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

Young Hong a, Jonathan Rice a, Divyansh Sharma b, Robert C.G. Martin II a,*

a Department of Surgery, University of Louisville, USA
b School of Medicine, University of Louisville, USA

A R T I C L E   I N F O

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A B S T R A C T

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.

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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 gemcitabine1 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 patient 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
pleura, peritoneum, bone, and adrenal glands. The liver has the highest incidence of distant metastases for pancreatic cancer because it is the first major organ to receive portal venous drainage from the pancreas. Thus, liver-directed therapy of oligometastatic liver lesions may provide a method of delaying progression of disease compared to those who receive only 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-sectional 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 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 periparative 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.

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. 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>
<thead>
<tr>
<th>Table 1 Patient demographics.</th>
<th>Patients (n = 7)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (yrs.)</td>
<td>63</td>
<td>300</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4 ± 3.5</td>
<td>300</td>
</tr>
<tr>
<td>Male</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>73</td>
</tr>
<tr>
<td>Medical History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Tobacco Use</td>
<td>1</td>
<td>13</td>
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<tr>
<td>Surgical History</td>
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<td>Abdominal</td>
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<td>13</td>
</tr>
<tr>
<td>Colon</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Appendix</td>
<td>1</td>
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</tbody>
</table>

Fig. 1. Metastatic pancreatic cancer treatment model.
Table 2
Diagnosis and systemic treatment summary.

<table>
<thead>
<tr>
<th>Metastases Location</th>
<th>Patients (n = 7)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>4</td>
<td>57.1%</td>
</tr>
<tr>
<td>Omentum</td>
<td>3</td>
<td>42.8%</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>3</td>
<td>42.8%</td>
</tr>
</tbody>
</table>

Number of Lesions

| One   | 3   | 42.8% |
| Two   | 3   | 42.8% |
| Three | 1   | 14.3% |

Chemotherapy

| FOLFOX | 6 cycles | 1 | 14.3% |
| 9 cycles | 1 | 14.3% |
| 12 cycles | 2 | 28.6% |
| Capecitabine | 3 cycles | 1 | 14.3% |
| 6 cycles | 1 | 14.3% |
| Gemzar | 3 cycles | 2 | 28.6% |
| 12 cycles | 2 | 28.6% |
| FOLFIRINOX | 12 cycles | 4 | 57.1% |
| Other* | 2 | 28.6% |

* Erlotinib, Sorafenib, Tarceva.

Demographics in Table 1. Metastatic disease was most commonly present in the liver (57.1%), omentum (42.8%), and peritoneum (42.8%) in our patients. There were 3 patients (42.8%) presenting with 1 metastatic lesion, 3 patients (42.8%) with 2 lesions, and 1 patient (14.3%) with 3 lesions preoperatively (Table 2). All the patients in our study received IRE in situ to either the primary pancreatic lesion in 6/7 (86%) or the metastatic lesion in 1/7 (14.3%). Some patients received additional procedures intraoperatively which are summarized in Table 3.

Treatments for metastatic pancreatic lesions include hepatic resection (42.8%), 3D Conformal Therapy (14.3%), and IRE in situ (14.3%) (see Table 4). Previous chemotherapy received by patients includes FOLFOX (57.1%), Capecitabine (28.6%), Gemcitabine (57.1%), and FOLFIRINOX (57.1%). The complete list of previous treatment received by patients is presented in Table 2. The overall median survival outcome of the 7 patients included in our analysis was 16 months (range 3–41 months). There was a total of 4 (57.1%) patients with disease-specific mortality while 1 (14.3%) patient died from non-disease related causes. There are 2 (28.6%) patients who are currently still alive with no evidence of disease after the oligometastasectomy and/or local control therapy with IRE. An institutional review of metastatic pancreatic cancer patients within the past 7 years who only received systemic therapy demonstrate the increasing 5-year survival from 4.9% to 18% (Table 6).

4. Discussion

At the time of initial diagnosis of pancreatic cancer, patients have resectable disease only 20% of the time, while 50–60% of patients having metastatic disease with very poor prognosis. The 5-year relative survival rate overall for pancreatic cancer is 7.6%, with 29.3% for localized disease but only 2.6% for distant metastasis. There is growing evidence of improved survival of selected patients with metastasectomy in other malignancies such as colorectal, lung, liver, and gastric cancer. As a result, investigations into expanding this strategy among patients with pancreatic ductal adenocarcinoma (PDAC) metastasis have started showing potential survival benefits, including local control of metastases in select patients with favorable tumor biology and response from systemic chemotherapy. This study aims to demonstrate that oligometastasectomy and/or localized therapy alone with IRE for PDAC is a viable treatment option for a select patient group, offering an alternative to the traditional non-operative approach for metastatic pancreatic cancer. In our institutional experience, 20% of patients had no evidence of disease (NED) with median overall survival of 16 months after oligometastasectomy combined with local, non-thermal ablation utilizing IRE. These results are in alignment with the literature summary of metastasectomy for pancreatic cancer (Table 5). The majority of our patients had 1 metastatic lesion (over half located within the liver). Other patients had multiple metastatic lesions in additional locations such as peritoneum, omentum, and distal pancreas.

4.1. Irreversible electroporation (IRE)

In our study, we utilized IRE in addition to metastasectomy as a strategy for carefully selected patients with oligometastasis. IRE is a technology that utilizes high voltage pulses to create permanent nanopores in the cell membrane, which induces apoptosis of targeted cells. Its role in locally advanced pancreatic cancer (LAPC) has allowed improved overall survival and local recurrence when compared to chemotherapy and resection alone. There also has been an expansion in the use of IRE for unresectable hepatocellular carcinoma lesions in patients with liver cirrhosis. Their short-term outcome of IRE has shown equal efficacy of ablation success yet with improved liver tolerance and safety compared to microwave ablation techniques. IRE can be performed by percutaneous, laparoscopic, and open approaches, but with preference given to the laparoscopic or open approach for several advantages. The laparoscopic or open approach allows an increased sensitivity of intraoperative ultrasound visualization of the primary lesion, accurate placement of multiple probes for optimal ablation, and post-ablation monitoring via ultrasound to visualize real-time changes in the lesion.
In concordance with the previously described literature, the data analyzed in the present study suggest an increased median survival for selected patients with oligometastatic pancreatic cancer with favorable tumor biology treated with ablative and/or resection. Fig. 1 illustrates the treatment strategy for patients who underwent oligometastasectomy with IRE for metastatic PDAC. The overall median survival of 16 months in our institutional experience aligns with published literature on metastasectomy for pancreatic cancer. Klempnauer et al. reported median survivals of 8.3 months after synchronous liver and pancreatic resection and 5.8 months after metachronous hepatic resection, suggesting additional organ resections may provide a mode of treatment for metastatic disease. Shrikhande et al. suggested that pancreatic resections with simultaneous liver resection for metastatic disease. Shrikhande et al. suggested that pancreatic resections with simultaneous liver resection for metastatic disease could be performed with acceptable safety in highly selected patients. Of the 11 PDAC patients with liver metastasis, those who underwent pancreatectomy with synchronous hepatectomy had significantly longer median survival than the patients who underwent exploratory laparotomy without any resection (11.4 vs. 5.9 months, P = 0.038). Tachezy et al. also suggested a survival benefit for patients undergoing synchronous pancreatec and hepatic resections for PDAC with overall survival prolonged in patients who underwent synchronous metastasectomy (median 14 vs 8 months, P < .001).

Despite current literature showing that pancreatectomy with metastasectomy can be performed safely without a significant increase in perioperative morbidity and mortality, the potential benefit on long-term survival is still debated. Singh et al. examined three PDAC patients who underwent synchronous metastasectomy and pancreaticoduodenectomy who died at 7, 14 and 18 months post-operatively. Klein et al. described a median overall survival in PDAC patients with hepatic metastases of 7.6 months after resection, with a two-year survival of about 5% (one patient). No patient achieved five-year survival after hepatic resection. All patients received adjuvant therapy with gemcitabine. Gleisner et al. reported that the median overall survival of periaompillary or PDAC patients who underwent hepatic resection of metastatic disease was not significantly different from the overall survival of matched patients who underwent palliative bypass (5.9 vs. 5.6 months; P = 0.46). This study included 17 (77.3%) PDAC patients and the majority of patients (86.4%) had a solitary hepatic metastasis, while Zanini et al. reported a median overall survival of 9.1 months (95% CI 8.6–9.7). The potential prognostic factor that may have significantly affected survival was the timing of metastases diagnosis (metachronous vs. synchronous). Median overall survival in patients with metachronous disease was 11.4 months (95% CI 0–21.1) and 8.3 months with synchronous disease (95% CI 6.9–9.7), p = 0.038. Recent study from Germany by Hackert et al. demonstrated the largest series of metastasectomy of liver and/or distal interaortocaval lymph nodes with overall median survival of 12.3 months in both groups with 5-year survival of 8.1% after resection of liver metastases and 10.1% for interaortocaval lymph nodes.

The study had several limitations which include the retrospective analysis with selection bias for the highly selective group of patients who were qualified to be included. As a result, the sample size is very small and thus the amount of extrapolation of the data for inferences and conclusions is limited. The type of systemic therapy was quite variable in our analysis and could be a potential confounder in the survival data. The decision for metastasectomy and/or IRE was based upon individual surgeon preference which
may be extrapolated across different hospitals or surgeons with same selection criteria, but must be validated carefully with precise patient selection and surgical technique. The selection criteria for potential candidates for surgical therapy for oligometastatic pancreatic cancer were based on radiographic and/or chemical tumor marker response to chemotherapy. These criteria could be expanded in the future for duration of response and potential additional information with mutational analysis as we discover more prognostic gene markers for recurrence. Furthermore, the IRE technique is quite variable across different centers due to the high learning curve for its use. However, despite the stated limitations in our analysis, our study supports the emerging literature demonstrating that an aggressive surgical approach for a once thought non-operative metastatic pancreatic patient is, in fact, feasible and safe with favorable survival benefit. We further demonstrate that metastasectomy is not the only modality to treat metastatic disease. IRE, a non-thermal ablative technique that does not injure major vascular structures, provides an additional tool for a novel local-control approach in metastatic disease.

The future implications of our study are to expand patient selection in a multi-institutional, randomized control trial that may definitively answer the question of benefit of oligometastasectomy and/or local ablative therapy in patients with metastatic pancreatic cancer. As systemic therapy regimens improve with various combinations of chemotherapy and the expansion of novel therapies, such as immunotherapies, the number of patients who may benefit from an aggressive surgical approach can be expanded with longer expected survival.

5. Conclusion

In conclusion, our study demonstrates the feasibility of an aggressive approach of oligometastasectomy and/or local ablative therapy with IRE for patients who have favorable tumor response to systemic therapy for oligometastatic PDAC. This study proposes a treatment strategy that helps propose proper selection in order to optimize patient selection. Despite limitations in our study, this initial data warrants further validation in a prospective, randomized study with a clear control comparison group. As systemic therapy improves in the near future, there can be an expanded application of an aggressive surgical therapy for once-thought nonoperative patients with metastatic pancreatic cancer.

Disclosures

None.

References