World Journal of Gastroenterology

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World J Gastroenterol 2026 August 7; 32(29): 117832

DOI: 10.3748/wjg.117832

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Observational Study

Five-fraction stereotactic magnetic resonance-guided adaptive radiotherapy targeting the primary tumor in metastatic pancreatic cancer

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Peer review: Externally peer reviewed.
Peer-review model: Single blind
Peer-review report's classification
Scientific quality: Grade B, Grade B
Novelty: Grade A, Grade B
Creativity or innovation: Grade B, Grade B
Scientific significance: Grade B, Grade B
P-Reviewer: Chen LY, PhD, Professor, China; Chuong M, MD, United States
Received: December 18, 2025
Revised: January 27, 2026
Accepted: April 14, 2026
Published online: August 7, 2026
Processing time: 210 Days and 20.8 Hours
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Abstract

BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with most patients present with or develop metastatic disease. Despite modern multiagent chemotherapy, survival remains poor. Locoregional progression of the primary tumor often causes pain, biliary obstruction, and gastrointestinal complications. Magnetic resonance-guided radiotherapy (MRgRT) enables daily adaptive planning and real-time motion control, allowing safe dose escalation in anatomically constrained regions. We hypothesized that stereotactic magnetic resonance–guided radiotherapy provides effective and safe local tumor control in patients with metastatic PDAC (mPDAC).

AIM

To investigate the feasibility, efficacy, and safety of MRgRT in mPDAC.

METHODS

This prospective single-center observational study enrolled consecutive patients with synchronous or metachronous mPDAC treated between January 2020 and January 2025. Radiotherapy was delivered on a 0.35-T MR-Linac with 33-40 Gy in five fractions. Primary endpoint was local control; secondary endpoints included overall survival (OS), time to distant progression, toxicity, and pain relief. Prognostic clinical and treatment parameters were explored using subgroup analyses.

RESULTS

Twenty-four patients were included. Local control at 12 months and 24 months was 76% and 67%, respectively. Median time to distant progression was 3 months. Median OS in the entire cohort was 13 months after radiotherapy and 20 months from diagnosis, with a 1-year OS rate of 49%. Palliative treatment intent was associated with shorter survival (5 months, $P = 0.001$). OS was longer in patients with single-organ disease ($P = 0.003$), stable metastatic disease after systemic therapy ($P = 0.0027$), carbohydrate antigen 19-9 < 500 U/mL ($P = 0.03$), and Eastern Cooperative Oncology Group 0 ($P = 0.023$). Two acute grade 3 gastrointestinal events (duodenal hemorrhage, biliary duct obstruction) occurred; no late grade ≥ 3 toxicities were observed. Pain relief was reported by 89% of symptomatic patients.

CONCLUSION

MRgRT is a feasible and well-tolerated treatment providing high local control and effective pain palliation in selected patients with mPDAC.

Key Words: Pancreatic cancer; Pancreatic ductal adenocarcinoma; Radiotherapy; Stereotactic body radiotherapy; Metastatic pancreatic ductal adenocarcinoma; Magnetic resonance-guided radiotherapy

Core Tip: Local progression of the primary tumor remains a major cause of morbidity in metastatic pancreatic ductal adenocarcinoma, even in the era of modern chemotherapy. This prospective observational study demonstrates that five-fraction stereotactic magnetic resonance-guided radiotherapy to the primary tumor is feasible and safe in patients with metastatic pancreatic ductal adenocarcinoma, achieving good local control, meaningful pain palliation, and low rates of high-grade toxicity. These findings support magnetic resonance-guided radiotherapy as a promising local treatment option within multimodal strategies for carefully selected patients with controlled metastatic disease.

Citation: Schumann MA, Gaasch A, Boyaci S, Fuchs F, Walter F, Marschner SN, Eze C, Westphalen CB, Holch JW, Beyer G, Kunz WG, Mayerle J, Niyazi M, Belka C, Corradini S, Rogowski P. Five-fraction stereotactic magnetic resonance-guided adaptive radiotherapy targeting the primary tumor in metastatic pancreatic cancer. *World J Gastroenterol* 2026; 32(29): 117832

URL: https://www.wjgnet.com/1007-9327/full/v32/i29/117832.htm

DOI: https://dx.doi.org/10.3748/wjg.117832

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive malignancies, with the majority of patients presenting with or eventually developing metastatic disease[1]. Despite advances in systemic therapy, prognosis for metastatic PDAC (mPDAC) remains dismal, with median overall survival (OS) of approximately 9-11 months under modern chemotherapy regimens such as folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) or gemcitabine/nab-paclitaxel[2,3]. While systemic therapy is central to patient management and prognosis, locoregional progression of the primary tumor frequently leads to significant morbidity through pain, biliary obstruction, or gastrointestinal complications[4,5], thereby warranting consideration of local therapeutic approaches even in metastatic setting.

Stereotactic body radiotherapy (SBRT) offers precise, high-dose irradiation in few fractions and has demonstrated favorable local control and symptomatic relief in locally advanced and selected mPDAC cohorts[6-9]. However, upper abdominal motion and the close proximity of critical gastrointestinal organs often limit dose escalation and reproducibility of target coverage. The introduction of magnetic resonance-guided radiotherapy (MRgRT) allows for daily adaptive planning and real-time motion management, potentially improving target conformity and organ-at-risk sparing [10].

While MRgRT has shown promising results in locally advanced disease, evidence in the metastatic setting remains limited[11-13]. In particular, the role of primary-directed therapy (PDT) using MRgRT in patients with stable or oligo-progressive mPDAC after initial chemotherapy, or in those unable to continue systemic therapy, is yet to be defined.

This study evaluates the feasibility, safety, and clinical outcomes of five-fraction stereotactic MRgRT targeting the primary tumor in patients with mPDAC. The study aims to assess the oncological outcome, toxicity outcomes, and pain relief across different treatment indications, and to explore potential prognostic factors associated with patient benefit.

MATERIALS AND METHODS

Study design and population

A prospective, observational, single-center basket study included consecutive patients treated with MRgRT at Ludwig-Maximilians-University Hospital Munich using the MRIdian system (ViewRay Inc, Oakwood Village, OH, United States). The study was approved by the local ethics committee (reference number: 20-0291), and all patients provided informed consent. For the present analysis, all patients with synchronous or metachronous mPDAC were included. The study was conducted in accordance with the Declaration of Helsinki in its most recent version. Treatment indications were confirmed by a multidisciplinary tumor board. All patients underwent staging with contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis.

MRgRT planning and delivery

Our institutional workflow for MRgRT with a 0.35-T hybrid MR-Linac system has been previously described[14-16]. In brief, patients underwent magnetic resonance imaging (MRI) simulation in breath-hold using true fast imaging with steady state precession sequences and planning CT for electron density mapping in the same setup. The datasets were co-registered using deformable image registration, target structures and organs at risk (OARs) were delineated on the MRI with support from diagnostic imaging. The gross tumor volume (GTV) included the visible pancreatic tumor and lymph node metastases, while the clinical target volume (CTV) included the GTV and incorporated adjacent lymph node and neural tract regions at risk for micrometastasis. A uniform isotropic expansion of 5 mm around the CTV defined the planning target volume (PTV). Initially, a concept with a single dose level to the whole volume (tumor and elective volume) was applied; however, from 2022 onwards, a risk-adapted two-level approach was predominantly used, incorporating a low-dose elective target volume and a simultaneous integrated boost (SIB). Target structures and OARs were delineated on the MRI. A planning risk volume for OARs, with an additional 3 mm margin, was subtracted from the PTV to create optimized PTVs (PTV opt).

MRgRT was prescribed at doses of 33 Gy to 40 Gy, delivered in five fractions, with at least two fractions per week. Planning objectives aimed for 95% coverage of optimized PTVs with 95% of the prescribed dose, depending on tumor size and proximity to critical OARs, and a maximum point dose of 125% of the prescribed dose. High-dose constraints for OARs included maximum point dose of 35 Gy and V33Gy ≤ 0.5 cc for the stomach, duodenum, and small bowel loops. For each fraction, a setup MRI was performed and registered with the simulation MRI, the OARs and pancreas were re-contoured based on daily anatomy, and the plan was adapted if prescribed target volume coverage and OAR constraints were not met. Continuous sagittal MRI at 4-8 frames per second monitored treatment delivery, with automatic beam interruptions for tumor motion exceeding defined boundaries.

Follow-up and outcome assessment

Patients underwent restaging every three months after treatment. The primary endpoint was local control (LC), defined as the time from MRgRT completion to a local recurrence or last follow-up. Local control was independently verified by an experienced radiologist. Secondary endpoints included time to distant progression (TTDP), defined as the time from MRgRT completion to the occurrence of new metastatic lesions or progression of existing metastatic sites outside the treated primary tumor or last follow-up, and OS, defined as the time from the diagnosis of metastatic disease or completion of MRgRT (as specified in each analysis) until death from any cause or last follow-up. Treatment-related toxicity was graded according to Common Terminology Criteria for Adverse Events v5.0 with events occurring within 3 months after MRgRT classified as acute and those appearing thereafter as late toxicity. Pancreatic cancer-related pain was assessed at baseline and during follow-up as part of routine clinical care. For the present analysis, a retrospective chart review of physician notes and medication records was conducted to extract information on pain intensity and analgesic use; when available, recorded numeric pain scores were extracted. Pain response at 3 months after MRgRT was categorized as improvement, stable symptoms, or worsening, based on documented patient-reported pain levels and changes in analgesic requirements. Exploratory subgroup analyses were performed to identify prognostic factors potentially associated with OS. These analyses were structured into three domains: Baseline disease and patient characteristics, systemic treatment-related factors, and radiotherapy-specific parameters.

Baseline disease and patient characteristics included metastatic burden [oligometastatic (≤ 5 metastases) *vs* polymetastatic], number of metastatic lesions (1-2 *vs* ≥ 3), extent of organ involvement (single organ *vs* multi-organ or peritoneal carcinomatosis), timing of metastatic presentation (synchronous *vs* metachronous), baseline functional status [Eastern Cooperative Oncology Group (ECOG) performance status], and pre-treatment serum carbohydrate antigen 19-9 (CA19-9) levels immediately prior to MRgRT (< 500 U/mL *vs* ≥ 500 U/mL).

Systemic treatment-related factors included the number of prior systemic therapy lines administered for metastatic disease (1 *vs* ≥ 2), radiographic response of the primary pancreatic tumor to induction chemotherapy (stable *vs* progressive primary tumor), and response of extrapancreatic metastatic sites (stable disease *vs* uncontrolled/progressive metastatic lesions). Radiotherapy-specific parameters comprised the prescribed MRgRT dose (40 Gy *vs* 33 Gy) and the use of comprehensive metastasis-directed therapy (MDT) encompassing all metastatic sites in conjunction with MRgRT (MRgRT of the primary tumor plus MDT *vs* MRgRT of the primary tumor alone).

Statistical analysis

Clinical endpoints were estimated using the Kaplan-Meier method, with subgroup comparisons performed using the log-rank test (GraphPad Prism, version 10.0.0; GraphPad Software, Boston, MA, United States). Median follow-up duration was calculated using the reverse Kaplan-Meier method. OS was evaluated from both the date of mPDAC diagnosis - defined as the first imaging (CT, MRI, or positron emission tomography) confirming metastatic disease - and from the date of MRgRT completion. LC and TTDP were assessed only from the date of MRgRT completion.

RESULTS

Patient cohort

Twenty-four consecutive patients with mPDAC treated between January 2020 and January 2025 were enrolled. Patient characteristics are shown in Table 1. The median age at diagnosis was 65 years (range: 49-84 years). Most patients presented with an ECOG performance status of 0 or 1 (92%). Most patients (54%) presented with synchronous metastatic disease, whereas 46% of patients had developed metachronous metastases in the course of their disease, including 13% who were initially diagnosed with resectable tumors, 8% with borderline resectable tumors, and 25% with locally advanced disease. Surgical resection was performed in 25% of patients, including 8% who underwent concurrent hepatic resections. The median CA19-9 levels at diagnosis of metastatic disease and directly before MRgRT were 365 U/mL (range: 17-2697 U/mL), and 132 U/mL (range: 10.5-2120 U/mL) respectively. At the time of MRgRT, 58% of patients were classified as having oligometastatic disease (≤ 5 metastases), whereas 42% exhibited polymetastatic disease. Metastatic sites were predominantly confined to the liver (50%), followed by the lungs (17%,) and abdominal or pelvic lymph nodes (8%). Additionally, two patients (8%) presented with multi-organ metastases, and four patients (17%) exhibited diffuse peritoneal carcinomatosis. Overall, 75% of patients had metastases confined to a single organ, whereas 25% demonstrated multi-organ involvement or peritoneal carcinomatosis.

Treatment characteristics

The indications for MRgRT were: (1) Consolidative therapy after at minimum stable disease following chemotherapy (38%); (2) Local control for isolated primary progression (21%); (3) Targeting all macroscopic lesions as part of a primary- and metastasis-directed approach for oligometastatic disease (13%); or (4) Palliative treatment for patients unable to tolerate (further) chemotherapy (29%) (Table 2). In the subgroup receiving MDT, one patient underwent SBRT for a lung lesion, one received brachytherapy to liver metastases, and one patient was treated with MRgRT to a liver metastasis.

Table 3 summarizes the treatment characteristics for the patient cohort. First-line palliative chemotherapy was administered to 92% of patients upon diagnosis of metastatic disease. Among these, 67% received FOLFIRINOX, while 17% were treated with gemcitabine/nab-paclitaxel. The median treatment duration was 12 cycles over seven months. Two patients did not receive any chemotherapy.

Median time from diagnosis of metastatic disease to the beginning of MRgRT was six months. All patients were treated in five fractions. Dose prescription was either a uniform dose of 33 Gy (54%) to the primary or the local recurrence or 33 Gy to an elective target volume with a SIB of 40 Gy to the macroscopic tumor (46%). The median size of the GTV was 44 cc (range: 12-101 cc), while the median CTV was 214 cc (range: 81-583 cc), following MRgRT, 83% of patients resumed chemotherapy with a median chemotherapy-free interval of three months.

Clinical outcomes

The median follow-up duration from the end of MRgRT, diagnosis of metastatic disease, and initial diagnosis were 13 months, 18 months, and 28 months, respectively. The 12- and 24-month LC rate was 76% and 67%, respectively (Figure 1). In total, six patients experienced local failure, including three in the high-dose group (40 Gy) and three in the low-dose group (33 Gy). Among these, one patient developed local recurrence, while the remaining five exhibited locoregional recurrence concomitant with progression in the initially metastatic organ. Median TTDP was 3 months. Progression of pre-existing metastatic sites occurred in 16 patients, while six patients developed distant metastases at new sites, all while maintaining stable local control. Median OS following MRgRT was 13 months, with a 12-months OS rate of 49%. Median OS from diagnosis of metastatic disease was 20 months. Nine patients reported pancreatic cancer–related pain at baseline. At 3 months post-treatment, eight patients (89%) showed pain improvement, including three who experienced complete resolution and discontinued analgesic medication. Additionally, reduced opioid use was documented

Table 1 Patients baseline characteristics, *n* (%)

Characteristics	
Number of patients	24
Sex	
Women	11 (46)
Men	13 (54)
Age, median age (range)	65 (49-84)
Age > 75	4 (17)
ECOG score	
0	11 (46)
1	11 (46)
2	2 (8)
Location of primary tumor	
Head	10 (42)
Body	3 (13)
Tail	2 (8)
Head/body	2 (8)
Body-tail	2 (8)
Local relapse	5 (21)
Onset of metastatic state	
Synchronous	13 (54)
Metachronous	11 (46)
Number of metastases	
≤ 5 metastases	14 (58)
> 5 metastases	10 (42)
Location of metastases	
Liver only	12 (50)
Lung only	4 (17)
Non-regional lymph nodes only	2 (8)
Peritoneal carcinomatosis	4 (17)
Multiple organs	2 (8)
Median CA19.9 at diagnosis of metastatic disease (range)	365 UI/mL (17-2697)
Median CA19.9 before MRgRT (range)	132 UI/mL (10.5-2120)

ECOG: Eastern Cooperative Oncology Group performance status; MRgRT: Magnetic resonance-guided radiotherapy; CA19-9: Carbohydrate antigen 19-9.

in five patients (56%).

Exploratory subgroup analysis

Patients with metastases confined to a single organ demonstrated a significantly prolonged median OS compared to those with multi-organ involvement or peritoneal carcinomatosis (14 months *vs* 5 months, $P = 0.003$) (Figure 2A). ECOG performance status was also significantly associated with survival outcomes, with patients classified as ECOG 0 exhibiting superior OS compared to those with ECOG 1-2 (15 months *vs* 10 months, $P = 0.023$) (Figure 2B). Similarly, baseline CA 19-9 levels < 500 U/mL were associated with significantly longer OS compared to levels ≥ 500 U/mL (23 months *vs* 11 months, $P = 0.03$) (Figure 2C). Furthermore, patients with stable distant metastases achieved significantly improved OS relative to those with uncontrolled metastatic disease (14 months *vs* 5 months, $P = 0.0027$) (Figure 2D).

Table 2 Indication for magnetic resonance-guided radiotherapy administration

		Primary tumor	
		Stable	**Progressive**
Extrapancreatic sites	**Stable**	Consolidative treatment (n = 9; 38%)	Local control: For isolated primary progression (n = 5; 21%)
	Progressive	Metastasis- and primary-directed therapy: Treatment of all macroscopic tumor sites (n = 3; 13%)	Palliative treatment: In case of chemotherapy intolerance or for pain relief (n = 7; 29%)

Due to rounding, the total of the percentages exceeds 100%.

Table 3 Treatment characteristics, *n* (%)

Treatment characteristics	
Chemotherapy preceding MRgRT	
Number of patients received chemotherapy	22 (92)
Median duration of chemotherapy (months)	7
Median number of cycles	12 cycles
(m)FOLFIRINOX	16 (67)
Gem/nabPac	4 (17)
Liposomal irinotecan + 5-FU and folinic acid (NAPOLI)	2 (8)
No chemotherapy	2 (8)
Radiotherapy	
Median total dose, Gy (range)	33 (33-40)
33 Gy/SIB 40 Gy	11 (46)
33 Gy	13 (54)
Gross tumor volume, median range (cc)	44 (12-101)
Clinical target volume, median range (cc)	214 (81-583)
Optimized planning target volume, median range (cc)	248 (65-662)
Metastasis-directed therapy	4 (17)
SBRT or brachytherapy	3 (13)
Resection of liver metastasis	1 (4)
Post-RT chemotherapy	19 (83)

MRgRT: Magnetic resonance-guided radiotherapy; FOLFIRINOX: Folinic acid, fluorouracil, irinotecan, oxaliplatin; Gem/nabPac; Gemcitabin/nab-paclitaxel; 5-FU: 5-fluorouracil; Gy: Gray; SIB: Simultaneous integrated boost; SBRT: Stereotactic body radiotherapy; RT: Radiotherapy.

Analysis by treatment indication revealed that OS did not differ significantly between patients receiving MRgRT for consolidation of a stable primary and those treated for local control of primary tumor oligo-progression (13.2 months *vs* 18.1 months, P = 0.3). However, both groups demonstrated significantly improved survival compared to patients who underwent MRgRT with palliative intent for pain management or polyprogressive disease in the setting of chemotherapy intolerance (5 months, P = 0.001) (Supplementary Figure 1).

Among variables demonstrating a trend toward significance, OS was numerically longer in patients with synchronous metastatic disease compared to those with metachronous presentation (14 months *vs* 5 months); however, this difference did not reach statistical significance (P = 0.11). Similarly, a non-significant numerical difference in OS was observed between the oligometastatic and polymetastatic cohorts (13 months *vs* 6 months, P = 0.4) (Supplementary Figure 2A and B).

No significant associations with OS were identified for the number of metastatic lesions (≤ 2 *vs* ≥ 3; P = 0.43), the application of a SIB to 40 Gy (SIB; P = 0.98), the administration of MDT (P = 0.90), or the number of prior systemic therapy lines administered for metastatic disease (1 *vs* ≥ 2; P = 0.62), or the radiographic response of the primary pancreatic tumor to induction chemotherapy (stable *vs* progressive primary tumor; 0.18) (Supplementary Figure 2C-G). With respect to secondary endpoints, the addition of MDT to all metastatic sites (17%, n = 4) did not result in a statistically significant

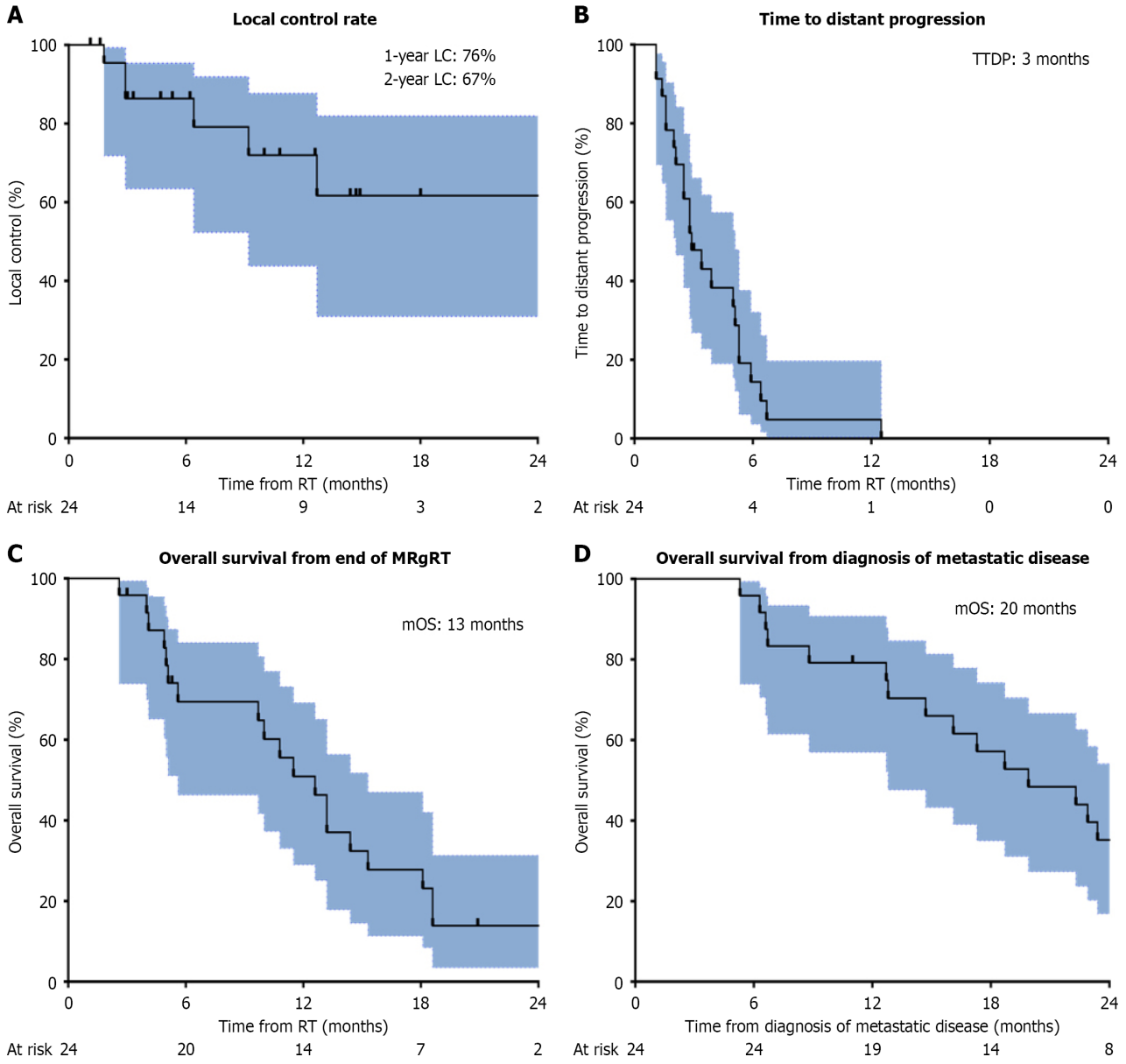


Figure 1 Kaplan-Meier estimates. A: Local control rates from the end of magnetic resonance-guided radiotherapy (MRgRT); B: Time from end of MRgRT to distant progression; C: Overall survival rates from end of MRgRT; D: Overall survival rates from diagnosis of metastatic disease. LC: Local control; RT: Radiotherapy; TTDP: Time to distant progression; MRgRT: Magnetic resonance-guided radiotherapy; mOS: Median overall survival.

improvement in TTDP (P = 0.96). Likewise, the application of an SIB to 40 Gy did not confer a significant improvement in LC (P = 0.47) (Supplementary Figure 3).

Toxicity and adverse events

The incidence of acute and late grade ≥ 3 toxicities due to MRgRT was low, with no acute events definitely attributed to MRgRT and two patients (9%) experiencing gastrointestinal acute grade 3 toxicities possibly related to MRgRT. One patient on anticoagulation during MRgRT experienced a grade 3 gastrointestinal bleeding 66 days post-MRgRT. Endoscopic evaluation revealed a circumferential, ulcerated tumor infiltration of the duodenal pars descendens accompanied by diffuse but self-limiting tumor-associated bleeding. The patient was discharged afterwards, in stable hemodynamic and hemoglobin condition. A retrospective dosimetric evaluation of all treatment fractions revealed a maximum duodenal dose in the region of the ulceration ≤ 34.4 Gy and a duodenal volume receiving ≥ 33 Gy ≤ 0.09 cc, representing clinically relevant but still compliant doses within our institutional constraints. Although a definitive distinction between bleeding caused by tumor infiltration and radiation-induced ulceration cannot be made, a mixed etiology is considered most likely. Another patient developed an obstruction of the common bile duct 63 days post-MRgRT due to migration of a biliary stent, resulting in elevated inflammatory and cholestatic laboratory parameters. The displaced stent was removed endoscopically and replaced with a fully covered self-expanding metal stent, restoring adequate bile flow into the duodenum. The patient was discharged in improved clinical condition. A direct effect of radiotherapy on stent displacement is considered unlikely; however, whether irradiation contributed to an exacerbation of the bile duct stenosis

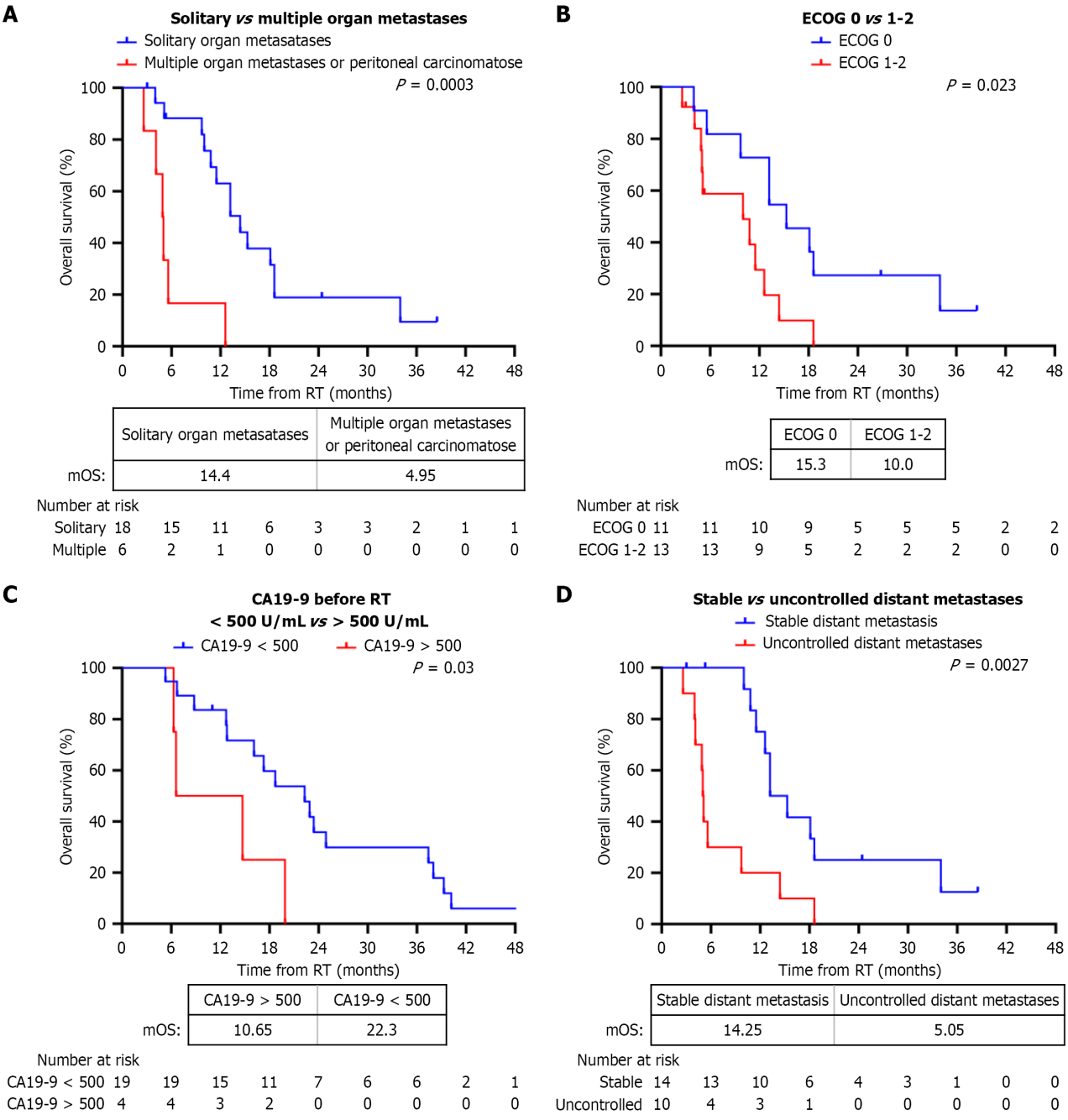


Figure 2 Kaplan-Meier estimates of overall survival from the start of magnetic resonance-guided radiotherapy, Eastern Cooperative Oncology Group performance status, baseline carbohydrate antigen 19-9 level at the beginning of magnetic resonance-guided radiotherapy, and radiographic response of distant metastases to chemotherapy. A: Stratified by solitary-organ metastases *vs* multiple-organ metastases; B: Eastern Cooperative Oncology Group performance status (0 *vs* 1-2); C: Baseline carbohydrate antigen 19-9 level at the beginning of magnetic resonance-guided radiotherapy (< 500 U/mL *vs* > 500 U/mL); D: Radiographic response of distant metastases to chemotherapy (stable *vs* uncontrolled). mOS: Median overall survival; ECOG: Eastern Cooperative Oncology Group; CA19-9: Carbohydrate antigen 19-9; RT: Radiotherapy.

cannot be conclusively determined. The maximum dose to the indwelling stent and thus to the bile duct was below 45.9 Gy and remained within commonly applied dose constraints reported in the literature[17]. A definitive distinction between radiation-induced injury and a stent-related complication could not be established in this case; therefore, the adverse event was classified as possibly related to MR-guided radiotherapy. No late grade 3 or any grade 4-5 events were observed.

DISCUSSION

The concept of PDT in mPDAC has gained renewed interest. Table 4 summarizes key studies from the past decade invest-

Table 4 Key studies investigating stereotactic body radiotherapy as primary-directed therapy in metastatic pancreatic ductal adenocarcinoma

Ref.	Study design	Patient population	Metastatic sites	Induction CTx	SBRT treatment	Dose	Overall survival	Local control	Toxicity
Su *et al*[24], 2015	Retrospective single-center analysis	16 mPDAC, 9 LAPC patients	NR	2/25 patients gemcitabine-based CTx	PDT	30-36 Gy/3 Fx; 40-48 Gy/4 Fx	Median: 9 months (mPDAC)	NR	Acute: 0% G ≥ 3; late: NR
Gkika *et al* [29], 2017	Retrospective single-center analysis	18 recurrent and omPDAC patients	Liver, lymph nodes	NR	PDT/MDT/combinations	PDT: Median BED_{10} 67 Gy; MDT: NR	Median: 13 months, 6-/12-month: 87%/58%	6-/12-month freedom from local progression 93%/67%	Acute: 5% G ≥ 3; late 5% G ≥ 3
Lischalk *et al* [30], 2018	Retrospective single-center analysis	20 synchronous mPDAC patients	NR	Gemcitabine-based (20%), FOLFOX (15%), FOLFIRINOX (10%), FOLFIRI (5%), other (10%)	PDT	Median 30 Gy/5 Fx	Median: 14 months, 12-month: 53%	Median local control: 7 months; 12-month LC: 43%	Acute: NR; late: 0%
Koong *et al* [31], 2020	Retrospective single-center analysis	27 omPDAC patients (≤ 3 metastases, ≤ 2 organs)	Liver, lung, peritoneum, other	89% at least one cycle prior to SBRT, predominantly gemcitabine-based	PDT	Single Fx (63%) median 25 Gy; 5 Fx (37%): Median 33 Gy	Median: 7 months, 12-month: 53%	12-month local failure rate: 25%	Acute or late 7%
Ji *et al*[23], 2021	Retrospective single-center propensity score matched analysis	34 synchronous omPDAC patients (≤ 5 metastases) *vs* 59 patients treated with CTx alone	Liver	Predominantly gemcitabine-based (98%)	PDT	Median 42.5 Gy in 5-7 Fx	Median: 9 months (PDT + CTx) *vs* 8 months (CTx), 12-month: 40% *vs* 21%	12-month cumulative incidence of local progression: 22% (SBRT + CTx) *vs* 53% (CTx) (P = 0.016)	4% G3
Elamir *et al* [37], 2022	Retrospective single-center analysis	6 synchronous and 14 metachronous omPDAC patients (≤ 5 metastases) *vs* 21 patients treated with CTx alone	Liver, lung	90% (predominantly gemcitabine/nab-paclitaxel and FOLFIRINOX)	PDT (25%)/MDT (100%)	PDT: Median 40 Gy/5 Fx; MDT: Median 50 Gy/5 Fx	Median: 42 months (SBRT + CTx) *vs* 18 months (CTx) from omPDAC diagnosis	Median local control: Not reached; 12-/24-month local control: 92%/83%	NR
Webking *et al* [13], 2023	Retrospective bi-institutional analysis	22 synchronous or metachronous omPDAC patients (≤ 6 metastases)	Liver, lung, lymph nodes, bones	FOLFIRINOX (64%) gemcitabine/nab-paclitaxel (36%)	PDT (MRgRT) + MDT (41%)	PDT: Median 50 Gy/5 Fx; MDT: NR	Median from diagnosis: 24 months; median from SBRT: 12 months	FFLRF: Median 12 months	9% G3
Ludmir *et al* [38], 2024 (EXTEND)	Randomized phase 2 multicenter trial [CTx *vs* CTx + MDT (+ PDT)]	40 synchronous (35%), metachronous (65%) omPDAC patients (≤ 5 metastases)	Liver, lung, lymph node, bone, other sites	73% (predominantly FOLFIRINOX or nab-paclitaxel-based CTx)	SBRT to all active sites (11 Pat with PDT in experimental arm)	PDT: Median 40 Gy/5 Fx; MDT: Predominantly 50 Gy/4 Fx or 70 Gy/10 Fx	Median 12 months (CTx + SBRT) *vs* 10 months (CTx) (P = 0.24)	NR; median PFS 10 months *vs* 3 months (P = 0.03)	16% G3 (all classified as not related to SBRT)
Jiang *et al*[28], 2024	retrospective comparison PDT *vs* PDT + MDT	217 synchronous omPDAC patients (≤ 5 metastases)	Liver, lung, bone, other sites	100% adjuvant CTx (predominantly gemcitabine/nab-paclitaxel and FOLFIRINOX)	PDT (n = 158) *vs* PDT + MDT (n = 59)	PDT: Median BED 60 Gy (30-45 Gy/5-8 Fx); MDT: Median BED 93 Gy (40-64 Gy/5-8 Fx)	Median 11 months (PDT + MDT) *vs* 9 months (PDT) (P < 0.001); 12-month: 37% *vs* 3%	NR; median PFS: 7 months *vs* 4 months (P < 0.001)	G3/4: 24% *vs* 20%
Schumann *et al* (current study), 2026	Prospective single-center observational study	24 synchronous (54%) and metachronous (46%) mPDAC patients	Liver, lung, lymph nodes, peritoneal carcinomatosis	92% (predominantly FOLFIRINOX or nab-paclitaxel-based CTx)	PDT (MRgRT) + MDT (13%)	PDT: 33 Gy (54%) or 40 Gy (46%) in 5 Fx; MDT: Median BED 95 Gy	Median: 13 months; 12-month: 49%	12-/24-month local control: 76%/67%	Acute: 5% G ≥ 3; late 5% G ≥ 3

BED: Biologically effective dose; CTx: Chemotherapy; FFLRF: Freedom from locoregional failure; FOLFIRI: Folinic acid, fluorouracil, irinotecan; FOLFIRINOX: Folinic acid, fluorouracil, irinotecan, oxaliplatin; FOLFOX: Folinic acid, fluorouracil, oxaliplatin; Fx: Fraction; G3/4: Grade 3/4; Gy: Gray; LC: Local control; MDT: Metastasis-directed therapy; mPDAC: Metastatic pancreatic ductal adenocarcinoma; NR: Not reported; omPDAC: Oligometastatic pancreatic ductal adenocarcinoma; PDT: Primary-directed therapy; SBRT: Stereotactic body radiotherapy; LAPC: Locally advanced pancreatic cancer; SBRT: Stereotactic body radiotherapy; MRgRT: Magnetic resonance-guided radiotherapy; PFS: Progression-free survival.

igating SBRT in this setting. Reported indications vary widely - from treating all active sites in oligometastatic disease, to local consolidation after chemotherapy, to isolated recurrences with stable distant disease, and purely palliative approaches. Correspondingly, published SBRT cohorts in mPDAC differ substantially with respect to metastatic burden (oligo- *vs* poly-metastatic disease, single- *vs* multi-organ involvement, synchronous *vs* metachronous spread), target selection (all active sites *vs* primary only), resection status, systemic therapy regimens and sequencing, as well as SBRT dose and fractionation.

In our cohort, 12-month local control after MRgRT was 76%, which lies at the upper range of previously published data (43%-78%). Local control is clinically important in mPDAC, as local progression often leads to substantial morbidity due to invasion of adjacent gastrointestinal and neural structures, resulting in biliary obstruction, gastrointestinal bleeding, and severe pain, which affects the vast majority of patients during the disease course[4,18,19]. Autopsy and clinical studies suggest that locally destructive tumor growth remains a common cause of death, even in the presence of metastatic disease, underscoring the potential value of local therapy in palliation and prevention of complications[5,20,21].

SBRT has demonstrated high rates of symptom relief in several series, with reported pain response rates between 65% and 85%, often accompanied by reduction in opioid requirements and stabilization of biliary or gastrointestinal function [9,22-24]. In our cohort, 89% of patients with baseline pain reported symptomatic improvement after MRgRT, and 56% were able to reduce opioid consumption, highlighting the dual benefit of good local control and effective palliation.

Survival interpretation requires consideration of the heterogeneity across studies. In our heterogeneous patient population - encompassing both oligo- and poly-metastatic disease treated for various indications - the median OS was 13 months from MRgRT and 20 months from diagnosis of metastatic disease. These results compare favorably with outcomes achieved using chemotherapy alone (approximately 9 months with gemcitabine/nab-paclitaxel and 11 months with FOLFIRINOX) and align well with prior primary-directed SBRT reports, which have demonstrated median OS ranging from 7 months to 14 months from the time of SBRT. Notably, OS in our cohort was indication dependent, with favorable survival largely driven by patients treated with consolidative intent after stable metastatic disease (median OS 13 months) or for isolated primary oligo-progression (18 months), whereas outcomes were poor in the palliative cohort (5 months). Cross-study comparisons therefore remain limited and may partly reflect selection bias.

Beyond radiotherapy, surgical strategies have also been explored as local treatment approaches in selected metastatic patients. Retrospective studies investigating surgical resection in oligometastatic PDAC have reported median OS from diagnosis of 8 months to as high as 56 months in highly selected patients[25,26]. However, postoperative morbidity rates of 15%-73% and 30-day mortality up to 8% underscore the procedural risks, which are especially relevant in the metastatic setting. Several prospective trials are currently ongoing to further evaluate the role of surgical resection combined with MDT in mPDAC, including the HOLIPANC (NCT04617457) and METAPANC studies (EU Clinical Trials No. 2023-503558-10-00)[27].

In our exploratory subgroup analysis, several prognostic factors emerged: Patients with metastases confined to a single organ had significantly longer survival than those with multi-organ involvement or peritoneal carcinomatosis. While this has not been consistently confirmed in SBRT series, the unfavorable prognosis associated with peritoneal spread compared with hepatic or pulmonary metastases is well established. Stable distant disease at the time of SBRT was also predictive of improved OS, consistent with the findings by Webking *et al*[13], who reported superior survival when SBRT

was delivered for local control rather than for symptom palliation or progressive disease.

As expected, better ECOG performance status correlated with longer OS, in line with Ji *et al*[23], who observed the greatest benefit of combined SBRT and chemotherapy in patients with favorable baseline performance. Baseline CA19-9, a surrogate marker of occult disease burden, also proved prognostic in our series - mirroring its established role in non-metastatic settings, where CA19-9 < 500 U/mL is considered a criterion for biological resectability.

Jiang *et al*[28] further reported that combining MDT with primary SBRT improved survival compared with PDT alone and identified a biologically effective dose (BED) > 60 Gy as beneficial. In the series by Gkika *et al*[29] and Lischalk *et al* [30], smaller PTV size also emerged as a prognostic factor for OS. We could not confirm these findings, likely due to limited sample size. Additional prognostic factors reported in other studies include primary tumor location in the pancreatic head and a longer interval between diagnosis and SBRT[23,31].

Taken together, these data emphasize the need for refined biological and clinical selection criteria to identify candidates most likely to benefit from local ablative therapy. Damanakis *et al*[32] proposed a definition of oligometastatic PDAC as disease limited to a single organ, with no more than four lesions in the liver or lung, and a CA19-9 level < 1000 U/mL. When applied to a cohort of 128 mPDAC patients treated with systemic therapy alone, those meeting all criteria achieved a median OS of 19 months compared with 7 months in the remaining group.

The dose levels used in our study (33 Gy and 40 Gy in five fractions) correspond to a BED_{10} of 54.8 Gy and 72 Gy, respectively. While the lower dose is generally considered palliative, retrospective data in locally advanced pancreatic cancer suggest improved outcomes with $BED_{10} \geq 70$ Gy[33]. No differences in local control or survival were observed between dose levels in our cohort, although this may be limited by small sample size. Both dose levels remain below the 50 Gy in five fractions (BED_{10} = 100 Gy) commonly used in modern LAPC trials[11,12], and whether dose escalation improves outcomes in metastatic disease remains unclear. Potential benefits in local control must be balanced against the competing risk of distant progression and the priority of minimizing toxicity in metastatic patients.

The only mPDAC series having consistently applied BED_{10} = 100 Gy is the MRgRT study by Webking *et al*[13]. Median OS after MRgRT (12 months) and grade ≥ 3 toxicity rates (9%) were remarkably similar to our findings, although cross-study comparisons must be interpreted cautiously. Based on currently available data, it therefore remains uncertain whether dose-escalated radiotherapy provides additional benefit in mPDAC.

Regarding the necessity of MR guidance for dose levels in the range of 33-40 Gy, grade ≥ 3 toxicity rates in mPDAC series using a conventional linac ranged from 0% to 24% (Table 4). No head-to-head comparisons between MR-guided and CT-guided SBRT for PDAC are currently available. Nevertheless, several dosimetric studies have shown that online adaptive MRgRT can improve target coverage and reduce dose to OAR[16,34,35]. These findings suggest a potential advantage of advanced techniques also in mPDAC. However, for centers without MRgRT, SBRT delivered on conventional linacs or with CT-based online adaptation appears feasible for doses up to 40 Gy[36]. Dose-escalated radiotherapy in mPDAC should be considered only in highly selected patients and in centers with access to advanced motion management and adaptive planning technologies. The ongoing phase III EXPAND trial (NCT0659343) investigating SBRT for oligometastatic PDAC with OS as the primary endpoint, will further clarify the role of local therapy and optimal radiation techniques in this setting.

Our study has several limitations that must be acknowledged. First, the relatively small sample size and single-center design limit the generalizability of our findings. Given that palliative systemic therapy remains the standard of care for mPDAC, only a limited number of patients were considered suitable candidates for MR-guided radiotherapy by the multidisciplinary tumor board, which contributed to the low accrual. Second, the cohort was heterogeneous with respect to metastatic burden, target selection, and systemic therapy regimens. While this heterogeneity may introduce bias, it also reflects real-world practice and allows exploratory assessment of prognostic factors across a broader clinical spectrum rather than in a highly selected subgroup. Furthermore, pain response and quality of life were not evaluated using standardized, protocol-based instruments, which restricts the robustness of symptom-related outcomes. Nevertheless, these data represent an important step toward defining patient subsets most likely to benefit from local therapy and provide valuable context for designing future prospective trials.

CONCLUSION

MRgRT is a feasible and well-tolerated local treatment in mPDAC, providing high local control and effective pain palliation with low toxicity. Despite cohort heterogeneity, survival outcomes compare favorably with those of standard chemotherapy alone. However, the favorable survival in our cohort was largely driven by the consolidative/oligo-progressive subgroups rather than the palliative cohort. These results support further prospective evaluation of MRgRT as part of multimodal strategies for carefully selected patients with metastatic disease.

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FOOTNOTES

Specialty type: Gastroenterology and hepatology

Country of origin: Germany

Author contributions: Schumann MA and Rogowski P designed and conducted the study and wrote the paper; Gaasch A and Boyaci S contributed to the analysis; Fuchs F, Walter F, Marschner SN, Eze C, Westphalen CB, Holch JW, Beyer G, Kunz WG, and Mayerle J provided clinical advice and revised the manuscript; Niyazi M, Belka C, Corradini S, and Rogowski P supervised the study.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Ludwig-Maximilians-University Hospital Munich (reference number: 20-0291).

Informed consent statement: All patients have signed informed consent to the study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at mohamd.schumann@med.uni-muenchen.de.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Corresponding Author's Membership in Professional Societies: European Society of Radiation Oncology; The German Society of Radiation Oncology.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Wang WB

Published by **Baishideng Publishing Group Inc**
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