Review Article

Neoadjuvant therapy in pancreatic cancer

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ABSTRACT

The overall survival for carcinoma pancreas is still around 5%. Surgical resection alone is associated with a low survival and high recurrence rates. Neoadjuvant therapy for carcinoma pancreas is aimed at improving survival and resectability by downsizing borderline resectable and unresectable tumors. However its role in the resectable group of patients is still not clear. This review discussed the current available evidence for use of neoadjuvant therapy in pancreatic adenocarcinoma.

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1. Introduction

Carcinoma pancreas is the 8th most leading cause of cancer related mortality across the globe, despite its low incidence.1 According to the National American cancer database of more than a lakh patients, the survival rate for patients without any cancer directed treatment was 5%.2 Comparatively, surgical resection alone yields better although still low 5-year survival figures; between 10 and 18% and up to 24% in some studies.3,4 In two large series published in the late 1990s, only 17% of all patients were able to undergo resection amongst more than 2000 patients with a low 5-year survival of 10.2% in each.4,5 Moreover, there is evidence for a high recurrence rate and decreased survival after recurrence following surgical resection alone. In a recent study, postoperative recurrences including loco-regional and distant occurred in 91% of patients and decreased the median survival to 10.4 and 5 months respectively.6 This forms the basis for inclusion of neoadjuvant therapy in the management of carcinoma pancreas.

2. Surgical resection for carcinoma pancreas

Better survival following surgery for carcinoma pancreas depends on resection margin status, lymph nodes and vascular involvement. Surgical resection alone is limited by these factors.

The retroperitoneal soft tissue margin is the most important prognostic factor for survival. There is a significant survival advantage for R0 (microscopically negative) resection. In a recent study from Mayo College, the median survival of 19 months for R0 resection was significantly higher when compared with 15 and 10 months for R1 (microscopically positive) and R2 (macroscopically positive) resections, respectively.7 Thus surgical resection for carcinoma pancreas should be aimed at performing an R0 resection.
Lymph node negative resections and especially those with a higher total and negative lymph node yield and a low lymph node ratio are compatible with a prolonged survival. Extended retroperitoneal lymphadenectomy has not been shown to add to the survival advantage of a standard dissection inspite of its feasibility. On the contrary, some studies have shown that microscopic venous invasion portends a poor prognosis.

Approximately 15–30% of patients with non-metastatic carcinoma pancreas are unresectable due to arterial involvement. The role of arterial resections during PD is still debatable. Superior mesenteric-portal vein resections have been performed with a long-term survival equaling that of standard resections. On the contrary, some studies have shown that microscopic venous invasion portends a poor prognosis.

The effect of venous involvement on long-term survival after pancreatecto-duodenectomy (PD) is still debatable. Superior mesenteric-portal vein resections have been performed with a long-term survival equaling that of standard resections. On the contrary, some studies have shown that microscopic venous invasion portends a poor prognosis.

The potential disadvantages include:

1. There is a risk of tumor progression during preoperative chemoradiation ranging from 34% to 50%.
2. The use of biliary stents prior to starting chemoradiation has been associated with increased rates of complications.
3. Neoadjuvant therapy has been associated with severe acute toxicity especially nausea and vomiting and may delay or avoid potentially curative surgery.

4. Neoadjuvant therapy for resectable pancreatic cancer

Various chemotherapeutic agents like 5 Fluorouracil (FU), mitomycin C (MMC), taxanes, gemcitabine (gem) have been used alone or in combination with either a standard or a rapid fractionation radiotherapy schedule.

In the studies from early 1990s, FU along with standard 50.4 Gy of radiation was used and this was followed by surgical resection after 4–5 weeks of completion of the regimen. Evans et al used this regimen in 28 patients with localized pancreatic adenocarcinoma and were able to explore 23 and resect 17 (60%) patients.

Another regimen, which was used in the earlier studies is the combination of continuous infusion (CI) FU and MMC. In a phase II study, 31 patients (26 PDAC) were subjected to CI FU MMC and 50.4 Gy of RT. Though the resectability rate was 38%, none of the patients had a margin positive resection and only 1 had a lymph node positive disease. The median survival of resected group was not reached at 29 months, while it was 8 months for the unresectable group. In a pilot study, CI FU, MMF based chemoradiation was used in 34 patients. Eventually, 25 (74%) patients were explored and of these 11 (32%) patients had a potentially curative surgical resection. The median overall (OS) and the disease free survival (DFS) of the resected patients were 45 and 27 months respectively, with a 5-year survival of 40%. The Eastern Cooperative Oncology Group also used a similar regimen in 53 patients. Of the 41 patients subjected to exploration, 24 (45%) were resected. The median survival of the resected vs. the entire group was 15.7 vs. 9.7 months. The low survival in the resected group in this study was due to the inclusion of advanced tumors.

Although resectability rates in the studies using FU MMC chemoradiotherapy regimen were low, but the survival rates for the resected patients were impressive.

The role of rapid fractionation chemoradiation in localized PDAC has been investigated in three studies from MD Anderson cancer center. In the first study, patients with a localized PDAC were subjected to CI FU and a rapid fractionation radiation of 30 Gy, 3 Gy/d × 5 days/week × 2 week schedule. Of the 35 patients, all were able to complete the chemoradiation with 9% incidence of grade 3 nausea and vomiting. The overall resectability rate was 57%. The resected patients were also subjected to 10–15 Gy of electron beam intraoperative radiation (EB-IORT). The 3 year survival in patients who underwent this combined modality therapy was 23%. Another study from this center using Paclitaxel infusion instead of CI FU followed by EB-IORT showed a...
higher toxicity, lower pathological response rates, similar resectability rate with a higher 3-year survival of 38%. In the third study, a total of 132 patients were either subjected to standard or a rapid fractionation chemoradiation utilizing either FU, paclitaxel or gemcitabine. The overall median survival was 21 months, and 31% DFS at last follow-up. There was no difference in survival duration between patients who received rapid-fractionation vs. standard-fractionation chemoradiotherapy. Gemcitabine based chemoradiation has been shown to be less toxic, offer high resectability rate (74–85%) with a high rate of margin (94%) and lymph node (65%) positivity. It has been shown to offer a DFS of 41% at 18 months and a better 5-year survival rate in the resected group (36% vs. 0%). A phase II randomized controlled trial (RCT) comparing cisplatin and gemcitabine to gemcitabine alone showed that combination regimen is as safe and associated with higher resectability (70% vs. 38%) and survival rate (62% vs 42% 1 year survival). Another study has shown high resectability and R0 resection rates, favourable overall and disease-free survival along with an improvement in the quality of life, nutritional status in patients receiving combination chemotherapy. Studies have also assessed the pathological response rates and prognostic factors following chemoradiation. In a French study, a major pathological response to chemoradiation in localized PDAC was seen in 9 out of 40 (22.5%) patients who underwent surgical resection and survival in these patients was significantly better than those with no or minor pathological response. It was also shown that tumor necrosis, positive lymph nodes, a large residual tumor load and poor tumor differentiation were independent negative prognostic factors affecting survival after neoadjuvant CRT. There have been only a few studies, which have compared preoperative and postoperative neoadjuvant therapy in localized PDAC. In a study from Fox Chase cancer center, 25/70 patients underwent pancreaticoduodenectomy after preoperative chemoradiation whereas 23 patients underwent upfront surgery. The mean delay in starting adjuvant therapy was of 45 days and 22% of patients could not undergo adjuvant therapy. Though there was no difference in treatment related toxicity, operative duration, length of hospital stay, post-op morbidity, mortality and survival, patients subjected to chemoradiation had lower rates of positive margin and lymph nodes. A phase III randomized trial (NEOPAC) comparing neoadjuvant gemcitabine (gem) and oxaliplatin vs. adjuvant gem is underway and its results are awaited. A recent meta-analyses of 111 studies divided pancreatic cancers into 3 groups. Group 1 comprised of resectable patients who were either treated with adjuvant therapy after resection or underwent neoadjuvant therapy prior to resection. Group 2 comprised of locally advanced or unresectable tumors who were downstaged and resected. Group 3 included undefined patients. Resection in group 1 and 2 was possible in 73.6 and 33.2% of patients respectively (Table 1). The authors concluded that neoadjuvant chemotherapy did not provide any survival benefit over those operated upfront in the resectable group whereas it enabled one third of patients with locally advanced pancreatic cancers to enjoy survival similar to group 1. Another recent meta-analysis has studied the role of neoadjuvant therapy in the resectable group. This study included 20 studies and 707 patients with localized pancreatic cancer (366 resectable) treated with preoperative gemcitabine. The authors recommended neoadjuvant therapy in the resectable group as surgery carries a high morbidity and mortality and patients who progress during the neoadjuvant therapy can be spared an unnecessary surgery.

### 5. Neoadjuvant therapy for borderline resectable pancreatic cancer

Conventionally, PDAC involving of superior mesenteric or hepatic artery or celiac axis are unresectable and are classified as T4 (stage III) tumors according to AJCC 2010. Subsets of these locally advanced PDAC have been classified as borderline resectable. This standardization of definition can help better understand the results of neoadjuvant therapy in this more favourable group of patients amongst the locally advanced tumors. The National Comprehensive Cancer Network (NCCN) 2013 defines the following tumor as borderline resectable:

1. Venous involvement of superior mesenteric vein (SMV) or portal vein (PV) demonstrating tumor abutment with impingement and narrowing of the lumen, encasement of SMV/PV without encasement of nearby arteries or a short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement.
2. Gastroduodenal artery encasement up to hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
3. Tumor abutment of the superior mesenteric artery (SMA) ≤180° of its circumference.

Most studies which include patients with locally advanced unresectable PDAC have subjectively defined unresectability and not tried to distinguish the unresectable from the borderline resectable. However, a few studies have reported the role of neoadjuvant treatment in this group of patients. One such study included 67 patients; 18 of these were borderline resectable to start with according to NCCN guidelines. All patients underwent gem based chemoradiation with or without cisplatin. The resectability rate was higher in the borderline resectable (33%) vs. unresectable group (6%). In another study from Massucco et al, 28 patients were stratified as borderline resectable and unresectable based on the pattern of vascular involvement on pretreatment CT scan. All these patients underwent gem based chemoradiation. Resection was possible in only 1/10 (10%)
Recent studies for neoadjuvant therapy in borderline resectable pancreatic cancer. In a multicenter phase II trial, 39 patients stratified as resectable, borderline resectable and unresectable were treated with gem based chemoradiation. The resectability rates in the 3 groups were 81%, 33%, and 7% and the 1 year survival rates were 94%, 76% and 47% respectively. These studies show that approximately 1/3 of the borderline resectable patients could undergo resection after chemoradiation. There is also scant data regarding survival benefit in this group. Table 2 summarizes various recent studies employing neoadjuvant therapy for borderline resectable tumors.

6. Neoadjuvant therapy for unresectable pancreatic cancer

Neoadjuvant therapy for unresectable PDAC has been investigated using several agents. In a study from early 1990s, CI FU and 50.4 Gy radiation was given to 16 patients with unresectable PDAC. Only 2 (13%) underwent resection with a median disease free survival of 20 and 22.5 months. In another study from late 1990s, 25 patients with locally advanced pancreatic cancer underwent chemoradiation involving FU with or without MMC or cisplatin or both. Only 5 (20%) patients underwent resection but only one with negative margin and nodes. In an Italian study, 5 of 32 unresectable PDAC were resected after oral doxifluridine and 50 Gy of radiation and 3 of these had a prolonged DFS longest being 65 months. In a study from Mt. Sinai Medical center, 68 patients with unresectable PDAC underwent FU, streptozocin and cisplatin based chemoradiation while 91 underwent upfront resection with or without adjuvant chemoradiation. Twenty (29%) patients in the former group underwent resection and 63 in the latter group underwent adjuvant treatment. The median survival in the former group was 23.6 vs. 14 months. In spite of the advanced stage, the median survival was significantly better in patients undergoing preoperative chemoradiation. Ammori et al used gem based chemoradiation for 67 patients with unresectable PDAC. Only 9 (13%) were resected with a significantly prolonged median survival of 18 months vs. 12 months for the unresectable group. In a retrospective comparison of the FU and gem based chemoradiation, the latter was associated with a significantly higher severe acute toxicity and thus a narrower therapeutic index. Two studies have highlighted the toxicity of gem based chemoradiation in combination with other agents. One of the studies was prematurely closed due to gem and FU based chemoradiation induced high toxicity. The other chemoradiation regimen in which gem was used in a dose of >300 mg/m² with cisplatin also demonstrated a high toxicity. The other chemotherapeutic agent, which has been investigated is paclitaxel, which had a resectability rate of <10% and 1 year survival of 30% in a phase II trial. These studies indicate a low resectability rate of locally advanced PDAC with the use of chemoradiation. However, patients in whom resection is possible have a better survival than the unresected group.

7. Targeted therapy

The two main agents tested as targeted agents in PDAC are bevacizumab and erlotinib. Bevacizumab is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody. VEGF has been shown to play an important role in growth and angiogenesis of pancreatic tumor cells in preclinical models.

The main reports for the use of bevacizumab are in metastatic setting along with gemcitabine. Though it has been shown to offer response rates of 21% in this setting, its addition to gemcitabine did not improve survival for advanced PDAC in a randomized phase III trial. The role of bevacizumab in the neoadjuvant setting was studied for unresectable tumors in a phase I trial. The addition of bevacizumab to capetabine, and radiation did not add to the toxicity but lead to an increased incidence of bleeding in cases with duodenal involvement. A partial response was seen in 20% and only 9% were resected. Erlotinib is a reversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. PDAC is known to express EGFR, which leads to activation of downstream signaling molecules leading to carcinogenesis. A phase III RCT showed a significant improvement in OS and DFS in the gem and erlotinib arm when compared to gem alone in patients with advanced pancreatic cancer.

A phase II study, American College of Surgeons Oncology Group (ACOSOG) Z 5041 trial is presently studying the role of neoadjuvant erlotinib and gemcitabine in operable PDAC.

8. Conclusion

Data is emerging that chemotherapy alone may be better than chemoradiotherapy for neoadjuvant therapy of patients with pancreatic adenocarcinoma. It may select out patients who may benefit from radiotherapy and surgery, which need more resource utilization for our country.

Table 2 Recent studies for neoadjuvant therapy in borderline resectable pancreatic cancer.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Regimen</th>
<th>Resectability (%)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hosein et al, 2012</td>
<td>18</td>
<td>FOLFORINOX</td>
<td>39</td>
<td>1 year OS 100%</td>
</tr>
<tr>
<td>Landry et al, 2010</td>
<td>21</td>
<td>Gem + RT</td>
<td>23</td>
<td>1 year PFS 83%</td>
</tr>
<tr>
<td>Lee et al, 2012</td>
<td>43</td>
<td>Gem-Cap (3→6)</td>
<td>39.5</td>
<td>Median OS: 23 months</td>
</tr>
<tr>
<td>Leone et al, 2012</td>
<td>39</td>
<td>Gem-Ox → Gem + RT</td>
<td>28</td>
<td>Median OS: 31 months</td>
</tr>
<tr>
<td>Arvold et al, 2012</td>
<td>70</td>
<td>Gem based (30)</td>
<td>38</td>
<td>Median OS: 19.4 months;</td>
</tr>
<tr>
<td>Andriulli et al, 2012</td>
<td>341</td>
<td>SFU/Cap + RT (40)</td>
<td>39</td>
<td>median PFS: 14.7 months</td>
</tr>
</tbody>
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Conflicts of interest

All authors have none to declare.

REFERENCES


