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Retrospective Study

Liver-Directed Therapy and Systemic Chemotherapy for Pancreatic Adenocarcinoma with Liver Metastases: Experience of 12-years

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ABSTRACT

Background
Pancreatic adenocarcinoma with liver metastases (PCLM) has a poor prognosis with a median survival of ≤6-months. Treatment options are limited as only a few patients can undergo curative surgery, therefore locoregional therapies such as liver-directed therapy (LDT) may offer an adjunct to systemic therapies. The purpose of this retrospective study is to evaluate the efficacy of incorporating trans-arterial radioembolization (TARE) with Yttrium-90 (Y90), trans-arterial chemoembolization (TACE), and radiofrequency ablation (RFA) with systemic chemotherapy in the treatment of PCLM.

Methods
We retrospectively evaluated 42 patients, with data available on 39 patients, with PCLM who underwent LDT between February 2007 and March 2019. Patient outcomes were assessed using response evaluation criteria in solid tumors (RECIST), Version 1.1 treatment-related adverse events were assessed using common terminology criteria for adverse events (CTCAE), version 5.0.

Results
Of 39 patients, 56% underwent TARE, 36% RFA, and 7.8% TACE. The median overall survival (mOS) was 5-months (range 4 to 5.5-months) from the application of LDT and the one-year mOS was 7.8-months (6.5 to 9.5-months). Overall and liver-specific disease response included complete response in 2.5%, partial response in 59%, stable disease in 21%, and progression of disease in 18% of patients. Grade 3 toxicities included abdominal pain in 13%, hyperbilirubinemia in 7.7%, fever in 7.7%, abscess in 2.6%, and thrombocytopenia in 5.1% of patients.

Conclusion
LDT can be safely combined with systemic chemotherapy for the treatment of PCLM. LDT may be the treatment opportunity for PCLM. Patient outcomes following this treatment strategy are promising but prospective evaluations are needed to validate these preliminary findings.

Keywords
Pancreatic adenocarcinoma; Liver metastases; Systemic chemotherapy; Liver-directed therapy; Pancreatic cancer; Yttrium-90; Radioembolization; TARE.

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer-related death in the United States.[1] In 2023, there are expected to be 64,050 new cases and 50,550 deaths from PDAC.[2] The only potentially curative treatment option for PDAC is surgical resection. Unfortunately, only 10-20% of patients are eligible for resection at the time of diagnosis presentation, and the majority of them eventually relapse following surgery.[3,4] More than 50% of all PDAC patients have metastases at the time of diagno-

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sis. Newer chemotherapy regimens such as FOLFIRINOX, or the combination of gemcitabine with nab-paclitaxel have improved outcomes for patients with metastatic PDAC with a median overall survival time of 8.5-11 months.[5,6] The liver is the most common site of metastasis in patients with PDAC both following resection of primary PDAC or at the time of initial diagnosis. Pancreatic adenocarcinoma with liver metastases (PCLM) has a poor prognosis with a median survival of ≤6-months.[7,8]

Improvement in surgical technology has led to effective treatment for selected patients with hepatic metastases in solid tumors, but this remains to be a rare situation in patients with PDAC.[6-9] The role of locoregional therapies such as liver-directed therapy (LDT) is less defined at present, albeit combining LDT as an adjunct to systemic therapies makes sense, a strategy proven to be beneficial with the use of radiotherapy with chemotherapy.[10] LDT is of different types such as trans-arterial radioembolization (TARE), trans-arterial chemoembolization (TACE), and radiofrequency ablation (RFA). TARE is a form of liver-directed brachytherapy that allows intra-arterial delivery of Yttrium-90 (Y90) radioactive particles into tumor tissue and has been shown to shrink tumors and enhance survival in other gastrointestinal tumors, such as hepatocellular carcinoma,[11,12] metastatic colorectal cancer,[13,14] and neuroendocrine cancer.[15,16] TACE either using conventional chemotherapeutic agents such as mitomycin C, cisplatin, and gemcitabine or administration of lipiodol has been shown to control the growth of liver metastases, especially in metastatic colorectal cancer.[17,18] RFA by inducing thermal injury to the tissue through electromagnetic energy deposition has been employed in select patients with liver metastases from many different primaries including pancreatic cancer.[19-21] However, the grave prognosis of PCLM may restrict the value of these modalities.

The purpose of this retrospective study was to evaluate the efficacy of incorporating LDT (TARE with Y90, TACE, and RFA) with systemic chemotherapy in the treatment of PCLM.

PATIENTS AND METHODS

The retrospective study reported in this paper was approved by the local institutional review board. We retrospectively evaluated 42 patients between February 2007 and March 2019, with data available on 39 patients with PCLM who underwent LDT including TARE with Y90 (SIR-Spheres, Sirtex Medical), TACE, and RFA. The majority of these patients underwent concurrent systemic chemotherapy for the treatment of PCLM.

Eligible patients had predominant hepatic disease with unresectable liver metastasis/metastases from pancreatic adenocarcinoma, e.g., the M1 no-surgery control group included patients who did not undergo surgical resection, but completed palliative chemotherapy instead. All patients were presented at a multidisciplinary pancreas board meeting where management decisions were discussed. Eligibility included limited extra-hepatic metastasis defined as <6 nodules with no nodule greater than 1.5 cm in lungs and stable for at least >4-months, abdominal lymph nodes, stable pancreatic primary which is <4 cm in size, absolute neutrophil count >1,500 /mL, hemoglobin >9 g/dL, platelets >100,000 / mL, bilirubin <2.0 mg/dL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio of <5 times higher than normal limit, creatinine level of <2.0 mg/dL, absence of hepatic cirrhosis (except for RFA), Eastern Cooperative Oncology Group (ECOG) performance score 0-1, and <20% lung shunting fraction (LSF).

Patients were excluded if the above criteria were not met, or those with a contraindication to angiography, extensive tumor replacement in the liver defined as >50% of liver involved with tumor, clinical evidence of peritoneal metastasis or ascites, or any serious ongoing infection.

Institutional guidelines were followed for any LDT procedures and at the discretion of the operating interventional radiologist. The treatment dose of resin Y90 was calculated according to the patient's body surface area for TARE. Precautions were adopted to minimize potential gastrointestinal ulceration using standard procedures. Dose reduction was performed for high lung shunts as per manufacturer recommendations. Patient demographics including history, physical laboratory, chemotherapy regimen, radiological imaging, and outcomes were collected.

Local and overall disease response was evaluated using response evaluation criteria in solid tumors (RECIST), Version 1.1 including disease response, median overall survival (mOS) from the time of diagnosis of metastatic disease, and mOS following receipt of LDT.[22] Follow-up imaging assessment was carried out usually two to three months after the final LDT session. Treatment-related adverse events were assessed using common terminology criteria for adverse events (CTACE), Version 5.0.[23]

Descriptive statistics were used to summarize patients' demographic features as well as treatment parameters. Statistical analysis software (SAS) software version 9.3 (SAS Inc., NC, USA) was utilized in the data analysis.

RESULTS

Of 39 patients, 56% underwent TARE, 36% RFA, and 7.8% TACE. The selection of modality was based on institutional standards and at the discretion of the referring physician. A summary of baseline patient characteristics is outlined in Table 1.

All patients had received at least one line of prior concurrent chemotherapy (range: 1-3) at the time of LDT. Thirty-six (36) patients (92%) underwent systemic chemotherapy concurrently during LDT sessions/sessions. Eighteen patients were receiving a 5-fluorouracil (5-FU)-based regimen, most commonly FOLFIRINOX or liposome irinotecan with 5-FU and leucovorin; nine patients were receiving concurrent gemcitabine-based therapy, including gemcitabine with nab-paclitaxel, gemcitabine-oxaliplatin, and gemcitabine-capecitabine and the rest with single agents, such as capecitabine, sutent, etc. Systemic therapy was stopped on average 12-days (range 11 to 22-days) before LDT and was resumed on average 21-days (range 14-28 days) after LDT. Table 2 summarizes the treatment parameters. All patients received a single course of

TARE for each diseased liver lobe. In 20% of patients who had bilobar liver disease, the combination treatments for both diseased lobes were defined in a single course. The mean Y90 radiation dose delivered to the right lobe was 1.00 GBq and to the left lobe was 0.64 GBq. There was an average interval of 28-days (range: 21 to 36-days) in between treatments for the patients receiving bilobar treatments.

Table 1. *Demographic Features of the Study Population*

Variables	Patients
Total	39
Male	21
Female	16
Age	65-years (range 43-77)
Performance Status	
0	7
1	32
Concurrent Chemotherapy	
5-FU based	18
Gemcitabine-based	9
Single agent	9
Baseline Laboratory Data	
Median total bilirubin	0.06 (range 0.02-2.5)
Median albumin	3.5 (range 2.2-4.7)
Hepatic Tumor Burden	
<25%	33
25-50%	6
Extra-hepatic Disease	
Lymph node	8
Lung	4
Bone	1
Others	1

Table 2. *Treatment Parameters*

Treatment	No. of Patients
RFA	**14**
Single session	7
Two sessions	7
TACE	**3**
Single session	2
Two sessions	1
TARE	**22**
Single lobe	18
Both lobe	18
Single session	15
Two sessions	7
Average Dose Administered Activity	
Right lobe	1.00 GBq (range 0.55-1.74)
Left lobe	0.64 GBq (range 0.35-0.91)

Eleven of the 39 patients were alive at the time of this retrospective analysis. The mPFS was 5-months (range 4 to 5.5-months) from the application of LDT and the one-year mOS was 7.8-months (6.5 to 9.5-months) (Table 3).

Table 3. *PFS and Median Survival*

LDT Modality	No. of Patients (n)	PFS (months)	Median Survival (months) from treatment of PCL
RFA	11	5.5(2-8)	9(6-12)
TACE	2	4.0(4-7)	6.5(4-8)
TARE	17	5.0(4-9)	7.8(4.5-11.0)

Overall liver-specific disease response included complete response in 2.5%, partial response in 59%, stable disease in 21%, and progression of disease in 18% of patients. Overall disease control (PR+SD) was 62% while one patient was not evaluable and median duration of response was 2.5-months (range: 2-6). Responses according to type of LDT were: RFA: (10/11)=90%, TACE: (1/3) 33% and, TARE: partial response (PR): (5/16) 31%. Majority of the patients (>50%) developed extra-hepatic metastases (lymph node (n=14), lung (n=5), peritoneal (n=4) and other (n=2) while or new liver metastases were noticed in 20% of the patients.

Grade 3 toxicities included abdominal pain in 13%, hyperbilirubinemia in 7.7%, fever in 7.7%, abscess in 2.6%, and thrombocytopenia in 5.1% of patients. No treatment-related grade 4 or 5 toxicities were seen.

DISCUSSION

Our retrospective study provides further evidence that incorporating multi-modality LDT with systemic chemotherapy, including newer cytotoxic agents in the treatment of liver-dominant Pancreatic adenocarcinoma with liver (PCL) can improve efficacy in this deadly disease with acceptable toxicity. With this heterogeneous disease and heterogeneous utilization of different modalities of LDT can be challenging to analyze. All methods of transvascular or thermal ablation techniques are limited by the size of the ablation zones developing following the procedure as well as by the number of lesions. A safety margin of at least 1 cm around the tumor is necessary for achieving complete ablation. Therefore, the maximum size of a lesion that can be successfully ablated is approximately 4-5 cm in diameter. For metastases too large for ablative therapy alone, downsizing can be achieved *via* TACE. Like ours, many institutions that offer expertise care in the field offer LDT with a qualitatively perceived benefit in patients who would otherwise have limited options for PCL. In the present study, all patients received systemic chemotherapy in conjunction with LDT. The commonly used regimens in the decreasing order were FOLFIRINOX, gemcitabine with nab-paclitaxel, gemcitabine-oxaliplatin, gemcitabine-capecitabine, liposome irinotecan with 5-FU and leucovorin, and capecitabine. One patient was on sutent as a maintenance therapy. Due to the small size, different chemotherapy regimens used, and retrospective nature of the study, we did not perform a comparison to the chemotherapy-only population or historical control. Previous reports have also suggested that LDT had a complementary effect when combined with systemic chemo-

therapy in PCL with manageable toxicities.[24-29]

The liver is the most common site for metastases in PDAC and is associated with a worse prognosis. Surgical resection of liver metastases is generally not performed in such patients and the use of systemic chemotherapy is preferred. Newer chemotherapy regimens including FOLFIRINOX and gemcitabine with nab-paclitaxel as first-line chemotherapies do offer an improvement in survival compared to gemcitabine monotherapy, a standard approved in 1996.[5,6,30] Only a few targeted agents have been approved for use in these patients, notably BReast CAncer gene 1 and BReast CAncer gene 2 (BRCA1/2), microsatellite instability (MSI)-high, and neurotrophic receptor tyrosine kinase (NTRK).[31-33] Immunotherapy has yet to show a breakthrough in the outcome of pancreatic cancer.[34] This all underlines the fact that treatment options remain limited for patients with PCLM. Therefore, it is logical to consider minimally invasive LDT as an alternative modality to treat these patients. It is of comfort and benefit that physicians have ample experience in treating other gastrointestinal tumors with these modalities, especially hepatocellular carcinoma (HCC).[10-12]

Medical literature shows recent reports of improved outcomes in PCLM patients who had metachronous or synchronous liver oligometastases of pancreatic cancer after radical surgery, in which patients exhibit long-term survival without recurrence after hepatectomy, are reported from major cancer centers.[35-38] Hepatectomy may result in a longer survival in a few patients, however, factors such as to number of metastases, extra-hepatic disease and time to post-operative recurrence are considered important criteria.[39] Although liver resection was a common type of LDT, there were few candidates for PCLM, and the surgical indications are debatable. Therefore, patients who received aggressive surgery were excluded from this study. This also requires a multidisciplinary and multi-modality approach with experts in the field and at high-volume cancer centers.

LDT can be repeated in some patients if clinically indicated and may provide survival benefits. In a study performed by Ouyang et al[40] the median overall survival (OS) improved several times TACE was performed at 14.1-months, 8.1-months, and 7.5-months in patients who underwent the procedure thrice, twice, and once respectively. Similar reports were published by Azizi et al.[41]

Though our study in addition to previous studies by other investigators showed that LDT can provide effective and safe treatment options for patients with PCLM, modalities of LDT are heterogeneous. As with any radical treatment options, the results of this study should be evaluated with regard both to acute and long-term toxicities of the combination therapy. Our patients had grade 3 toxicities consisting of abdominal pain in 13%, hyperbilirubinemia in 7.7%, fever in 7.7%, abscess in 2.6%, and thrombocytopenia in 5.1% of patients. These results of toxicities are those of previous studies.[24-28,39,40]

We acknowledge the limitations that accompany our study. This was carried out in a retrospective nature which included inherent biases such as the possibility of selection bias and lack of a control group for comparison. A relatively small sample size is also a limitation as this was conducted solely at our institutions as a retrospective analysis. However, keeping these points in mind, we believe our patients represented a reasonably similar profile to the general population in this patient population with PCLM. All patients were treated at the discretion of the treating physician. Patients were monitored as they would be in any clinical setting. However, we still believe that our cohort adds significance to adding LDT safely to systemic therapy in these patients resulting in a survival benefit for liver dominate PCLM.

Offers a better outcome Pancreatic ductal adenocarcinoma continues to be one of the leading causes of cancer-related mortality in the United States and surgery is the only potentially curative treatment option for these patients. Multidisciplinary coordination is of paramount significance in these circumstances.

CONCLUSION

LDT can be safely combined with systemic chemotherapy for the treatment of PCLM. Patient outcomes following this treatment strategy are promising but prospective evaluations are needed to validate these preliminary findings. Liver-directed therapies represent a target for future study.

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INSTITUTIONAL REVIEW BOARD PERMISSION

Yes.

PATIENT'S CONSENT

Not required.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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