Original Article

Safety and efficacy of locoregional therapy for metastatic pancreatic ductal adenocarcinoma to the liver: a single-center experience

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Background: Many patients with pancreatic ductal adenocarcinoma (PDAC) are diagnosed with liver metastatic disease (mPDAC), and few are surgical candidates. Interventional oncology (IO) locoregional therapies (LRT) have proven beneficial in other primary and metastatic hepatic malignancies. Systemic chemotherapy is the standard of care for patients with mPDAC. This study assessed the safety and efficacy of LRT including thermal ablation, chemoembolization, and radioembolization for mPDAC.

Methods: A retrospective analysis was performed of 28 patients with mPDAC referred to IR clinic for consideration of LRT from 01/2006 to 08/2017, of whom 20 underwent treatment. Laboratory values were analyzed at 0, 3, and 6 months post-treatment. Imaging response was evaluated at 1, 3, and 6 months post-intervention by modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. Adverse events (AE) were classified by CTCAE v5.0. Overall survival (OS) from the diagnosis of PDAC, survival from the time of mPDAC diagnosis, and survival from the time of LRT were calculated.

Results: Median OS (mOS) was 25 months. Median survival from time of mPDAC diagnosis and post LRT were 16.25 and 9.7 months, respectively. At one month post-intervention, 12 of 17 patients demonstrated disease response (CR or PR per mRECIST). Survival among responders was 9 months *vs.* 6 months for patients with stable or progressive disease (P=0.08). There were two grade 3 AE which included post-embolization syndrome and transient renal failure. Chemotherapy was briefly delayed in one of these patients, but ultimately resumed.

Conclusions: The use of LRT in patients with mPDAC is safe. Additionally, no significant chemotherapy limiting toxicities were observed. Responders to therapy demonstrated a survival benefit trend in this small and heterogeneous cohort. Further investigations with randomized trials are warranted.

Keywords: Pancreatic adenocarcinoma; chemoembolization; pancreaticoduodenectomy (PDX); interventional; metastatic pancreatic

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Introduction

PDAC is the fourth leading cause of cancer death in both men and women in the United States. Approximately half of patients present with advanced metastatic disease at diagnosis with a 5-year survival of 3% (1).

Chemotherapy is the mainstay of treatment for patients with metastatic disease, but nearly 40% of patients experience major side effects leading to decreased quality of life and treatment intolerance (2-5). Median overall survival (mOS) for systemic therapy under trial conditions ranges from 8.5–11 months (4-6). Radiation therapy, either concurrent chemoradiation or in sequence, provides effective primary local tumor control with an indeterminate survival benefit (7,8).

Pancreaticoduodenectomy (PDX) is the only potentially curative therapy for early stage pancreatic adenocarcinoma. R0 resections are subject to over an 80% risk of locoregional recurrence with median survival under trial conditions for non-metastatic disease between 17.9 and 23.6 months (9). Few studies have assessed the role of hepatic metastasectomy for PDAC with conflicting results that demonstrate unclear survival benefit (10-17).

With the advent of interventional oncology (IO), there has been increasing interest in the utilization of image-guided locoregional therapy (LRT) for the treatment of PDAC with hepatic metastasis (mPDAC). Radiofrequency ablation (RFA), cryoablation, irreversible electroporation (18), and microwave ablation (MWA) have all demonstrated efficacy and low morbidity (19,20). Transarterial chemoembolization (TACE) has also been investigated with demonstrable correlation in survival with local tumor imaging response and reported mOS of 9–19 months (21-23). Trans-arterial radioembolization (TARE) has been successfully used in metastatic pancreatic adenocarcinoma with a mOS of 9–22 months (24,25). The utilization of individual interventional oncologic modalities can vary greatly based on tumor morphology, anatomy, hepatic reserve, and institutional preference. This heterogeneous manifestation of disease and equally variable implementation of locoregional technology can be challenging to analyze. Nevertheless, many institutions offer LRT with a qualitatively perceived benefit in patients who would otherwise have limited options for mPDAC. We performed a retrospective evaluation of patients with mPDAC undergoing image-guided LRT to evaluate the safety and efficacy of this approach.

Methods

This study received institutional review board approval. A retrospective analysis of all LRTs performed for mPDAC by the Interventional Radiology (IR) Division between 01/2006-08/2017 was performed. Patient identification was accomplished using the Illuminate InSight search engine and its inherent natural language processing capabilities (Softek Illuminate, Inc., Overland Park, KS).

Analysis of the medical record was performed for all included patients. Patient demographics, extent of disease at diagnosis, prior chemotherapy, prior radiotherapy, prior or subsequent surgical therapy, and Eastern Cooperative Oncology Group (ECOG) performance status were collected. All patients underwent clinic evaluation and consultation in IR clinic prior to treatment. Data was collected for OS, survival since hepatic metastasis, and survival since LRT. For patients receiving multiple interventions, survival was calculated from the date of the initial intervention. Reported lab values were recorded for time points immediately prior to intervention as well as 3 and 6 months following intervention. Procedure related adverse events (AE) and lab value elevations were classified using Common Terminology Criteria for Adverse Events v5.0 (CTCAE 5.0).

Available imaging results for each patient were retrospectively reviewed by a board certified radiologist with fellowship training in abdominal imaging. Magnetic resonance imaging data was used when available. Imaging data was collected at baseline, as well as at 1, 3, and 6 months post-intervention, and every three months thereafter. Responses were defined as in-field (within the treatment liver volume) or out-of-field (outside of the treated liver volume). Both target lesion response and systemic response were graded using the modified Response Evaluation Criteria in Solid Tumors (mRECIST). mRECIST was modified for use with portal venous or delayed phase imaging, since mPDAC is typically not arterially hyperenhancing like hepatocellular carcinoma, and is more conspicuous on later phases of contrast. PET imaging was not available for enough patients to contribute to the analysis.

Results

Twenty patients, 11 females and 9 males, were included in the study (*Table 1*). All patients had a prospectively

Table 1 Baseline patient characteristics

Characteristic	N or median [range]
Patients	20
Male	9
Female	11
Age	66 [44–79]
ECOG performance status	
0	13
1	7
Prior chemotherapy	
Gemcitabine based	4
5-FU based	5
Both	10
Other	1
Concurrent chemotherapy	
Yes	9
No	11
Prior surgical resection	
Yes	9
No	11
Disease at diagnosis	
M0	12
M1	8
Baseline lab values	
Total bilirubin	0.4 (0.1–1.3)
Albumin	4 (2.5–6.4)
CA19-9	2,109 [64–111,197]
Creatinine	0.8 (0.5–1.1)
INR	1.1 (1.1–1.56)
ALP	129 [67–257]
AST	28.5 [16–97]
ALT	25 [11–96]
Type of intervention	
MWA	10
RFA	5
Cryoablation	1
TACE	3
TARE	8
Whole liver	2
Right lobe	4
Left lobe	1
Segmental	1

The data are expressed as n or median (range). ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MWA, microwave ablation; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

documented ECOG score of 0 or 1. The majority of patients had undergone prior chemotherapy and surgical therapy. Four patients underwent multiple IR interventions (maximum 3). One patient initiated chemotherapy concurrently with intervention. One patient had prior stereotactic body radiation therapy to a site of liver metastasis and 8 patients had external radiation therapy to the primary tumor or surgical bed. Twelve patients underwent primary tumor resection, and in two cases, resection was performed after LRT of hepatic metastasis.

The type of LRT performed varied and was chosen by the treating physician based on individual patient characteristics in addition to tumor phenotype and distribution. Ablative techniques including thermal ablation and segmental ablative TARE [>190 Gy medical internal radiation dose (MIRD) using glass microspheres] were favored for well consolidated small lesions (*Figure 1*). Regional arterial therapies with TACE (Oncozene, Boston Scientific, 50–75 mg doxorubicin) and palliative TARE (<120 Gy MIRD for glass microspheres or body surface area dosimetry for resin microspheres) were used for multifocal disease.

Sixteen of twenty patients were treated with the intent of controlling limited volume hepatic disease. Two of these patients later received PDX, with one undergoing synchronous hepatic wedge resection of the ablation site and the other undergoing wedge resection 5 months later. The four remaining patients were treated to palliate extensive and symptomatic liver disease using TARE or TACE. Among patients treated with TARE, 2 received bilobar administration, 5 unilobar, and 1 segmental. Of the 20 patients, 9 underwent intervention concurrently with chemotherapy. LRT was timed between chemotherapy administrations, or in some cases, chemotherapy administration was delayed by 1–2 weeks to accommodate LRT.

Follow up imaging was available at 1 month for 17 patients, at 3 months for 9 patients, and at 6 months for 6 patients (*Table 2*). In-field lesion response was complete response (CR) or partial response (PR) by mRECIST criteria in 12 of 17 (70.5%) and 7 of 9 (77.7%) patients at 1 and 3 months, respectively. Out-of-field response was characterized as CR or PR in 3 of 17 (17.6%) and 1 of 9 (11.1%) patients at 1 and 3 months, respectively (*Table 2*). mOS from diagnosis for the entire study group was 25 months (range, 3.5–52 months). mOS following diagnosis of hepatic metastasis was 16.25 months (range, 2.5–39 months). mOS following intervention was 9.7 months (range, 0.75–37 months). When patients were

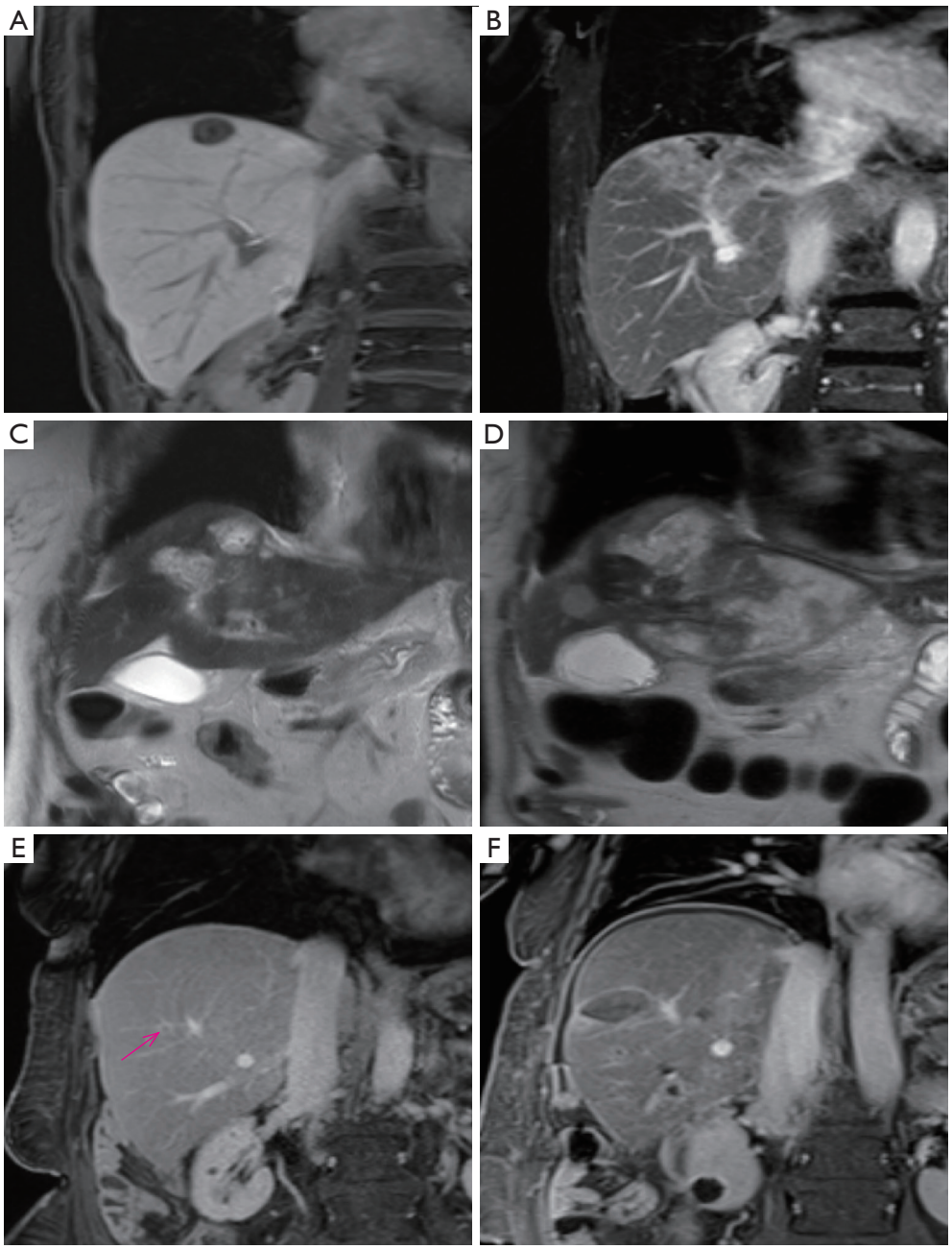

Figure 1 Representative cases of various LRT modalities. (A) Pre-procedure T1 fat saturated delayed post contrast MR abdomen demonstrating a metastatic focus in the hepatic dome; (B) T1 post contrast MR three months post-Y90 administration demonstrating expected post ablative radioembolization segmental hyperemia within the treated angiosome; (C) pre-TACE coronal T2 haste image of the left hepatic lobe demonstrating a large metastatic lesion in the superior portion of segment II; (D) coronal T2 haste image 3 months post-TACE demonstrating extensive post-embolization necrosis; (E) preoperative T1 fat saturated MR abdomen with contrast demonstrating a small, peripherally enhancing, lesion in segment VIII (arrow); (F) T1 fat saturated MR abdomen 3 months post-MWA demonstrating ablation defect in segment VIII without residual enhancement. LRT, locoregional therapy; TACE, transarterial chemoembolization; MWA, microwave ablation.

Table 2 Target lesion response by mRECIST criteria from date of initial intervention

Disease response	1 month		3 months		6 months	
	Treatment site	Other disease	Treatment site	Other disease	Treatment site	Other disease
CR	10	1	6	0	3	0
PR	2	2	1	1	1	0
SD	3	4	2	1	1	2
PD	2	10	0	8	1	4
Total	17	17	9	10	6	6

mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

stratified according to presence of response (CR and PR) of the in-field lesions *vs.* absence of response [stable disease (SD) and progressive disease (PD)] at 1 month post-intervention, median survival was 9 *vs.* 6 months (P=0.08). Median survival in responders *vs.* non-responders at 3 months was 11 *vs.* 7.75 months (P=0.07). Three patients were alive at the time of analysis, and two patients were lost to follow up at 5 and 3.5 months following diagnosis of hepatic disease. CA19-9 levels were available for 9 patients 3 months after treatment and were decreased from baseline (49–94%) in 6 of those patients.

There were four grade 1 and two grade 3 AEs by CTCAE v5.0 criteria. Four patients experienced grade 1 pain and/or nausea managed at home. A grade 3 elevation of alkaline phosphatase occurred in one patient 2 months after TACE and was related to an episode of cholangitis. One patient developed post-embolization syndrome following TACE and required <72 hours supportive care and a 1–2-week delay in resumption of chemotherapy. A second patient developed transient acute renal failure with myoglobinuria following hepatic MWA and required temporary dialysis. The definitive cause of renal failure in this patient was never established, and the patient never received IV contrast.

Discussion

The prognosis of PDAC with distant metastasis is universally poor, with 5-year survival rates of less than 3% (1). Despite advances in chemotherapy, significant improvements in survival have been slow to emerge. There is mounting evidence for LRT to play a role in the care of patients with mPDAC. Surgical resection has been shown to be safe with minimal increase in morbidity when carried out synchronously with primary tumor resection (12,13,15,17). However, given the large proportion of patients who are not surgical candidates or who develop metachronous disease, LRT is an appealing alternative.

Park *et al.* studied 34 patients who underwent treatment of hepatic metastases with RFA immediately after or during pancreatectomy. Median survival after diagnosis of metastatic disease was 14 months. Kim *et al.* retrospectively reviewed 15 patients who underwent TACE after hepatic recurrence following curative resection with survival times following diagnosis of hepatic disease and initial TACE of 9.6 and 7.5 months, respectively (22). Vogl *et al.* studied 69 patients who received TACE with a combination of mitomycin C, cisplatin, and gemcitabine reporting a mOS of 19 months. In addition, they demonstrated an 11 month increase in survival among patients who had PR per RECIST criteria (21). In a retrospective review of 16 patients who underwent TARE concurrently with chemotherapy, Kim *et al.* demonstrated a median survival from diagnosis of metastatic disease and receipt of initial TARE of 22 and 12.5 months, respectively (24).

Our data demonstrate that LRT of mPDAC has an excellent safety profile in appropriately selected patients. LRT can also be performed without disruption of chemotherapy in the majority of patients. Among our 20 patients, there were two Grade 3 AEs and one chemotherapy-limiting toxicity. The mOS of 9.7 months following LRT is comparable to other modality-specific reports in the available literature. The low morbidity of LRT makes it widely applicable among high-performing patients. Notably, two patients in our study received PDX following ablation therapy of solitary hepatic metastases. These patients had OS of 30.5 and 38 months and survival post LRT of 29.5 and 37 months, respectively. While it is difficult to draw conclusions from these two cases alone, the possibility of down-staging mPDAC patients with favorable

biology in order to undergo PDX is an exciting topic for future research efforts.

Several limitations are inherently present in this retrospective analysis. Our sample size of 20 patients is small, and limited conclusions can therefore be drawn from survival data. Due to the retrospective nature of the study, there is no control group for comparison. The presentation of mPDAC can be highly variable in both biology and anatomic involvement and the most appropriate locoregional treatment is tailored to these charactersitics. As such, retrospective analysis of mPDAC patients who receive LRT is inherently heterogeneous with various prior chemotherapy regimens and types of LRT. There is strong selection bias given the excellent performance status of our patients. The retrospective nature of this study did not allow for analysis of the effect of intent-to-treat. Referral practices and work-flow patterns have changed over the last 15 years. The creation of a formal Interventional Oncology clinic in the last few years will enable future acquisition of more meaningful statistics that cannot be applied to the series presented herein. While our study was not sufficiently powered to demonstrate statistical significance based on in-field lesion response, there was a strong trend toward improved survival, consistent with findings in the literature (21). Our patient-tailored application of variable LRT techniques demonstrated an excellent safety profile with high imaging response rate and did not disrupt systemic therapy. In light of the mounting retrospective evidence, prospective trials are warranted to definitively establish the role for LRTs.

Conclusions

The use of LRT in the treatment of metastatic pancreatic cancer is safe and does not significantly limit chemotherapy. Responders in our study demonstrated a trend toward improved survival. Further prospective evaluations are warranted.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study received institutional review board approval.

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