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The use of IRE in multi-modality treatment for oligometastatic pancreatic cancer

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ABSTRACT

Introduction: Pancreatic ductal adenocarcinoma (PDAC) often presents late with only 20% of patients being candidates for resection while majority already have advanced metastases with median overall survival of 3–6 months. Currently, the role of oligometastasectomy and local therapy options in PDAC is unknown in patients who have favorable response to systemic chemotherapy. The aim of this study is to analyze the survival outcome of oligometastasectomy and local IRE therapy in select patients who are treated with systemic chemotherapy for PDAC metastases.

Methods: We utilized a prospective database from 2010 to 2016 to identify patients with local surgical therapy after induction systemic chemotherapy for oligometastatic PDAC (Stage 4). The initial local therapy treatment of distant metastatic lesions was followed by adjuvant chemotherapy. Subsequently, resection of the primary PDAC in conjunction with irreversible electroporation (IRE) was performed after favorable response by RECIST criteria.

Results: Seven patients were identified with metastatic PDAC treated with oligometastasectomy and/or local therapy. There was single metastatic lesion in 43% (3/7) of which 57% (4/7) were localized in the liver. The treatment of the primary pancreatic cancer was performed utilizing IRE in situ in 6/7 (86%) of patients in our study with resection or radiation of oligometastasis. The median survival in our study group was 16 months with 28% (2/7) patients who remain NED (range 16–41 months).

Conclusion: Combination of systemic chemotherapy and oligometastasectomy with adjunctive local IRE therapy is a feasible treatment strategy in highly select patients with oligometastatic PDAC that demonstrate favorable tumor biology with objective response to systemic therapy.

1. Introduction

As a result of the poor prognosis for patients with metastatic pancreatic cancer (American Joint Committee on Cancer (AJCC) stage 4), optimal palliative strategies to extend survival are of great importance for patients presenting with metastatic disease. Currently, the treatment modalities for metastatic pancreatic cancer are primarily systemic chemotherapy based on gemcitabine[1] or the more aggressive regimen FOLFIRINOX, which showed an additional 4.3-month survival according to the PRODIGE trial.[2] While the most recent advances in chemotherapy have not increased survival beyond several months, the enhanced response rates (approximately 30–40%) of these chemotherapy regimens have led to increased enthusiasm for strategies for improving patients survival.[3] In addition, this principle of induction chemotherapy allows for a better understanding of the biology of these distant metastases. Stable oligometastasis maybe more clinically favorable than those with widely diffuse metastatic disease, creating an opportunity for local control therapies to improve survival outcomes.

As a result, within this select group of patients with favorable tumor biology of metastatic pancreatic disease, there remains a subgroup of patients who present with only oligometastasis.[4] Their presentation raises the question if the strategy of oligometastasectomy with local therapy may offer a more durable disease-free interval than traditional systemic chemotherapy alone.[4–6] The liver is the most common location for metastatic lesions of pancreatic cancer, with additional sites including the lung and

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pleura, peritoneum, bone, and adrenal glands.[6–8] The liver has highest incidence of distant metastases for pancreatic cancer because it is the first major organ to receive portal venous drainage from the pancreas.[9] Thus, liver-directed therapy of oligometastatic liver lesions may provide a method of delaying progression of disease compared to those who receive only receive systemic chemotherapy.

The aim of this study was to assess the role of combination of oligometastasectomy and/or local therapy for select patients with metastatic pancreatic cancer who demonstrate favorable responses after systemic chemotherapy. The primary endpoint of the study is the survival outcome in patients treated with isolated metastases in comparison with patients who only received systemic chemotherapy at our institution.

2. Methodology

A single-institution prospective database of patients with metastatic pancreatic cancer (AJCC Stage 4) who underwent oligometastasectomy and/or local therapy of distant metastases along with resection and/or local therapy with irreversible electroporation (IRE) of primary pancreatic cancer after systemic chemotherapy from 2010 to 2016 was performed. Patients were selected for oligometastasectomy after multidisciplinary discussion based on patient factors such as favorable response on cross-axial imaging, biomarker response of CA 19-9 after systemic chemotherapy, performance status, inherent tumor biology as a function of time to metastasis, and feasibility of metastasectomy and/or IRE. Our institution's algorithm for selection of these patients begins at the initial staging of synchronous stage IV pancreatic cancer. If patients present with single organ and finite disease (<=3 lesions) then consideration for oligometastasectomy and/or local therapy is initiated. Most patients received induction systemic therapy of FOLFIRINOX or Gemcitabine-Abraxane in order to assess the biology of the tumor. If the patient's disease burden remains the same or improves (i.e., objective response rate per RECIST criteria of 1 or more target metastatic lesions), then oligometastasectomy and/or local therapy for the metastatic lesions is considered in conjunction with peri-operative chemotherapy. This therapy can include laparoscopic ablation or resection of metastatic lesions in addition to, Y-90 bead irradiation or external beam radiation. Patients are then continued on systemic therapy for another 4–5 months to assess for signs of progression. If there are no signs of progression with stable disease, consolidative therapy to the primary pancreatic cancer lesion is addressed with pancreatic resection with IRE margin accentuation or IRE alone (in-situ) (Fig. 1 illustrates this algorithm.).

Patients with oligometastasis from primary pancreatic cancer with metastases located in the liver, omentum, or peritoneum were included in the analysis (AJCC Stage 4). We compared our perioperative and postoperative outcomes data with other published studies of oligometastatic treatment of pancreatic cancer and the institutional survival outcome for patients with metastatic disease who only received chemotherapy.

The clinical and histopathologic data assessed prospectively into the database were: age, sex, clinical history, surgical history, procedure type, additional procedures, and previous chemotherapy. Depending on the location of the metastases, patients underwent metastasectomy and/or percutaneous or open ablative therapy utilizing IRE. The treatment modality was selected by the operative surgeon, based on intraoperative assessment, previous treatments, and patient comorbidities. IRE treatment procedures were performed with the NanoKnife device using monopolar or bipolar probes.[10]

In order to compare our results, a comprehensive review of the literature was performed through PubMed, EMBASE, LISTA (EBSCO), and Web of Science. The initial database searches were conducted using the keywords “Solitary Metastasis” and “Pancreatic Cancer,” in the title/abstract field and “treatment” in the abstract field. This yielded 67 articles. An additional 9 articles analyzing “oligometastatic pancreatic cancer,” neoadjuvant therapy, and surgical resection/exploration were hand-selected and added to the search. From the combined 83 articles, 40 articles were excluded after being screened for the following criteria: publication date 2005–2016, English only, Human Subjects only. Duplicate studies were removed, as well as 13 case studies. The remaining 30 articles were examined in their entirety and searched for quality and valuable reported data relevant to the key inclusion materials.[11] The remaining 13 articles were used to compile information about the survival outcome based on different treatment modality.

3. Results

Between 2010 and 2016 at a single academic tertiary university hospital referral center, 7 patients with oligometastatic pancreatic cancer were selected for oligometastasectomy and/or IRE after being selected for having radiographic tumor stability or partial response by RECIST criteria from as well as no signs of progression using both RECIST and CA19-9 levels. Only after that stability on systemic therapy is consolidative therapy to the primary pancreatic cancer lesion addressed with pancreatic resection with IRE margin accentuation or IRE alone (in-situ). The median age of the patients was 54.7 ± 11.1 years. The most common comorbidities that were presented were hypertension, cardiac disease, pulmonary disease, and tobacco use. Surgical history was recorded along with patient

Table 1
Patient demographics.

	Patients (n = 7)	Percentage (%)
Median Age (yrs.)	63	
BMI (kg/m^2)	25.4 ± 3.5	
Male	2	27
Female	5	73
Medical History		
Hypertension	3	40
Cardiac Disease	1	7
Pulmonary Disease	1	7
Tobacco Use	1	13
Surgical History		
Abdominal	1	13
Colon	1	7
Appendix	1	7

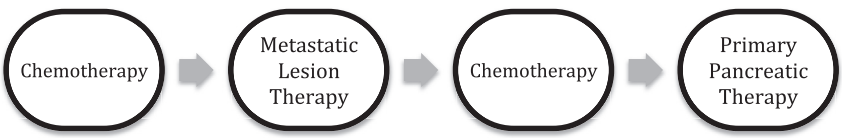

Fig. 1. Metastatic pancreatic cancer treatment model.

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