Past, Present, and Future of Neoadjuvant Therapy for Pancreatic Cancer

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Abstract
Pancreatic cancer is a leading cause of cancer death with overall 5-year survival of 5%. For the small proportion of patients who present with localized disease, surgical resection remains a necessary treatment component to achieve lasting survival. Over the past 20-30 years, multi-modal therapy involving the addition of chemotherapy and/or radiation has emerged as an important adjunct to surgery in order to prolong survival. However, patients undergoing resection are often affected by surgical complications, early recurrences, and inability to receive the recommended adjuvant therapy. For these reasons, neoadjuvant therapy has emerged as an attractive option, and in the United States, there has been a significant trend towards neoadjuvant treatment for resectable and borderline-resectable pancreatic tumors. In this review, historical evidence leading to the emergence of neoadjuvant treatment and recent studies of neoadjuvant regimens are summarized. Finally, an overview of ongoing randomized clinical trials is presented.

Keywords: Pancreatic Cancer, Neoadjuvant Therapy, Chemotherapy, Chemoradiation
1. Introduction

Pancreatic cancer is the third leading cause of cancer death in the United States. The prevalence of this deadly disease is rising, and mortality estimates suggest it will surpass colon cancer to become the 2nd leading cause of cancer death by 2030. Approximately 80% of patients with pancreatic ductal adenocarcinoma (PDAC) present with metastatic disease at time of diagnosis, and even with modern chemotherapy regimens, median survival is limited to 8-11 months. Meanwhile, the remaining 20% of patients will have locoregional disease which is potentially amenable to resection, and can be classified according to National Comprehensive Cancer Network (NCCN) guidelines as being 1) resectable 2) borderline-resectable, or 3) locally advanced, unresectable. These staging criteria are based on the tumoral-vasculature relationship and determine the feasibility of complete tumor removal, with or without vascular reconstruction.

Chemotherapy remains the mainstay of treatment for patients with metastatic or locally advanced disease, while radiation therapy is sometimes utilized to prevent or alleviate symptoms in patients who are not candidates for a curative-intent resection. Treatment options for patients with resectable and borderline resectable disease ideally consists of multimodal therapy which should include some combination of surgery, chemotherapy, and radiation therapy; this multimodal approach can significantly impact long-term survival outcomes. With multimodal therapy, five-year survival for patients undergoing resection can be as high as 27%. However, the ideal combination and sequence of multimodal treatment delivery, i.e. surgery followed by adjuvant therapy versus neoadjuvant therapy followed by surgery, has remained a heated topic of debate in the oncologic and surgical communities.

Randomized trials comparing neoadjuvant versus adjuvant treatment strategies for patients with resectable or borderline resectable PDAC are lacking, and this has led to wide variation in practice patterns and opinions about the optimal timing of surgery. However, there has been a national trend towards increased utilization of neoadjuvant therapy for patients with resectable disease, and in fact the surgery-first approach in borderline resectable disease is no longer endorsed. This review summarizes the history of neoadjuvant therapy for pancreatic cancer, reviews major landmark studies pertaining to adjuvant and neoadjuvant therapy, and summarizes ongoing clinical trial that will provide future direction.

2. Neoadjuvant Treatment Considerations

Proponents of neoadjuvant therapy for pancreatic ductal adenocarcinoma argue many benefits for early delivery of systemic chemotherapy and/or locoregional chemoradiation therapy. Due to the aggressive nature of pancreatic ductal adenocarcinoma, even patients with resectable disease are believed to likely harbor radiographically occult metastatic disease (micrometastases). This is evidenced by patients undergoing curative-intent resection demonstrating very high rates of disease recurrence with an associated 5-year survival under 20%. Additionally, delaying surgery for 3-6 months allows time for restaging prior to surgery, at which time biologically aggressive disease may declare itself in the form of newly discovered metastases in liver, lung or other sites. For patients with initially resectable tumors, disease progression and/or metastases while receiving neoadjuvant therapy is believed to
occur in 15-20% of patients, with the remaining 80-85% proceeding to pancreatic resection.\textsuperscript{10,11} While there is no direct evidence that patients experiencing disease progression would not have benefited from early surgery, it is generally argued that selecting out the subset of patients who experience disease progression while on neoadjuvant treatment protocols can eliminate futile, major surgery. These patients can be spared the morbidity of major pancreatectomy that would have likely conferred little to no survival benefit, and additionally results in a more cost-effective treatment approach.\textsuperscript{12}

Margin status following resection is an important feature of high-quality surgical care. R0 resections are associated with improved survival, with some data demonstrating that an R1 resection is associated with similar outcomes when compared to patients treated with chemotherapy and radiation without surgery.\textsuperscript{8,13,14} For these reasons, achieving an R0 resection is the primary goal for surgeons, and efforts to increase the likelihood of R0 resection is of the utmost importance. Neoadjuvant therapy has been shown to increase the likelihood of achieving a margin-negative resection, especially for patients with borderline resectable disease, where >90% R0 resection rates can be observed when neoadjuvant therapy is delivered.\textsuperscript{8,13,15,16} Furthermore, for patients who initially present with locally-advanced unresectable tumors, up to 1 in 4 may be converted to resectable disease following neoadjuvant treatment, and of those resected, R0 resections can occur in >80%.\textsuperscript{15}

An added benefit of the neoadjuvant approach is the high rate of completion of multi-modality therapy. It is well described that approximately 30% of patients do not go on to receive chemotherapy after pancreatic resection, and thus a chemotherapy-first approach ensures patients get systemic therapy for what is likely a systemic disease.\textsuperscript{17,18} Additionally, surgical alteration of blood flow and oxygen delivery to the residual tumor bed may decrease the effectiveness of radiation and chemotherapy when delivered in the adjuvant setting.

For patients with resectable disease, the primary argument put forth by proponents of a surgery-first approach is that surgery offers the only chance for long-term survival and possible cure. Delaying a potentially curative treatment may risk disease progression, thus losing the window of opportunity in which surgical intervention is possible; some early studies found that up to 50% of patients never went on to pancreatic resection, despite initially presenting with resectable tumors.\textsuperscript{19,20} However, a 2010 meta-analysis by Gillen et al. showed 73.6% of patients with resectable disease were able to undergo resection after completing neoadjuvant treatment.\textsuperscript{21} Furthermore, without clear evidence of systemic disease, the toxic side effects of chemotherapy may lead to patient preference for choosing upfront surgery. Finally, when attempts to obtain a definitive tissue diagnosis fail, a surgery-first approach is appropriate in the setting of high clinical suspicion for pancreatic cancer.

3. History of Multi-modal Therapy

The emergence of neoadjuvant therapy for pancreatic cancer occurred out of both necessity and opportunity, tracing back to the emergence of adjuvant therapy. Indeed, many lessons learned from adjuvant studies have been extrapolated into the neoadjuvant setting, and only very recently have large randomized trials examining neoadjuvant therapy emerged. Potentially curative surgical resection has long been the standard treatment for localized pancreatic cancer.\textsuperscript{22} However, 85% of resected patients ultimately develop metastases or local recurrence within 9-15 months, with median
life expectancy of only 12-15 months. The necessity for better treatment spurred investigational studies beginning in the 1980’s into multi-modal therapy with adjuvant chemoradiotherapy and chemotherapy based on 5-fluorouracil (5-FU). A pivotal early study of adjuvant therapy was the Gastrointestinal Tumor Study Group (GITSG) trial, which demonstrated significantly improved median survival (20 months vs. 11 months) and improved 2-year survival (43% vs. 18%) in patients who received adjuvant chemoradiotherapy followed by maintenance 5-FU chemotherapy (compared to those randomized to surgery alone). Adjuvant therapy soon became universally recommended for patients with resected pancreatic cancer. A summary of randomized trials of adjuvant therapy trials provided in Table 1.

Table 1: Randomized Trials of Adjuvant Therapy for Resected Pancreatic Cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>Margin</th>
<th>n</th>
<th>Adjuvant Therapeutic Comparison</th>
<th>Survival (mo) Arm 1 vs 2</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG24,25</td>
<td>R0</td>
<td>49</td>
<td>Arm 1: CRT (5-FU, 40 Gy)</td>
<td>20 vs. 11 p=0.035</td>
<td>Study terminated prematurely.</td>
</tr>
<tr>
<td>1985, 1987</td>
<td></td>
<td></td>
<td>Arm 2: Observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bakkevold et al.26</td>
<td>R0</td>
<td>61</td>
<td>Arm 1: CT (AMF)</td>
<td>23 vs. 11 p=0.02</td>
<td>PC and Ampullary Ca.</td>
</tr>
<tr>
<td>1993</td>
<td>(47 PC)</td>
<td></td>
<td>Arm 2: Observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC27</td>
<td>R0+R1</td>
<td>218</td>
<td>Arm 1: CRT (5-FU, 40 Gy)</td>
<td>24.5 vs 19.0 p=0.208</td>
<td>Included Ampullary Ca. For PC only, survival 17 vs. 13 months (p=0.099)</td>
</tr>
<tr>
<td>1999</td>
<td>(114 PC)</td>
<td></td>
<td>Arm 2: Observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESPAC-128</td>
<td>R0+R1</td>
<td>289</td>
<td>Arm 1: CRT (5-FU, 20 Gy)</td>
<td>20.1 (Arm2/3) vs 15.5 (Arm 1/4) p=0.009</td>
<td>CRT conferred worse survival.</td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td></td>
<td>Arm 2: CT (5-FU)</td>
<td></td>
<td></td>
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<tr>
<td>Arm 3: CRT + CT</td>
<td></td>
<td></td>
<td>Arm 4: Observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm 2: Observation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONKO-00129,30</td>
<td>R0+R1</td>
<td>368</td>
<td>Arm 1: CT (Gemcitabine)</td>
<td>22.8 vs 20.2 p=0.01</td>
<td>Fewer local recurrence in CRT group (11% vs 24%)</td>
</tr>
<tr>
<td>2007, 2013</td>
<td></td>
<td></td>
<td>Arm 2: Observation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 97-04.31</td>
<td>R0+R1</td>
<td>451</td>
<td>Arm 1: CT (5-FU)+ CRT (5-FU, 50.4 Gy)</td>
<td>16.9 vs 20.5 p=0.09</td>
<td>Arm 2 showed survival benefit (p=0.05) on MVA.</td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td>Arm 2: CT (Gem) + CRT (5-FU, 50.4 Gy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Laethem et al.32</td>
<td>R0+R1</td>
<td>90</td>
<td>Arm 1: CT (Gem)</td>
<td>24.4 vs 24.3</td>
<td>Fewer local recurrence in CRT group (11% vs 24%)</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td></td>
<td>Arm 2: CT (Gem) + CRT (Gem, 50.4 Gy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt et al.33</td>
<td>R0+R1</td>
<td>132</td>
<td>Arm 1: CRT (5-FU, cisplatin, IFN, 50.4 Gy) + CT (5-FU)</td>
<td>26.5 vs 28.5 p=0.99</td>
<td>85% Grade 3/4 toxicity in Arm 1.</td>
</tr>
<tr>
<td>2012</td>
<td></td>
<td></td>
<td>Arm 2: CT (5-FU)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

At the same time, the notion of neoadjuvant therapy emerged as many patients who underwent curative resection failed to receive postoperative adjuvant therapy due to complications, delayed recovery or failure to return to an adequate baseline. Early trials of neoadjuvant therapy were largely carried out in patients with locally advanced pancreatic cancer (LAPC). In one of the first studies of neoadjuvant therapy for pancreatic cancer, Pilepich et al. demonstrated that radiation therapy was effective in converting six of seventeen patients from unresectable to resectable disease status. Later, Jessup et al. utilized a neoadjuvant regimen of 5-FU based chemoradiation in sixteen unresectable patients and ultimately found conversion to resectable disease in two. More promising results were seen in a study by Hoffman et al., where the authors reported that 11 of 34 patients with LAPC were able to undergo potentially curative resection after treatment with chemoradiotherapy. As the potential benefit of neoadjuvant therapy became apparent, further investigation of neoadjuvant and adjuvant regimens continued throughout 1990-2000, and mainly consisted of chemotherapy with 5-fluorouracil with or without concomitant chemoradiotherapy.

Multiple GITSG studies investigated the use of different combinations of chemotherapeutic agents such as 5-FU, doxorubicin, streptozocin and mitomycin-C without any significant differences in overall survival. Thus, 5-FU remained the backbone chemotherapeutic for all stages of pancreatic cancer for many years until the late 2000’s, and data supporting its use in the adjuvant setting were extended for use in select patients receiving neoadjuvant treatment. However, neoadjuvant therapy in this era commonly consisted of chemoradiation alone, without delivery of any systemic treatments.

To address the role of locoregional chemoradiation versus full-dose chemotherapy targeting systemic disease, The European Study Group for Pancreatic Cancer-1 trial (ESPAC-1) sought to evaluate adjuvant treatment strategies with 5-FU chemotherapy versus chemoradiation to 20-Gy in patients who completed curative-intent pancreatic resection. By using a 2x2 factorial design consisting of 4 arms, investigators found that the groups receiving chemotherapy alone or chemotherapy and chemoradiation had a significant survival benefit compared to the combined groups receiving chemoradiation alone and observation alone (5-year survival 21% vs 8%). Analysis of the two arms receiving chemoradiation showed 5-year survival of only 10%, compared to 20% in the two arms not receiving chemoradiation. The authors concluded that chemoradiation was harmful in the adjuvant setting and that chemotherapy alone was responsible for imparting a survival benefit, possibly because chemoradiation occurred soon after surgery, thereby causing a delay in the initiation of chemotherapy. Unfortunately, the trial was not powered to detect a survival difference between individual arms of the study, however, median survival was longest in those receiving chemotherapy alone at 21.6 months, and was shortest in the chemoradiation arm at 13.9 months.

The ESPAC-1 trial has received a significant amount of criticism around trial design, lack of standardized radiation regimens, and low-dose radiation treatment to only 20-Gy, instead of the traditional 50.4-Gy dosing. Due to these criticisms and skepticism surrounding the results, adjuvant chemoradiation is still used in the United States. A subsequent multi-institutional retrospective study has suggested a role for adjuvant radiation in a subset of patient who are lymph-node positive, while another large multi-center study has suggested use of chemotherapy...
alone, with no additional benefit derived from adding chemoradiation.\textsuperscript{49,50}

Gemcitabine-based therapy began to emerge after promising studies in the 1990’s demonstrated acceptable safety and improved efficacy compared to fluorouracil for patients with locally advanced disease.\textsuperscript{51} A decade later, the CONKO-001 trial demonstrated improved disease-free survival for patients who underwent curative-intent resection followed by adjuvant gemcitabine for 6 months compared to observation alone.\textsuperscript{29} The final report of the CONKO-001 trial in 2013 also showed prolonged overall 5-year survival of 20.7% in the gemcitabine arm compared to only 10.4% for those receiving surgery followed by observation.\textsuperscript{30} The use of gemcitabine in the adjuvant setting was further explored in the RTOG 97-04 phase III trial of 451 patients who were randomized to receive either 3 weeks of gemcitabine or 5-fluorouracil (5-FU) chemotherapy, followed by fluorouracil-based chemoradiation to 50.4 Gy, and finally 12 additional weeks of chemotherapy. Three-year survival was 31% in the gemcitabine arm compared to 22% for fluorouracil. Although not statistically significant for the primary endpoint, multivariable analysis correcting for pre-specified tumor factors showed a survival advantage for gemcitabine with \( p=0.05 \).\textsuperscript{31} Following CONKO-001 and RTOG 97-04, gemcitabine was established as the first-line chemotherapeutic in the adjuvant setting, and again, data from the adjuvant setting was often extrapolated to justify gemcitabine-based neoadjuvant chemotherapy treatment.\textsuperscript{52}

Two recent phase III trials in 2011 and 2013 examined new combination chemotherapy regimens in patients with metastatic disease. The PRODIGE Intergroup trial in Europe demonstrated that a regimen of FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) resulted in significantly prolonged median survival at 11.1 months compared to 6.8 months for those receiving gemcitabine alone.\textsuperscript{4} Two years later, an additional international multi-center trial demonstrated that the addition of albumin bound paclitaxel (nab-paclitaxel) to a gemcitabine regimen could prolong survival to 8.5 months, compared to 6.7 months for gemcitabine alone.\textsuperscript{3} The results from these trials in the metastatic setting have led to FOLFINIROX regimens being increasingly used for neoadjuvant therapy, and indeed, several randomized trials are underway to investigate this further for both resectable and borderline resectable patients.\textsuperscript{53}

### 4.1. Neoadjuvant Chemotherapy Regimens

Currently, no randomized trials have been completed to guide treatment in the neoadjuvant setting. For this reason, chemotherapy treatment decisions are largely extrapolated from adjuvant or metastatic treatment regimens, or from small non-randomized prospective phase II studies. Gemcitabine and fluoropyrimidine based regimens remain the mainstay of treatment options, and are often combined with taxanes or platinum-based agents. The most common fluoropyrimidines studied are 5-fluorouracil and capecitabine, the latter having the convenience of being available in oral form. A summary of prospective studies of neoadjuvant therapy are provided in Table 2.
### Table 2: Prospective Neoadjuvant Trials for Resectable and Borderline Resectable Pancreatic Cancer

<table>
<thead>
<tr>
<th>Authors</th>
<th>Resectability</th>
<th>Systemic Therapy</th>
<th>Radiation/Chemoradiation</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmer et al., 2007</td>
<td>RPC (n=50)</td>
<td>Arm A: Gem</td>
<td>n/a</td>
<td>-Terminated early by DMC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm B: Gem + Cis</td>
<td></td>
<td>-Arm A: 38% resected, 75% R0, 42% 1-yr OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Arm B: 70% resected, 75% R0, 62% 1-yr OS</td>
</tr>
<tr>
<td>Landry et al., 2010</td>
<td>BRPC (n=21)</td>
<td>Arm A: n/a</td>
<td>Arm B: Gem + Cis + 5-FU</td>
<td>-Terminated early due to low accrual.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Arm A: 30% resected, 66% R0, 19.4 mo median OS for all pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Arm B: 18% resected, 50% R0, 13.4 mo median OS for all pts</td>
</tr>
<tr>
<td>Golcher et al., 2015</td>
<td>RPC (n=66)</td>
<td>Arm A: primary surgery</td>
<td>Arm A: primary surgery</td>
<td>-Terminated early due to low accrual.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm B: n/a</td>
<td>Arm B: Gem-cis-XRT 50.4 Gy</td>
<td>-Arm A: 30% resected, 66% R0, 19.4 mo median OS for all pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Arm B: 18% resected, 50% R0, 13.4 mo median OS for all pts</td>
</tr>
<tr>
<td>Casadei et al., 2015</td>
<td>RPC (n=38)</td>
<td>Arm A: primary surgery</td>
<td>Arm A: primary surgery</td>
<td>-Terminated early due to low accrual.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm B: Gem</td>
<td>Arm B: Gem-XRT 45 Gy</td>
<td>-Arm A: 75% resected, 25% R0, 19.5 mo median OS for all pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Arm B: 61% resected, 39% R0, 22.4 mo median OS for all pts</td>
</tr>
<tr>
<td><strong>Non-randomized phase I and II Trials</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Talamonti et al., 2006</td>
<td>RPC (n=20)</td>
<td>Gem</td>
<td>XRT 36 Gy (concurrent)</td>
<td>-17 (85%) resected, 94% R0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-26 mo. median OS for resected pts.</td>
</tr>
<tr>
<td>Mornex et al., 2006</td>
<td>RPC (n=41)</td>
<td>5-FU + Cis</td>
<td>XRT 50 Gy (concurrent)</td>
<td>-63% resected, 80% R0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-11.7 mo median OS for resected pts</td>
</tr>
<tr>
<td>Heinrich et al., 2008</td>
<td>RPC (n=28)</td>
<td>Gem + Cis</td>
<td>n/a</td>
<td>-89% resected, 80% R0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-19.1 mo median OS for resected pts</td>
</tr>
<tr>
<td>Evans et al., 2008</td>
<td>RPC (n=86)</td>
<td>n/a</td>
<td>Gem-XRT 30 Gy</td>
<td>-74% resected, 89% R0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-22.7 mo median OS for all pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-34 mo median OS for resected pts</td>
</tr>
<tr>
<td>Varadhachary et al., 2008</td>
<td>RPC (n=90)</td>
<td>Gem + Cis</td>
<td>Gem-XRT 30 Gy</td>
<td>-58% resected, 96% R0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-17.4 mo median OS for all pts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-31 mo median OS for resected pts</td>
</tr>
<tr>
<td>Turrini et al., 2010</td>
<td>RPC (n=34)</td>
<td>n/a</td>
<td>Docetaxel-XRT 45 Gy</td>
<td>-50% resected, 100% R0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-32 mo median OS for resected pts</td>
</tr>
<tr>
<td>Sahora et al., 2011</td>
<td>BRPC (n=15)</td>
<td>Gem + Oxaliplatin</td>
<td>n/a</td>
<td>-47% resected for BRPC, 33% for LAPC, 69% overall R0</td>
</tr>
<tr>
<td></td>
<td>LAPC (n=18)</td>
<td></td>
<td></td>
<td>-22 mo median OS for resected pts</td>
</tr>
<tr>
<td>Sahora et al., 2011</td>
<td>BRPC (n=12)</td>
<td>Gem + Docetaxel</td>
<td>n/a</td>
<td>-33% resected for BRPC, 31% for LAPC, 87% overall R0</td>
</tr>
<tr>
<td></td>
<td>LAPC (n=13)</td>
<td></td>
<td></td>
<td>-16.3 mo median OS for resected pts</td>
</tr>
<tr>
<td>Lee et al., 2012</td>
<td>BRPC (n=18)</td>
<td>Gem + Capecitbine</td>
<td>n/a</td>
<td>-61% resected for BRPC, 24% for LAPC, 82% overall R0</td>
</tr>
<tr>
<td></td>
<td>LAPC (n=25)</td>
<td></td>
<td></td>
<td>-23.1 mo median OS for resected pts</td>
</tr>
<tr>
<td>Pipas et al., 2012</td>
<td>RPC (n=4)</td>
<td>n/a</td>
<td>Cetuximab-Gem-IMRT 54 Gy</td>
<td>-100% resected for RPC, 78% for BRPC, 50% for LAPC, 92% overall R0</td>
</tr>
<tr>
<td></td>
<td>BRPC (n=23)</td>
<td></td>
<td></td>
<td>-24.3 mo median OS for resected pts</td>
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<tr>
<td></td>
<td>LAPC (n=6)</td>
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</tbody>
</table>
Neoadjuvant gemcitabine monotherapy has been studied in several small phase I and II trials of patients with resectable disease, with acceptable toxicity profiles and high rates of patients proceeding to R0 resection. G77,57,78 Gemcitabine-based therapy has remained common since CONKO-001 and RTOG 97-04 results showed benefit in the adjuvant setting, though certainly it is an evolving paradigm.30,31 Prior to more recent efficacy data highlighted above, combination gemcitabine regimens with the addition of cisplatin have been studied. Palmer et al. examined a cohort of 50 patients with resectable disease who were randomized to receive gemcitabine or gemcitabine plus cisplatin.59 Those receiving combination neoadjuvant chemotherapy had a higher rate of proceeding to pancreatic resection (70% vs. 38% for gemcitabine alone), and there were no observed increases in surgical complications, with high rates of R0 resections (75%) in both arms. Combination gemcitabine and cisplatin for patients with resectable disease was further studied by Heinrich and colleagues, with 26 of 28 patients proceeding to pancreatectomy, 80% undergoing R0 resections, and a demonstrated median overall survival of 19.1 months.59 Partial pathologic response was observed in 53% of patients. Varadhachary et al. reported the MD Anderson experience with neoadjuvant gemcitabine and cisplatin chemotherapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Group</th>
<th>Treatment</th>
<th>Radiation Therapy</th>
<th>OS/Resect. Rate</th>
<th>RFS/Resect. Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al., 2013</td>
<td>RPC (n=23), BRPC (n=39), LAPC (n=6)</td>
<td>Gem + Oxaliplatin</td>
<td>XRT 30 Gy (concurrent w/ chemo)</td>
<td>-57% resected for RPC, 72% for BRPC, 33% LAPC, 84% overall R0</td>
<td>-21.1 mo median OS for resected pts</td>
</tr>
<tr>
<td>Shinoto et al., 2013</td>
<td>RPC (n=26)</td>
<td>n/a</td>
<td>Carbon-ion radiotherapy 36 Gy (short course)</td>
<td>-81% resected, 90% R0</td>
<td>-18.6 mo median OS for all pts</td>
</tr>
<tr>
<td>Tinchon et al., 2013</td>
<td>BRPC (n=10), MPC (n=2)</td>
<td>FOLFIRINOX</td>
<td>n/a</td>
<td>-83% resected for all pts.</td>
<td></td>
</tr>
<tr>
<td>Motoi et al., 2013</td>
<td>RPC (n=19), BRPC (n=16)</td>
<td>Gemcitabine + S-1</td>
<td>n/a</td>
<td>-86% resected overall, 87% overall R0</td>
<td>-19.7 mo median OS for all pts</td>
</tr>
<tr>
<td>Wo et al., 2014</td>
<td>RPC (n=10)</td>
<td>n/a</td>
<td>Capecitabine-XRT or IMRT to 55 Gy (short course)</td>
<td>Closed-early due to increased intra-operative complications.</td>
<td></td>
</tr>
<tr>
<td>Sahora et al., 2014</td>
<td>BRPC (n=11), LAPC (n=19)</td>
<td>Gem + Bevacizumab</td>
<td>n/a</td>
<td>-37% resected overall</td>
<td>-13 mo median OS for all pts</td>
</tr>
<tr>
<td>O’Reilly et al., 2014</td>
<td>RPC (n=38)</td>
<td>Gem + Oxaliplatin</td>
<td>n/a</td>
<td>-71% resected, 74% R0</td>
<td>-27.2 mo median OS for all pts</td>
</tr>
<tr>
<td>Hong et al., 2014</td>
<td>RPC (n=50)</td>
<td>n/a</td>
<td>Capecitabine-Proton RT (short-course)</td>
<td>-77% resected, 84% R0</td>
<td>-17.3 mo median OS for all pts</td>
</tr>
<tr>
<td>Chan et al., 2016</td>
<td>RPC (n=1), BRPC (n=12), LAPC (n=8)</td>
<td>n/a</td>
<td>Vorinostat-Capecitabine-XRT 30 Gy</td>
<td>-33% BRPC resected, 75% RO</td>
<td>-13 mo median OS for all pts</td>
</tr>
<tr>
<td>Masui et al., 2016</td>
<td>BRPC (n=18)</td>
<td>Gem + S-1</td>
<td>n/a</td>
<td>-83% resected, 80% R0</td>
<td>-21.7 mo median OS for all pts</td>
</tr>
<tr>
<td>Okada et al., 2017</td>
<td>BRPC (n=10)</td>
<td>Gem + Nab-Paclitaxel</td>
<td>n/a</td>
<td>-80% resected, 70% R0</td>
<td></td>
</tr>
<tr>
<td>Nagakawa et al., 2017</td>
<td>BRPC (n=27)</td>
<td>Gem + S-1</td>
<td>IMRT 50.4 Gy (concurrent)</td>
<td>-70% resected, 95% R0</td>
<td>-22.4 mo median OS for all pts</td>
</tr>
</tbody>
</table>

combined with radiation, and 62 of 90 (69%) patients proceeded to surgery, with 52 undergoing resection. Median survival was 31 months for the group completing multi-modality therapy, compared to 10.5 months for those not proceeding to surgery. Similar results were seen when utilizing gemcitabine-based chemoradiation without chemotherapy, with median survival of 34 months in resected patients.

A variety of other agents including bevacizumab, oxaliplatin, and docetaxel have been added to gemcitabine regimens in phase I/II studies of patients with non-metastatic pancreatic cancer. The exact role of these drugs and additional benefit gained in patients with resectable and borderline resectable disease has yet to be fully delineated. Nab-Paclitaxel is another chemotherapeutic of interest in the neoadjuvant setting. Pancreatic ductal adenocarcinomas are known to induce an intense desmoplastic response characterized by dense fibrous tissue surrounding the tumor, which is believed to impede the delivery of chemotherapy to cancer cells. Nab-paclitaxel, in particular, has been shown to disrupt the collagen architecture, which may increase efficacy of concurrent chemotherapy. Safety and feasibility have been examined with neoadjuvant nab-paclitaxel plus gemcitabine in patients with resectable and borderline resectable tumors, thus paving the way for future randomized studies to fully evaluate efficacy of this regimen.

Based on trials in patients with stage IV disease, a modified FOLFIRINOX regimen has become a popular treatment choice over gemcitabine for patients receiving neoadjuvant therapy, especially those with borderline resectable disease or locally advanced disease. A 2015 meta-analysis examined thirteen studies encompassing 253 patients with BRPC or LAPC who received FOLFIRINOX with or without radiation. 43% of patients underwent resection following FOLRININOX treatment and restaging, and the R0 resection rate was 85%. One year later, a retrospective study by Hackert et al. reported a significantly higher resection rate of 60% in a cohort with LAPC treated with FOLFIRINOX, compared to 46% resection rate after gemcitabine, and 52% following other treatment regimens. However, this higher resection rate did not correlate to any significant differences in median overall survival between the three groups (16.0 vs. 16.5 vs. 14.5 months, respectively). Kim et al. reported data on 22 patients undergoing FOLFIRINOX alone without radiation therapy and showed promising results with 91% R0 resection rate and disease-free survival of 22.6 months, calling into question the need for neoadjuvant radiotherapy when FOLFIRINOX is used. The apparent efficacy of FOLFIRINOX for LAPC and BRPC is encouraging, and its role in neoadjuvant therapy will likely continue to expand.

### 4.2. Neoadjuvant Radiation Therapy Regimens

Radiotherapy (RT) alone is rarely used for treatment of pancreatic cancer given high rates of failure and local progression in up to 80% of cases. RT has been supplanted by chemoradiotherapy (CRT), which most often refers to the practice of using small radiosensitizing doses of chemotherapy before or during radiation beam delivery. Compared to radiation therapy alone, CRT has demonstrated superior survival and lower toxicity for a variety of malignancies, including pancreatic, esophageal, breast, and head and neck cancer. The combined experience with CRT in pancreatic and other cancers has led to CRT becoming the most common method for delivery of external beam radiation in patients with pancreatic exocrine tumors in the United States. Several reports in the literature also use the term chemoradiotherapy to refer to RT that is
delivered concurrently with full-dose chemotherapy. For example, studies have reported using gemcitabine-based chemoradiotherapy with gemcitabine doses anywhere from 50 mg/m² to 1000 mg/m². While chemoradiotherapy is traditionally conceived as a method to achieve local tumor control, studies utilizing high dose chemotherapy are also contributing to systemic disease treatment. This wide dosing range of chemotherapy used for chemoradiation regimens likely contributes to variable responses and survival outcomes between studies, and thus comparisons should be made cautiously.

The majority of patients with pancreatic cancer will die from metastatic disease, however, approximately 30% of patients die from progression of the primary tumor, thus highlighting the importance of adequate locoregional therapy in the form of CRT and/or surgery. Furthermore, radiation may improve margin-negative resection rates with the belief that this will translate into improved long-term outcomes.

Modern radiation therapy (RT) for pancreatic cancer consists of a variety of techniques designed to deliver concentrated radiation to the tumor bed and avoid normal tissue and the associated toxicities, most commonly in the form of acute gastrointestinal symptoms related to radiation effects on the stomach, small bowel, and colon. Common modalities include 3-dimensional conformal radiation therapy (3DCRT), stereotactic body radiotherapy (SBRT), and intensity-modulated radiation therapy (IMRT). 3DCRT techniques represented one of the earliest advancements beyond crude 2-dimensional radiation delivery, and this technique was utilized in the seminal RTOG 97-04 trial of adjuvant therapy. IMRT has even greater ability to limit effect on nearby tissues, notably small bowel and stomach, and can still deliver significant doses to the entire tumor volume, including the periphery. Yovino et al. examined IMRT in 71 patients undergoing resection followed by adjuvant CRT, and found very low frequency of acute GI toxicity compared to historical toxicities in major clinical trials.

The role of SBRT expanded due to ability to deliver the cumulative radiation dose in fewer fractions. SBRT is an attractive choice in the neoadjuvant setting with less interruption of systemic therapy and a shorter treatment courses. This allows for restaging and surgical resection on an earlier schedule. This same rationale applies to the adjuvant setting, where the role of long courses of radiation is called into question given the development of more effective chemotherapy regimens such as FOLFIRINOX and gemcitabine plus nab-paclitaxel. Additionally, by using higher doses in fewer fractions, SBRT may exert a greater biologic effect. To date, SBRT has mainly been used for locally advanced disease, where results are encouraging. Further study will elucidate its possible role for RPC and BRPC patients.

Proton therapy (PT) is a modality which offers several unique properties that can potentially increase energy delivered to the tumor tissue, with minimal effects beyond this target. Indeed, PT has been studied in phase I and II trials as a neoadjuvant therapy in resectable patients. Hong et al. found that after neoadjuvant PT and capecitabine, 77% of patients proceed to resection and median survival was 27 months for this subset undergoing surgery. Local recurrence was observed in only 17% of cases. PT has been further investigated by showing minimal levels of low-grade toxicities and no high-grade toxicities.

The roles of CRT and chemotherapy in locally advanced pancreatic cancer have been an active area of investigation in recent years. Initial evidence from randomized
trials suggested that chemotherapy with gemcitabine alone was superior to chemotherapy + 5-FU/cisplatin-based chemoradiation using conformal techniques. A subsequent ECOG trial using similar radiation dosing with 3DCRT demonstrated a benefit of adding CRT to chemotherapy for patients with LAPC. The ECOG trial compared gemcitabine chemotherapy alone to gemcitabine-based chemoradiotherapy and systemic gemcitabine treatment. Results showed improved survival of 11.1 months for those receiving dual therapy, compared to 9.2 months for gemcitabine alone (p=0.017).

The SCALOP trial was recently published which examined CRT regimens in patients with locally advanced tumors. After receiving chemotherapy with both gemcitabine and capecitabine, 74 patients were randomized to gemcitabine-based or capecitabine-based chemoradiation to a radiation dose of 50.4 Gy. Those receiving capecitabine had marginally better progression-free and overall survival, however the results were not statistically significant due to small sample sizes. However, there were fewer toxicities in patients receiving capecitabine, and these results suggest a capecitabine-based regimen may be superior to gemcitabine for patients undergoing CRT.

Capecitabine-based CRT was evaluated in the LAP07 trial in which patients with LAPC underwent 4 months of chemotherapy and those without disease progression were then randomized to continue chemotherapy, or switch to CRT to 54 Gy. Results showed no difference in median overall survival between the chemotherapy (16.5 months) and CRT (15.2 months) groups. Although CRT did result in a significantly decreased rate of local progression, there were no differences in proportion of patients undergoing surgery between the treatment arms (6% after chemotherapy, 3% after chemoradiotherapy). This trial calls into question the utility of 3DCRT for LAPC, and highlights the need for more effective systemic and locoregional treatments.

5. Future Directions

Historically, multi-center trials addressing neoadjuvant therapies have been challenging, with many terminating early due to poor accrual. However, there are numerous ongoing randomized trials that seek to address many of the most pressing issues pertaining to the neoadjuvant approach. Additionally, preliminary data from a multi-institutional feasibility study show that patient accrual was better than expected, and will hopefully overcome this major barrier that hampered earlier studies.

These ongoing studies will address issues such as 1) optimal timing of surgery, i.e. neoadjuvant therapy versus upfront surgery for both resectable and borderline resectable pancreatic cancer, 2) the optimal chemotherapy regimen in the neoadjuvant setting (e.g. FOLFIRINOX versus gemcitabine/nab-paclitaxel), 3) added benefit of chemoradiation versus chemotherapy alone for borderline resectable disease, 4) and potential benefit of various immunotherapy regimens and cancer vaccines. Current randomized phase II or phase III clinical trials pertaining to neoadjuvant therapy for pancreatic cancer are summarized in Table 3. The results from these multi-institutional and international studies are highly anticipated, and will shape the future direction of neoadjuvant therapy for pancreatic cancer. While surgery will remain a mainstay of treatment for patients with potentially curative disease, long-term survival will not improve until we are able to address the systemic nature of the disease through improved multi-modal care delivery.
Table 3: Ongoing Randomized Phase II/III Trials of Neoadjuvant Therapy for Pancreatic Cancer

<table>
<thead>
<tr>
<th>Study ID/Title</th>
<th>Cancer Stage</th>
<th>Neoadjuvant Regimen Comparison</th>
<th>Study Location</th>
</tr>
</thead>
</table>
| NCT02839343 (Alliance Trial A021501) | BRPC | Arm1: mFOLFIRINOX  
Arm2: mFOLFIRINOX + XRT | USA |
| NCT02562716 (SWOG Trial 1505) | RPC | Arm1: mFOLFIRINOX  
Arm2: Gemcitabine/nab-paclitaxel | USA |
| NCT00727441 | RPC | Arm1: GVAX  
Arm2: GVAX/ Intravenous cyclophosphamide  
Arm3: GVAX/oral cyclophosphamide | USA |
| NCT00313560 | RPC | Arm1: Erlotinib  
Arm2: Placebo | USA |
| NCT02241551 | BRPC | Arm1: mFOLFIRINOX + SBRT  
Arm2: Gemcitabine/nab-paclitaxel + SBRT | USA |
| NCT01458717 (NEOPAC) | BRPC | Arm1: CRT w/ gemcitabine  
Arm2: Upfront Surgery | Korea |
| NCT01521702 (NorPACT-1) | RPC | Arm1: Gemcitabine/oxaliplatin  
Arm2: Upfront Surgery | Norway |
| NCT02676349 (PANDAS-PRODIGE 44) | BRPC | Arm1: mFOLFIRINOX + CRT  
Arm2: mFOLFIRINOX | France |
| NCT01900327 (NEOPA) | RPC | Arm1: CRT w/ gemcitabine  
Arm2: Upfront Surgery | Germany |
| NCT02717091 | BRPC | Arm1: mFOLFIRINOX  
Arm2: Gemcitabine/nab-paclitaxel | Japan |
| NCT02305186 (UVA-PC-PD101) | BRPC | Arm1: CRT w/ capecitabine + pemrolizumab  
Arm2: CRT w/ capecitabine | USA |
| NCT02047513 (NEONAX) | RPC | Arm1: Upfront surgery + adjuvant gemcitabine/nab-paclitaxel  
Arm2: Neoadjuvant gemcitabine/nab-paclitaxel | Germany |
| NCT02125136 (NEOLAP) | LAPC | Arm1: mFOLFIRINOX  
Arm2: Gemcitabine/nab-paclitaxel | Germany |
| NCT02172976 | RPC | Arm1: FOLLIRINOX  
Arm2: Upfront Surgery | Germany |
| NCT02439593 | LAPC | Arm1: CRT  
Arm2: Thermo-CRT | Switzerland |
| NCT01150630 | RPC | Arm1: Adjuvant PEXG  
Arm2: Neoadjuvant and adjuvant PEXG  
Arm3: Upfront surgery + Adjuvant gemcitabine | Italy |
| NCT02959879 (PANACHE01) | RPC | Arm1: FOLFOX  
Arm2: FOLFIRINOX  
Arm3: Upfront Surgery | France |
| NCT02446093 (PaTK02) | BRPC + LAPC | Arm1: GMCI + mFOLFIRINOX + CRT  
Arm2: mFOLFIRINOX + CRT | USA |
| NCT02336672 | BRPC + LAPC | Arm1: Chemotherapy, unspecified regimen  
Arm2: Chemotherapy + EUS-guided cryothermal ablation | Italy |
<table>
<thead>
<tr>
<th>NCT01836432</th>
<th>BRPC + LAPC</th>
<th>Arm1: FOLFIRINOX + Algenpantucel-L + CRT</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Arm2: FOLFIRINOX + CRT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm3: Gemcitabine/nab-paclitaxel + Algenpantucel-L + CRT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm4: Gemcitabine/nab-paclitaxel + CRT</td>
<td></td>
</tr>
</tbody>
</table>

6. References


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