Treatment of locoregional disease: adjuvant versus neoadjuvant

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The efficacy of adjuvant therapy after the resection of pancreatic adenocarcinoma has been demonstrated by several randomized studies. Postoperative treatment applied either as chemotherapy alone or in combination with chemoradiotherapy is therefore considered a recommended standard in resectable pancreatic cancer (PC). Multiple arguments speak in favor of preoperative systemic therapy. Specifically, the conception of PC as a metastatic disease even at the early stage of apparent resectability supports the strategy of upfront systemic therapy. Unfortunately, randomized studies comparing neoadjuvant with adjuvant regimens have not been performed, and the superiority of one strategy over the other still has to be confirmed. Future clinical research may even combine neoadjuvant and adjuvant treatment. New avenues of individualized treatment may also be reached by the inclusion of molecular parameters of the tumor and pharmacogenomic profiles of the patient into decision making.

Key words: adjuvant therapy, chemoradiation, chemotherapy, neoadjuvant therapy, pancreatic cancer

introduction

The question of adjuvant versus neoadjuvant therapy can only be asked with regard to primarily resectable pancreatic cancer (PC). This question excludes borderline resectable PC. Because of a markedly elevated risk of margin-positive resection, these patients should preferably receive neoadjuvant therapy to render tumors resectable. This question also excludes patients with locally advanced PC who are defined as primarily unresectable and, by definition, do not qualify for primary surgery and subsequent adjuvant therapy. Accordingly, the present overview is limited to patients with resectable PC at first diagnosis. These patients constitute a subgroup of ∼15%–20% of PC patients. Provided that perioperative therapy is applied, median survival times are in the range of 20–24 months and the 5-year survival exceeds 20% in several randomized studies.

diagnosis of resectable PC

The diagnosis of PC requires high-quality, multiphase imaging implemented by contrast-enhanced pancreatic protocol computerized tomography (CT) or by magnetic resonance imaging [1]. In selected cases, additional information may be required from endoscopic ultrasound (EUS) or endoscopic retrograde cholangiopancreatography. Positron emission tomography (PET) scans may be implemented in the case of uncertain findings obtained by the standard imaging [2]. In two studies, application of 2-fluoro-2-deoxy-D-glucose-PET changed the oncological management in 16% and 27% of patients, respectively [3]. Also ‘laparoscopy’ is not a generally accepted component of the diagnostic work-up because high-quality, cross-sectional imaging provides sufficient evidence in most patients [4]. It may, however, be indicated in patients with a large tumor mass, specifically with body and tail lesions, in the presence of markedly elevated CA 19-9 levels (>100 ng/ml) and suspected peritoneal metastasis [5–7].

The resectability of pancreatic tumors should be determined in multidisciplinary tumor boards. According to the American Joint Committee on Cancer staging criteria, T1–T3 tumors are deemed resectable. Tumors are either confined to the pancreas (T1 and T2) or extend beyond the pancreas, but do not involve the celiac axis or the arteria mesenterica superior (T3) [8].

The decision on resectability is not only based on radiological criteria, but also patient-related parameters such as performance status, comorbidity and patients’ will should be taken into account [9].

Patients who are scheduled to primary resection do not require prior verification of neoplastic disease by cytology or tumor biopsy. However, histological confirmation of pancreatic adenocarcinoma is mandatory if neoadjuvant treatment is planned [7]. This is preferably done by EUS-directed fine-needle aspiration, but can also be achieved by CT-guided needle biopsy.

neoadjuvant therapy

Based on computational modeling, Haeno et al. [10] determined that PC growth is initially exponential and that metastasis is likely present even at early diagnosis. Following this hypothesis, surgery alone cannot fully eradicate the tumor, and upfront systemic therapy may be the treatment of choice...
The concept of treatment would then focus on early systemic therapy of incurable disease. Since, at present time, we cannot differentiate between curable and incurable resectable disease, this consideration may affect the basic strategy of therapy; it will, however, not change the definition of neoadjuvant or adjuvant treatment. The following advantages may favor the neoadjuvant approach [12]. (i) Neoadjuvant treatment may allow downsizing of the tumor, increase the rate of subsequent R0 resection and may thus contribute to an improved survival. (ii) Neoadjuvant therapy can be evaluated as an in vivo sensitivity test to systemic therapy. (iii) It may also be used as an opportunity to select for patients not developing metastasis during the time of neoadjuvant treatment who may, in fact, have the greatest benefit from locoregional treatment such as surgery or radiation. (iv) Chemoradiotherapy (CRT) may be more effective in the preoperative setting because of better tumor oxygenation. Although this appears to be a biologically sound argument, it has not been prospectively tested in patients. (v) Neoadjuvant treatment may be better tolerated than adjuvant therapy. Due to postoperative morbidity, there is a lower probability to apply planned treatment in the postoperative setting.

Disadvantages of neoadjuvant therapy are tumor progression during neoadjuvant therapy resulting in unresectability. Another important problem is the necessity of pathological verification which may prove to be difficult specifically in small tumors.

At present time, neoadjuvant therapy is not a standard of care in resectable PC patients, since data from randomized studies are not available. Most of the more recently published trials were performed as phase (I-)II studies and employed chemoradiation with or without gemcitabine-based chemotherapy [13].

Uncontrolled, retrospective analyses suggest that the effect of neoadjuvant versus adjuvant therapy on overall survival (OS) is equivalent. In a retrospective analysis, Spitz et al. [14] observed comparable survival times for patients receiving either neoadjuvant (19.2 months) or adjuvant (22.0 months) chemoradiotherapy. Median survival times of 23 and 31 months determined in two meta-analyses are well in keeping with the two-year survival of resected patients.

In two meta-analyses, the proportion of patients progressing during neoadjuvant therapy was 16% and 21% (Table 1) [13, 15]. This fraction can possibly be reduced by more active induction therapy. On the other hand, it may be argued that patients developing metastatic disease during induction therapy will be spared unnecessary surgery. In addition, it may be of interest to note that the proportion of primarily progressing patients compares well with the fraction of patients turning out to be unresectable during primary surgery [14].

If a preoperative reduction in tumor burden is the primary goal, this can be achieved only by use of highly effective treatment. Greatest local tumor control is expected from a multimodal approach which includes radiotherapy. In several clinical studies, preoperative chemoradiotherapy achieved survival times in the range of 20 months. The meta-analysis by Andriulli included 20 independent studies investigating neoadjuvant therapy with gemcitabine with or without CRT. The overall response rate reported by the authors was only 12% [95% confidence interval (CI) 4–23] and is lower than the objective response rate of 34% determined by Gillen et al. in a meta-analysis with more widely defined inclusion criteria (Table 1) [13, 15]. Clearly, it is the goal of future research to explore the impact of more effective chemotherapy regimens such as the FOLFIRINOX protocol on the outcome. So far, the great superiority of FOLFIRINOX over single-agent gemcitabine has only been proven in metastatic PC [16].

### Table 1. Meta-analyses of neoadjuvant therapy in resectable patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of studies</th>
<th>Number of patients</th>
<th>ORR (%)</th>
<th>PD (%)</th>
<th>OS overall (months)</th>
<th>OS resected (months)</th>
<th>OS non-resected (months)</th>
<th>2-year OS (months)</th>
<th>Grade 3–4 toxic effect (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andriulli et al.</td>
<td>20</td>
<td>366</td>
<td>12</td>
<td>16</td>
<td>18.8</td>
<td>30.6</td>
<td>9.2</td>
<td>67.2 (38–87)</td>
<td>29</td>
</tr>
<tr>
<td>Gillen et al.</td>
<td>35</td>
<td>NA</td>
<td>34.4</td>
<td>21</td>
<td>NA</td>
<td>23.3</td>
<td>8.4</td>
<td>47.4 (25–70)</td>
<td>26.3</td>
</tr>
</tbody>
</table>

*aTwo-year survival of resected patients.

ORR, objective response rate; PD, progressive of disease; OS, overall survival.
The data of the CONKO-001 study are essentially confirmed by a smaller Japanese study which also showed a significantly longer DFS obtained by gemcitabine when compared with observation (HR = 0.60, \( P = 0.01 \)). Gemcitabine also caused a prolongation of median survival (HR = 0.77, \( P = 0.19 \)), and this did, however, not reach the level of significance [21].

ESPAC-3 investigated the optimal choice of adjuvant chemotherapy. In a large randomized study, this trial demonstrated the equivalent efficacy of gemcitabine and bolus 5-FU resulting in the median OS times of 23.6 and 23.0 months, respectively. According to the authors, gemcitabine should be favored over 5-FU because of lower rates of toxicity such as stomatitis (0% versus 10%, \( P < 0.001 \)) or diarrhea (2% versus 13%, \( P < 0.001 \)).

In summary, adjuvant chemotherapy allows the prolongation of OS to a median of 20–24 months. Both agents, gemcitabine and 5-FU, are active, but show differences in toxicity profiles. Although the absolute gain in median survival was moderate, adjuvant chemotherapy did show a doubling of 5-year survival rates and accordingly has a marked long-term effect (Table 2).

### adjuvant chemoradiation

Within a 2 × 2 factorial design, the ESPAC-1 study pooled patients who received CRT according to the gastrointestinal tumor study group (GITSG) regimen or a sequence of CRT and chemotherapy (Table 3) [18]. When CRT was compared with no CRT, median survival was inferior in the CRT group (15.9 versus 17.9 months), as was 5-year survival (10% versus 20%, \( P = 0.05 \)). The relevance of this finding remains unclear, since the study used a split-course radiation which is not the standard of care any more. Additional survival analyses indicated that patients in the CRT arm had a median survival of 13.9 months (95% CI 12.2–17.3 months), whereas survival was improved when patients received CRT followed by chemotherapy (19.9 months; 95% CI 14.2–22.5 months). This again points to the importance and efficacy of adjuvant chemotherapy in resectable PC.

The RTOG (Radiation Therapy Oncology Group) 9704 trial applied 5-FU-based CRT in both arms, but randomized pre- and post-CRT treatment with gemcitabine versus 5-FU [22]. When only pancreatic head tumors were evaluated, the median OS showed a trend in favor of gemcitabine (20.5 versus 17.1 months, \( P = 0.08 \)), but the 5-year survival was quite comparable (22% versus 18%) [23]. Since CRT was identical in both arms, the RTOG 9704 study actually compared gemcitabine with continuous infusion 5-FU. To some extent, this study, therefore, supports the data from the ESPAC-3 study where adjuvant chemotherapy with gemcitabine and bolus 5-FU resulted in a nearly identical outcome.

Van Laethem et al. performed a small randomized phase II study to assess the feasibility and tolerability gemcitabine-based CRT after R0 resection. In this trial, patients were randomized to receive either two cycles of gemcitabine followed by gemcitabine-based CRT or gemcitabine alone for four cycles. The median DFS and OS were nearly identical in both [18].}

### Table 2. Selected randomized trials investigating adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>Number of patients</th>
<th>Treatment arms</th>
<th>Duration of treatment (months)</th>
<th>Median time to recurrence/DFS (months)</th>
<th>Median OS (months)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kosuge et al. [39]</td>
<td>2006</td>
<td>45</td>
<td>5-FU + cisplatin q 4–8 weeks for two cycles</td>
<td>2 (−3)</td>
<td>8.6</td>
<td>12.5</td>
<td>26.4</td>
</tr>
<tr>
<td>ESPAC-1 [18]</td>
<td>2004</td>
<td>147</td>
<td>5-FU/FA</td>
<td>6</td>
<td>13.3</td>
<td>15.8</td>
<td>14.9</td>
</tr>
<tr>
<td>CONKO-001 [19, 20]</td>
<td>2007</td>
<td>179</td>
<td>Gemcitabine weekly × 3 q 4 weeks for six cycles</td>
<td>6</td>
<td>13.4</td>
<td>22.1</td>
<td>22.5</td>
</tr>
<tr>
<td>Ueno [21]</td>
<td>2009</td>
<td>58</td>
<td>Gemcitabine weekly × 3 q 4 weeks for six cycles</td>
<td>3</td>
<td>6.9</td>
<td>20.2</td>
<td>11.5</td>
</tr>
<tr>
<td>ESPAC-3 [40]</td>
<td>2009</td>
<td>537</td>
<td>Gemcitabine weekly × 3 q 4 weeks for six cycles</td>
<td>6</td>
<td>14.3</td>
<td>23.6</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>551</td>
<td>5-FU/FA bolus d1-5, q 4 weeks for six cycles</td>
<td>14.1</td>
<td>14.1</td>
<td>23.0</td>
<td>NA</td>
</tr>
</tbody>
</table>

\[^aP = 0.009.\] \[^bP = 0.005.\]

OS, overall survival; DFS, disease-free survival; 5-FU, 5-fluorouracil; FA, folinic acid; ESPAC, European Study Group of Pancreatic Cancer; CONKO, German Charité Onkologie.
treatment arms, whereas the local recurrence rate was markedly lower in the CRT arm (11% versus 24%) [24].

**Intensification of adjuvant chemotherapy in combination with radiation**

Based on encouraging efficacy data from monocentric phase II studies, a German randomized trial investigated adjuvant CRT with cisplatin, infusional 5-FU and interferon-α in the experimental arm and applied a 5-FU bolus regimen in the comparator arm [25, 26]. The median survival was surprisingly long, but not significantly different in both treatment arms (32.1 versus 28.4 months, \( P = 0.49 \)), as was DFS (24.8 versus 22.1 months, \( P = 0.43 \)). As expected, the local recurrence rate was lower in the CRT arm (29% versus 56%). Due to its high toxicity and due to the lack of a clearly superior treatment effect, it is unlikely that this regimen will enter routine clinical practice.

Within a randomized phase II study, Reni et al. compared adjuvant treatment with gemcitabine to the polychemotherapy PEGF (cisplatin, epirubicin, gemcitabine, 5-fluorouracil) regimen. In both arms, chemotherapy was applied for 3 months followed by 5-FU-based CRT [27]. The median DFS at 1 year, evaluated as the primary end point, was 49% in the gemcitabine arm and 69.4% in the PEGF arm. The median OS was 26.2 versus 31.6 months, respectively.

In summary, median survival times associated with the combination of intensified adjuvant chemotherapy and CRT were longer than those previously observed with gemcitabine or 5-FU/folinic acid alone [18, 19]. The small size of the studies and possibility of selection bias, however, do not allow to draw firm conclusions.

**Evaluation of the local recurrence rate**

After surgery, a disease-free interval of 8–13 months is expected, and most recurrences occur within 2 years [28]. Analysis of the site of first relapse may be used as a tool to define the efficacy of locoregional treatment after surgery. A cross-trial comparison suggests that after chemoradiotherapy local recurrence rates were in the range of 10%–30%, whereas they appear to be somewhat higher (20%–30%) after adjuvant chemotherapy (Table 4). In two randomized trials, local recurrence rates were only half as high after chemotherapy–CRT compared with chemotherapy alone [24, 25]. The lower rates of local recurrence were, however, not associated with a significantly improved survival in either of the studies. This observation may refer to the fact that PC is primarily a systemic disease, the course of which is rather controlled by chemotherapy than by the locoregional activity of CRT.

**Does CRT have a place in adjuvant therapy?**

The first lesson was learned from the ESPAC-1 trial which indicated that chemoradiotherapy had a negative effect on survival compared with no chemotherapy. Although radiation techniques have improved since then, the effects on survival did not so far. Van Laethem et al. [24] compared gemcitabine applied over two cycles followed by CRT to gemcitabine alone.
and obtained identical survival times. Also the study by Marten et al. [25] comparing an intensive CRT regimen followed by 5-FU to chemotherapy with 5-FU alone did not show a significant superiority of the radiation regimen. Although the latter studies are small and certainly do not allow final conclusions, the results are essentially in accordance with the broader view across randomized trials, where superior survival times were not obtained with CRT compared with chemotherapy alone (Tables 2 and 3).

**additive treatment after margin-positive resection**

Results from several randomized studies suggest that postoperative treatment after R1 resection should be performed differently than in R0-resected patients (Table 5). In the ESPAC-1- and the CONKO-001 study, margin-positive resection was performed at a rate of 17%–18% [19, 29]. While R0-resected patients had a clear benefit from adjuvant chemotherapy, this was not the case in R1-resected patients. Butturini et al. [30] performed a meta-analysis to assess the influence of resection margins and adjuvant CRT or chemotherapy on the patient outcome. Based on an analysis of individual patient data from randomized trials, they reported that in R1-resected patients CRT resulted in a 28% reduction in the risk of death compared a 4% risk increase if patients received only chemotherapy. In contrast, after R0 resection, chemotherapy induced a 35% risk reduction, whereas CRT caused a 19% increase of risk of death. These data are further supported by the RTOG 97-04 chemoradiation trial [22] where gemcitabine pre- and post-CRT was compared with 5-FU pre- and post-CRT. In contrast to the chemotherapy trials, the surgical margin status did not affect the outcome (HR = 1.05). Altogether, these results lead to the hypothesis that the combination of postoperative chemotherapy and CRT might be an effective strategy specifically after margin-positive surgery.

**perspectives of neoadjuvant therapy**

Convincing data from a prospectively planned randomized study are needed before the neoadjuvant treatment of resectable PC may enter clinical routine. There is a general

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**Table 4. Site of first relapse in selected trials**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Regimen</th>
<th>n</th>
<th>Local relapse (%)</th>
<th>Distant relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant chemoradiotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG 9704 [22, 23]</td>
<td>Gemcitabine → CRT → gemcitabine</td>
<td>195</td>
<td>25</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>5-FU → CRT → 5-FU</td>
<td>205</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>CAPRI [25]</td>
<td>(IFN + cisplatin + 5-FU) CRT → 5-FU</td>
<td>41</td>
<td>29</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Bolus 5-FU/FA</td>
<td>45</td>
<td>56</td>
<td>NA</td>
</tr>
<tr>
<td>Reni [27]</td>
<td>Gemcitabine (3 months) → CRT (5-FU)</td>
<td>51</td>
<td>17</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>PEFG (3 months) → CRT (5-FU)</td>
<td>49</td>
<td>10</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>45</td>
<td>24</td>
<td>40</td>
</tr>
</tbody>
</table>

**Table 5. Survival after margin-positive resection**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>Resection status</th>
<th>Number of patients</th>
<th>Treatment</th>
<th>Median DFS (months)</th>
<th>P-value</th>
<th>Median OS (months)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R1</td>
<td>45</td>
<td>Chemotherapy</td>
<td>NA</td>
<td>NA</td>
<td>11</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>42</td>
<td>No chemotherapy</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>CONKO-001 [19]</td>
<td>2007</td>
<td>R0</td>
<td>145</td>
<td>Gemcitabine</td>
<td>13.1</td>
<td>&lt;0.001</td>
<td>22.1</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td>148</td>
<td>Observation</td>
<td>7.3</td>
<td>20.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>R1</td>
<td>34</td>
<td>Gemcitabine</td>
<td>15.8</td>
<td>&lt;0.001</td>
<td>21.7</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27</td>
<td>Observation</td>
<td>5.5</td>
<td>20.8</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

DFS, disease-free survival; OS, overall survival; ESPAC, European Study Group of Pancreatic Cancer; CONKO, German Charité Onkologie.

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*Site of recurrence not reported in 10% of patients.

CRT, chemoradiotherapy; 5-FU, 5-fluorouracil; IFN, interferon; PEFG, cisplatin, epirubicin, 5-fluorouracil, gemcitabine; CONKO, German Charité Onkologie; EORTC, European Organisation for Research and Treatment of Cancer; RTOG, Radiation Therapy Oncology Group.
expectation that the introduction of highly active polychemotherapy regimens such as the FOLFIRINOX regimen will improve the efficacy of neoadjuvant therapy. Preliminary evidence of the efficacy of FOLFIRINOX in locally advanced disease is already available in the abstract form [31–34]. Also the integration of CRT into the preoperative regimen remains an important topic of development. Specifically, the use of intensity modulated radiation therapy may help to limit toxic effect and to allow concomitant application of highly effective chemotherapy.

**perspectives for adjuvant therapy**

(i) At present time, adjuvant chemotherapy remains the standard of care after complete resection of ductal adenocarcinoma of the pancreas. Adjuvant CRT appears to result in a lower local recurrence rate which, however, does not clearly relate to prolonged OS. There is some evidence to suggest that CRT may be beneficial after margin-positive resection.

(ii) Open questions specifically regard the way chemotherapy should be performed to achieve optimal results. With the introduction of highly effective regimens, such as the FOLFIRINOX protocol, a new era of clinical investigation commences for perioperative treatment [16].

(iii) Another question regards the optimal duration of adjuvant chemotherapy. Given that systemic disease is prevalent in most patients with resectable tumors, there is a good rationale for prolonged duration of therapy. This would require the exploration of maintenance strategies and the use of effective and, in the long run, well-tolerated agents.

(iv) Last, but not least, the integration of CRT into adjuvant chemotherapy remains an open question, which is, however, addressed in the presently ongoing European Organisation for Research and Treatment of Cancer/Radiation Therapy Oncology Group 0804 phase III study. Using a 2 × 2 factorial design, this study will investigate the importance of erlotinib and CRT in adjuvant treatment. After a first randomization, patients receive five cycles of adjuvant chemotherapy with either gemcitabine or gemcitabine–erlotinib. Patients without tumor progression are then submitted to a second randomization where one cycle of chemotherapy is compared with one cycle of chemotherapy followed by fluoropyrimidine-based CRT [23].

**perspectives of individualized therapy**

A relevant perspective to optimize perioperative therapy may consist in the development of individualized treatment strategies. One approach may consist in the use of Dpc4 (Smad4) expression to predict the pattern of recurrence. Iacobuzio-Donahue et al. [35] demonstrated that the loss of Dpc4 expression correlated with widespread metastasis, whereas this was uncommon in locally confined disease. These data were essentially confirmed by Crane et al. [36] who evaluated 69 patients with locally advanced PC and again found that Dpc4 expression correlated with a local rather than a distant dominant pattern of disease progression. In a most recent multicentric cohort analysis, Bachet et al. analyzed 471 patients who had undergone the resection of pancreatic adenocarcinoma. In patients with negative Smad4 expression, they observed only a trend toward decrease in OS. However, CXCR4 expression was identified as the only independent negative prognostic biomarker associated with distant metastatic recurrence [37]. Another approach may be to guide the choice of the optimal chemotherapy regimen by pharmacodynamic parameters associated with the cytotoxic agents in use. First data are already available to indicate that hENT1 expression can serve as a predictor of survival after adjuvant gemcitabine therapy [38].

**disclosures**

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**references**


