was historically delivered in conventionally fractionated or short-course hypofractionated palliative dose and fractionations, the use of more modern approaches such as SBRT for the palliation of symptoms related to local tumor invasion is being explored due to potential benefits, including reduction in the number of fractions and minimizing time off of systemic therapy, while maintaining good pain response and local tumor control rates. Metastasis-directed radiation therapy for patients with oligometastatic pancreatic cancer (OMPC) is similarly being explored and has been well tolerated in initial studies, with the potential to facilitate systemic therapy treatment breaks and potentially improve survival outcomes, though prospectively designed studies are currently lacking. The addition of SBRT as an immunomodulatory agent to enhance the effect of immunotherapy in pancreatic cancer is an area of continued investigation.

Conclusions: Despite the aggressive course of MPC, radiation therapy can play an important role in palliation of local tumor invasion, with the potential for benefit as metastasis-directed therapy in the setting of oligometastatic disease and as an adjunct to immunotherapy, though further prospective study is required.

Keywords: Pancreatic cancer; metastatic; oligometastatic; radiotherapy; stereotactic body radiation therapy (SBRT)

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Introduction

Pancreatic cancer is the third-leading cause of cancer death among men and women in the United States (1). Just over half of all patients with pancreatic cancer present with metastatic disease, which is associated with a dismal 5-year survival rate of 3.1% (2). Historically, the role of radiation therapy in the setting of unresectable pancreatic cancer was chemoradiotherapy, often to 50.4 Gy in 28 fractions, or short-course hypofractionated radiotherapy (3). In recent years, investigation of the use of stereotactic body radiation therapy (SBRT) to the pancreatic tumor primary has been pursued, given relatively high rates of locally invasive disease even in the setting of metastatic disease (4). Additionally, the role of metastasis-directed radiotherapy in oligometastatic pancreatic cancer (OPMC) is an area of active investigation as a consequence of increased interest in the oligometastatic state in solid tumor malignancies as a whole, given randomized trials demonstrating a survival benefit (5,6) to radiotherapy in patients with a limited number of metastases. The question remains as to whether modern radiotherapy technology is best used to optimize palliative radiotherapy versus as a means to maximize local tumor control. Similarly, the exact role of ablative radiotherapy in the oligometastatic setting has yet to be determined.

In this review, as compared to prior reviews on this subject, we provide an updated presentation of the current evidence for the role of radiotherapy in metastatic pancreatic cancer (MPC). Specifically, we will elucidate the role of modern radiation therapy techniques in MPC as a palliative measure and as a potential tool in the setting of oligometastatic disease. We will also describe ongoing efforts to use SBRT to enhance the effect of immunotherapy in pancreatic cancer. We present this article in accordance with the Narrative Review reporting checklist (available at https://dmr.amegroups.com/article/view/10.21037/dmr-22-54/rc).

Methods

A search of the PubMed database was conducted for articles containing the search terms “metastatic pancreatic cancer”, “oligometastatic pancreatic cancer”, and “radiotherapy” published between January 1, 1980 and July 30, 2022 (Table S1). Retrospective and prospective studies available in the English language that reported outcomes for patients with MPC who received radiotherapy were reviewed and included based on the authors’ judgment.

Palliative radiation therapy for metastatic pancreatic adenocarcinoma

Radiation therapy in the setting of MPC historically has been used with palliative intent. Patients with MPC at the time of death frequently have concurrent local tumor invasion, with evidence suggesting that patients with a limited number of metastatic sites of disease frequently die of local tumor invasion (4). Potential symptoms of pancreatic adenocarcinoma include gastric outlet or duodenal obstruction, gastric or duodenal ulceration and associated bleeding, obstructive jaundice, venous obstruction and associated ascites, and abdominal pain (7,8). Palliative radiation therapy to the primary pancreatic tumor has been used to reduce symptoms related to local tumor invasion (9), with pain relief being a common byproduct of palliative radiotherapy (10). The pathophysiology of abdominal pain in the context of pancreatic cancer is thought to be related to tumor invasion of the celiac plexus resulting in celiac plexopathy (11).

Certainly, standard palliative fractionation regimens such as 30 Gy in 10 fractions can be utilized for palliation of primary tumor-related symptoms in the setting of metastatic disease. Tumor-related pain and bleeding can be particularly responsive to palliative radiation. Mass effect related complications can be less predictable in their response to radiation, but intervention in the setting of impending symptoms can be considered. Importantly, in recent years, the advent of SBRT has allowed for significantly more focused delivery of radiation, such that shorter fractionation schedules that deliver high biologically effective dose (BED) can be considered, minimizing time off of systemic therapy while achieving good local tumor control for a tumor type that can often be radio-resistant in the setting of low BED (12). Indeed, SBRT has demonstrated high response rates for pain in the treatment of locally advanced pancreatic cancer (LAPC) (13). A limited number of retrospective studies examining the use of SBRT in the setting of LAPC also included a small number of patients with metastatic disease (14-17), with encouraging rates of pain response. A handful of recent studies have also explored the use of SBRT to the primary tumor specifically for patients with metastatic disease. A few such studies will be discussed (*Table 1*).

Koong *et al.* (18) retrospectively analyzed a cohort of 27 patients with OMPC, defined as patients with 1–3 metastatic lesions, treated with SBRT to the primary

Table 1 Studies assessing SBRT for local palliation of MPC

Author	Year	Design	N	Patient Population	Intervention	RT dose	Main findings	Toxicity
Koong (18)	2020	RR	27	OMPC	SBRT to primary tumor (n=27)	Median doses by fractionation: 1 fraction: 25 Gy; 5 fraction: 33 Gy	Median OS 7 mos (95% CI: 3–10 mos); 1-yr LF 25% (95% CI: 10–44); reduced mean intensity of pain (SS); 46% reduction in continuous opioid use	G3+ late toxicity: 2 pts
Ji (19)	2021	RR	89	OMPC (liver-only)	Neoadjuvant ChT + SBRT to primary tumor (n=34); neoadjuvant ChT alone (n=65)	Mean 41.4 Gy (range, 25–50 Gy) in 5–7 fractions	1-yr OS 39.4% *vs.* 21.3%, P=0.059, favoring SBRT; 3-mo local symptomatic palliation rate 87.0% *vs.* 54.5% in propensity score matched group (SS)	No SS difference in G1–2 or G3+ toxicities between the two treatment arms. Notably, 1 pt with history of duodenal ulcer with G3 duodenal ulcer hemorrhage in SBRT arm
Hammer (20)	2022	Phase II	18	Pancreas (n=16); other GI malignancy (n=2)	SBRT to the celiac plexus	25 Gy in 1 fraction	Baseline median NRS 6/10 (IQR, 5.0–7.5) declined to 3/10 (IQR, 1.0–4.3; P<0.005) at 6 weeks post-treatment	G1–2: 39% pts; G3+: 0% pts

SBRT, stereotactic body radiation therapy; MPC, metastatic pancreatic cancer; N, sample size; RT, radiotherapy; RR, retrospective review; OMPC, oligometastatic pancreatic cancer; Gy, Grey; OS, overall survival; mos, months; CI, confidence interval; yr, year; LF, local failure; SS, statistically significant; G, grade; pts, patients; ChT, chemotherapy; NRS, numerical rating score; IQR, interquartile range.

tumor. The majority (89%) received upfront chemotherapy, most commonly using a gemcitabine-based regimen, while 26% received chemotherapy following radiation. The median radiation dose for single-fraction treatments was 25 Gy (range, 12.5–25 Gy), while the median dose for 5-fraction treatments was 33 Gy (range, 25–40 Gy). Image guidance consisted of gold fiducial placement for target localization, with 4D-CT simulation for motion management. At a median follow-up of 7 months, the median overall survival (OS) was 7 months [95% confidence interval (CI): 3–10]. The 1-year cumulative incidence of local failure was 25% (95% CI: 10–44%). Mean intensity of pain as measured by the Stanford Pain Scale was significantly reduced following SBRT (P=0.01), with a 46% reduction in continuous opioid use. There were two cases of grade 3 or higher late toxicities. One involved grade 3 fatigue; the other was an episode of acute duodenal obstruction treated with duodenal stent placement.

Ji *et al.* (19) compared the efficacy of chemotherapy with or without SBRT to the primary lesion in patients with liver-only OMPC. Of the 89 patients included in the study with liver-only OMPC, defined as a tumor burden consisting of no more than 5 liver metastases less than 4 cm in size, 34 patients underwent SBRT to the primary site, with chemotherapy delivered in the upfront or consolidative setting; the rest received chemotherapy alone. Mean SBRT dose was 41.1 Gy (range, 25–50 Gy) delivered in 5–7 fractions. The primary outcome, 1-year OS, was numerically higher in the SBRT plus chemotherapy group compared to those receiving chemotherapy alone but did not reach statistical significance in either the unmatched (39.4% *vs.* 21.3%, P=0.059) or propensity-score-matched cohorts (34.0% *vs.* 16.5%, P=0.115). In an exploratory subgroup analysis, patients with head of pancreas tumors or good performance status who were treated with SBRT and chemotherapy had improved OS compared to those treated with chemotherapy alone. Furthermore, after propensity score matching, patients treated with SBRT plus chemotherapy were observed to have lower rates of abdominal and back pain compared to those treated with chemotherapy alone (87.0% *vs.* 54.5%, P=0.016).

Hammer *et al.* (20), reported the results of a pilot study of stereotactic radiation specifically to the celiac plexus for celiac plexopathy in patients with upper GI malignancies, the majority of whom had pancreatic cancer. In this single-arm phase II trial, 16 patients with pancreatic cancer and 2 with other upper GI malignancies with celiac pain of at least 5 out of 10 on the Numerical Rating Scale (NRS) were treated with SBRT to a dose of 25 Gy in 1 fraction to the celiac plexus, defined for treatment planning purposes as the anterolateral

aspect of the T12 to L2 vertebral levels contoured with a 5 mm brush. A 5 mm expansion on the celiac plexus was then prescribed to 20 Gy. Gross tumor in the proximity of these volumes could be included at the treating physician's discretion. 4D-CT simulation was used for all patients, with abdominal compression added if tolerated. Prophylactic anti-emetics were given on the day of treatment. Concurrent systemic therapy was prohibited. The primary endpoint was change in NRS at 3 weeks post-treatment. The median NRS at 3 weeks decreased to 3 out of 10 [interquartile range (IQR), 1.0–4.3, P<0.005 *vs.* baseline] from a baseline of 6 out of 10 (IQR, 5.0–7.5); at 6 weeks post-treatment, median NRS declined to 2.8 out of 10 (IQR, 0–3.3, P<0.005 *vs.* baseline). Four patients experienced complete resolution of their pain. Thirty-nine percent of patients experienced grade 1 to 2 toxicities, most commonly acute GI toxicities; no patients experienced grade 3 or higher toxicity.

These studies underscore the potential for radiotherapy in MPC yet also highlight the current dearth of evidence to guide management, as patients who were selected for treatment for oligometastatic disease may have been enriched for clinical factors that portended a better outcome. Two trials assessing the role of stereotactic radiation for palliation of pain in pancreatic malignancies are currently enrolling. As a follow-up to the study by Jacobson *et al.*, a larger multi-center international single-arm phase II trial (21) is currently open for enrollment, with a target accrual of 125 patients. The treatment will again consist of single-fraction stereotactic radiosurgery to the celiac plexus, with the primary endpoint being the rate of complete or partial pain response at 3 weeks assessed with the Brief Pain Inventory scale. The second, the MASPAC trial (22), is a randomized controlled trial evaluating the benefit of magnetic resonance (MR)-guided SBRT to the primary tumor in patients with MPC. The treatment will consist of standard of care chemotherapy with or without SBRT to a total of 33 Gy in 5 fractions prescribed to the 80% isodose line to the primary tumor. The primary endpoint will be improvement in pain as measured by the "mean cumulative pain index." These trials will provide further prospective data regarding the impact of RT on quality of life that can be used to guide management decisions in MPC.

Metastasis-directed radiation therapy in oligometastatic pancreatic adenocarcinoma

The current standard of care management of MPC consists of multi-agent chemotherapy, usually composed of folinic acid, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) or gemcitabine plus nab-paclitaxel (23,24). In the metastatic setting, there is increasing consideration towards classifying patients with a limited number of metastatic sites as having oligometastatic disease. It is postulated that local therapy including radiotherapy for OMPC may provide a survival benefit, as suggested by multiple prospective studies in other solid tumor malignancies (5,6). Retrospective studies of local therapy in the setting of OMPC have been conducted, primarily with surgery (i.e., metastatectomy) as the local therapy of choice (25,26), while a prospective study, the HOLIPANC trial (27), is an ongoing single-arm phase II study of patients with liver-only oligometastatic pancreatic adenocarcinoma with stable disease after neoadjuvant chemotherapy who will be treated with synchronous resection of the primary tumor and hepatic metastases. Prospective data specifically evaluating metastasis-directed radiotherapy in OMPC are lacking. However, multiple retrospective studies have evaluated the benefit of radiation therapy in OMPC. Three such studies will now be discussed (*Table 2*), which suggest SBRT to oligometastatic sites of disease is well-tolerated, provides high rates of local control, may facilitate treatment breaks from systemic therapy, and may improve progression-free and overall survival (28-30).

Scorsetti *et al.* (28) reported outcomes from a single-institution retrospective analysis of 41 patients with OMPC, defined as 5 or fewer metastases across 2 or fewer sites, treated to a total of 64 metastases with SBRT. The majority had metachronous disease (95.1%). The most commonly treated sites of metastases were in the lung (29.3%) and liver (56.1%). Five patients (12.2%) had additional metastatic lesions not treated with SBRT. The dose of SBRT varied, with most lung lesions treated to 48 Gy in 4 fractions. There was greater heterogeneity in the dose and fractionation to liver metastases, with patients treated from 54–75 Gy in 3 fractions, or 45–63 Gy in 6 fractions. Abdominal compression was used for the treatment of liver metastases, while four-dimensional-computed tomography (4D-CT) simulation was used for liver or lung lesions. The majority of patients (78.1%) did not receive further planned systemic therapy after SBRT. Local control (LC) at 1 and 2 years were 88.9% and 73.9%, respectively. Progression-free survival (PFS) at 1 and 2 years were 21.9% and 10.9%, respectively, while overall survival at 1 and 2 years were 79.9% and 46.7%, respectively. On multivariable analysis of PFS, sex [hazard ratio (HR) =4.59, 95% CI: 1.90–11, P=0.0001], time to metastases (HR =0.96, 95% CI: 0.93–

Table 2 Studies of metastasis-directed therapy in MPC

Author	Year	Design	N	Patient population	Inclusion criteria	Intervention	RT dose	Main findings
Scorscetti (28)	2020	RR	41	OMPC	≤5 metastases, ≤2 sites	SBRT to metastases (12.2% with additional metastases not treated)	Most common dose/fx by location: lung: 48 Gy/4 fx; liver: 54–75 Gy/3 fx, 45–63 Gy/6 fx	2-yr LC 73.9%; 2-yr PFS 10.9%; 2-yr OS 46.7%; extra-target disease associated with PFS
Lee (29)	2021	RR	76	MPC	All with liver metastases; 14% with extra-hepatic metastases	SBRT to liver metastases	Median 50 Gy/5 fx	12-mo LC 66%; 12-mo PFS 7%; 12-mo OS 38%; ChT break >6 mos after RT: 32% of pts
Elamir (30)	2022	RR	41	OMPC	(<5 metastases) in *de novo* pts or <3 mos after surgical resection of primary; CA19-9 <1,000 U/mL; pts included ChT alone arm required to have no progression on ChT for ≥5 mos	ChT + SBRT (n=20); ChT alone (n=21)	Median BED10 =100, IQR, 100–132 Gy; most commonly treated with 1–5 fx	2-yr LC 82.5%; median poly-PFS 40 *vs.* 14 mos (HR =0.2, 95% CI: 0.07–0.54, P<0.01) favoring SBRT; median OS 42 *vs.* 18 mos, HR =0.21, 95% CI: 0.08–0.53, P<0.01) favoring SBRT; ChT break of 6+ mos in 85% of SBRT cohort *vs.* 33.3% in ChT cohort

MPC, metastatic pancreatic cancer; N, sample size; RT, radiotherapy; RR, retrospective review; OMPC, oligometastatic pancreatic cancer; SBRT, stereotactic body radiation therapy; fx, fractions; Gy, Grey; yr, year; LC, local control; mo, month; PFS, progression-free survival; OS, overall survival; mos, months; pts, patients; ChT, chemotherapy; CA19-9, carbohydrate antigen 19-9; BED10, biologically effective dose assuming alpha/beta of 10; IQR, interquartile range; HR, hazard ratio; CI, confidence interval.

0.99; P=0.031), and extra target disease (HR =7.36, 95% CI: 2.24–24.15; P=0.001) were significantly associated with PFS.

Lee *et al.* (29) reported on outcomes from a multi-institutional retrospective analysis of 76 patients with MPC treated with SBRT to liver metastases. Sixty-eight percent of patients presented with metachronous liver metastases. A minority of patients (14%) had sites of extrahepatic metastases at time of treatment, most commonly in the lungs. Median SBRT dose and fractionation was 50 Gy in 5 fractions. With a median follow-up of 10.9 months, 12-month LC was 66%, 12-month PFS was 7%, and 12-month OS was 38%. Thirty-two percent of patients had a chemotherapy treatment break of 6 or more months following completion of radiation. Multivariable analysis showed ECOG performance status of 2–3, progressive liver metastases while on chemotherapy, and a higher carbohydrate antigen 19-9 (CA19-9) at the time of radiotherapy were associated with inferior overall survival.

Elamir *et al.* (30) conducted a retrospective analysis of patients with OMPC, defined as patients with five or fewer metastatic sites of disease in either the *de novo* setting or diagnosed 3 or more months after surgical resection of their primary disease, with CA19-9 <1,000 U/mL, treated with chemotherapy with or without SBRT to all metastatic lesions. Twenty patients received SBRT, while the 21 patients included for comparison who received chemotherapy only were required to have had no progression for at least 5 months. SBRT consisted of 1–5 fractions of treatment to a minimum dose of 7.65 Gy per fraction [median biologically effective dose assuming alpha/beta of 10 (BED10) =100, IQR: 100–132 Gy], while one patient was treated with 67.5 Gy in 15 fractions. At a median follow-up of 16 months, 1- and 2-year local control rates of lesions treated with SBRT were 91.6% and 82.5%, respectively. The study measured the rate of polyprogression-free survival, defined as progression of greater than five metastatic tumors, and found that patients in the SBRT cohort had a median polyprogression free survival of 40 *vs.* 14 months (HR =0.2, 95% CI: 0.07–0.54, P=0.0009) compared to the chemotherapy cohort. Similarly, OS was improved in the SBRT cohort (median OS 42 *vs.* 18 months, HR =0.21, 95% CI: 0.08–0.53, P=0.0003). Seventeen out of 20 (85%) patients in the SBRT cohort had a chemotherapy treatment break of 6 or more months, compared to 7/21 (33.3%) in the chemotherapy cohort.

One limitation of all three studies is a lack of reporting on toxicity data from SBRT (28-30), though increased toxicity from metastasis-directed therapy in other disease sites has been documented, such as in the SABR-COMET trial in which the rate of grade 2 or higher treatment-related toxicity was 20 percentage points higher in the SABR arm than in the control arm (6). Nevertheless, these studies demonstrate the potential benefit of metastasis-directed radiation therapy in patients with a limited number of metastatic sites of disease. There exists inter-study variability in the criteria for oligometastatic disease in the pancreatic cancer setting. A number of clinical characteristics have been used to define a clinically relevant oligometastatic subtype in MPC, including the number of organs with metastases, the total number and specific sites of metastatic deposits, CA19-9 levels, as well as a favorable response to first-line chemotherapy (30,31). Further study of optimal inclusion criteria is needed, including the potential value of incorporating novel biomarkers such as circulating tumor DNA (32) and molecular alterations that may predict differential response to therapy (33). Prospective studies are required to further elucidate the selection criteria and outcomes of patients with OMPC.

SBRT and immunotherapy in metastatic PDAC

The rapidly accumulating body of evidence demonstrating the benefit of immunotherapy in an array of cancer types stands in contrast to the limited success of immunotherapy in pancreatic cancer (34), though case reports suggest the potential efficacy of immune-mediated therapy in appropriately selected patients with MPC (35,36). The reasons for this lack of efficacy may relate to the immunosuppressive tumor microenvironment in pancreatic cancer (37,38). Radiation therapy can promote an immunologic response via multiple mechanisms, including induction of immunogenic cell death (39), tumor antigen presentation via increased expression (40,41), and promotion of T-cell homing to the tumor bed (42-44). The immunomodulatory effects of radiotherapy may result in a more favorable response to immunotherapy when used in tandem (45). Current clinical studies specifically in MPC have evaluated the safety and efficacy of SBRT in addition to immune checkpoint inhibition. In a phase I study by Xie and colleagues, the safety of durvalumab and/or tremelimumab in combination with SBRT to 8 Gy in 1 fraction or 25 Gy in 5 fractions to the primary pancreatic tumor or post-operative recurrence was evaluated in 59 patients. There were no dose-limiting toxicities observed, and 2/39 (5.5%) patients with evaluable disease had a partial response to treatment (46), which the authors note was higher than the 3.1% response rate observed in patients on a separate study of patients with MPC treated with combination durvalumab and tremelimumab (47). The CheckPAC trial evaluated a cohort of patients with refractory MPC treated with a combination of SBRT to 15 Gy in 1 fraction to a single primary or metastatic lesion with nivolumab, ipilimumab, or both in tandem. A partial response lasting 4.6 months was observed in 1 patient receiving SBRT/nivolumab, while 6 patients who received SBRT and nivolumab/ipilimumab achieved a partial response with a median duration of 5.4 months, including 1 patient still alive at the time of reporting with a continued response of 55 months. Grade 3 or higher treatment-related toxicity was observed in 24.4% and 30.2% of patients in the SBRT/nivolumab and SBRT/nivolumab/ipilimumab groups, respectively (48). In a single-arm phase II study by Parikh and colleagues (49), patients with metastatic microsatellite stable colorectal (n=40) and pancreatic (n=25) cancer were treated with 3 cycles of ipilimumab and nivolumab, with radiotherapy administered on day 1 of cycle 2 as 24 Gy in 3 fractions every other day or every two days. In patients with MPC, the disease control rate was 20% (5/25 patients, 95% CI: 7–41%); in those patients who received radiotherapy per protocol, the disease control rate was 29% (5/17 patients; 95% CI: 10–45%). As Parikh and colleagues note, these response rates compare favorably to those in patients with advanced/MPC who received FOLFIRINOX followed by gemcitabine monotherapy as second-line therapy (50).

While cross-trial comparisons are imperfect, the favorable response rates compared to that seen in trials of systemic therapy alone, including immunotherapy alone trials, suggest the continued study of SBRT in combination with immunotherapy in MPC is warranted. Mismatch repair deficiency, which is a positive predictor of response to immune checkpoint inhibition (51,52), is estimated to occur in a mere 1% of patients with pancreatic cancer (53). Thus there is a need to develop predictive biomarkers of response to immunotherapy in pancreatic cancer, and, as demonstrated by the study by Parikh and colleagues (49), SBRT may represent an opportunity to enhance the response to immunotherapy in patients with MPC. Questions also remain regarding the optimal dose/fractionation (54-56), target (57), and timing (58,59) of radiotherapy to generate maximal antitumor immune response while mitigating concomitant immunosuppressive effects of radiotherapy. In

particular, the timing or sequencing of radiotherapy with immunotherapy may impact the receipt of radiotherapy as a result of immune-related adverse events, as observed in the study by Parikh and colleagues in which radiotherapy was delivered after an initial cycle of immune checkpoint inhibition rather than concurrently with cycle 1; thirty-two percent of patients in the overall cohort discontinued immunotherapy prior to receipt of radiotherapy due to immune-related adverse events (49). The optimal timing of radiotherapy may also depend on the mechanism of action of the immunotherapy being used in conjunction with radiotherapy (59). These factors must be carefully considered in the design of future trials testing radiation therapy and immunotherapy combinations for MPC as in other disease sites.

Conclusions

Key limitations of this review include its use of a single database (PubMed) which yielded mainly small retrospective reviews. However, in summary, the role of radiotherapy in MPC, historically delivered with standard palliative dose and fraction, is evolving. The advent of modern radiotherapy techniques that allow for greater dose escalation may allow higher-dose stereotactic radiotherapy to play an increasingly prominent role in MPC, whether as a palliative measure in the setting of celiac plexopathy, or as a potential modality to improve oncologic outcomes in the oligometastatic setting or in combination with immunotherapy. A limited number of retrospective studies suggest that SBRT to the primary tumor particularly in the setting of oligometastatic disease is well tolerated and provides effective pain relief. Furthermore, metastasis-directed therapy using SBRT in the oligometastatic setting is being explored, with initial retrospective reports suggesting it is safe and well tolerated, with high local control rates and the potential to facilitate systemic therapy treatment breaks. The role of radiotherapy as a supplement to immunotherapy in MPC is an area of active investigation. Randomized trials assessing quality of life and cost-effectiveness of radiotherapy would be beneficial to further understand the value of radiotherapy in the context of MPC. In the interim, clinicians considering the use of SBRT as a palliative measure for the primary tumor as well as in the setting of metastasis-directed therapy should continue to practice shared decision-making with a thorough discussion of the risks and benefits as well as a communication regarding the limitations of the current evidence base. Similarly, radiotherapy delivered specifically as a means to induce an antitumor immune response should be provided on prospective studies at this time.

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Supplementary

Table S1 Summary of literature search strategy used for this review

Items	Specification
Date of search	July 30, 2022
Databases and other sources searched	PubMed
Search terms used	“metastatic pancreatic cancer”, “oligometastatic pancreatic cancer”, “radiotherapy”
Timeframe	January 1, 1980–July 30, 2022
Inclusion and exclusion criteria	Inclusion: primary studies, randomized trials, reviewed Exclusion: case reports
Selection process	TA Lin conducted selection, A Narang verified sources

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