Surgical possibilities for pancreatic cancer: Extended resection

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Summary

Design: It was the aim of this study to investigate the influence of extended retroperitoneal tissue clearance on long-term survival in patients with ductal adenocarcinoma of the head of the pancreas.

Patients and methods: From 10/1988 to 3/1998 a prospective observation study was initiated in 108 patients with malignant growth in the head of the pancreas to compare patients with regional lymphadenectomy (RLA) versus extended retroperitoneal tissue clearance (ELA). In 36 patients other tumors than ductal adenocarcinomas were found, so that 72 patients with a partial pancreaticoduodenectomy and a histologically established diagnosis of ductal adenocarcinoma were included. Pancreaticoduodenectomy was combined with RLA in 26 cases and with ELA in 46 patients.

Results: Comparing only R0-resected patients (n=58) no significant difference in long-term survival rates between the RLA and the ELA group was found. Hospital mortality was 3.8% in the RLA group and 6.5% in the ELA group. Significant or nearly significant results were shown for the following parameters:

- Stage of the disease: Patients after partial pancreaticoduodenectomy of a stage III cancer of the head of the pancreas showed a 63% 5-year survival rate compared to 15% in patients in stage III or IV (p=0.0087).
- Grading: No patient with a poorly differentiated ductal adenocarcinoma of the head of the pancreas survived the first year in comparison to 55% of patients with well or moderately differentiated tumors (p=0.0022).
- N-stage: 5-year survival of patients in N0 stage was 46.9% and 15% for N1 stage patients (p=0.081).
- Portal vein infiltration: No patient with a R0-resection and histologically proven tumor infiltration of the portal vein survived the first year whereas 63% of patients did so after curative resection without portal vein involvement (p=0.0063).

Conclusion: Our data indicate that extensive retroperitoneal tissue clearance does not improve long-term survival rates compared to regional lymphadenectomy restricted to the right side of the mesenteric artery.

Key words: carcinoma of the head of the pancreas, extended lymphadenectomy

Introduction

Over the last twenty years treatment of ductal adenocarcinoma of the head of the pancreas was determined by many efforts to improve survival rates by extension of surgical radicality or by multimodal approaches. However, treatment of pancreatic carcinoma is still determined by the following facts:

- Despite the improvements of diagnostic tools the diagnosis of an early stage represents a rare event in pancreatic carcinoma. Therefore patients referred for treatment usually present advanced stages of the disease.
- Resection rates are still low in the range of 10% to 20% [1,2,3].
- Long-term survival has not improved essentially, with five-year survival rates of 30% at best [4-9].
- Operative risks are decreased and acceptable rates of mortality after pancreaticoduodenectomy are achieved. At time only surgery comprises the chance of cure for patients suffering from ductal pancreatic carcinomas. In 1988 Ishikawa [9] published an improved five-year survival of 28% in patients after pancreaticoduodenectomy for adenocarcinoma of the head of the pancreas due to an extended radical retroperitoneal lymphadenectomy. Therefore further studies have to evaluate the potential benefit of extended surgery on patients survival, accuracy of tumor and treatment staging and on postoperative and long-term implications on patients quality of life.

Patients and methods

Due to Ishikawa's data [9] we changed our operative strategy and included extensive retroperitoneal tissue clearance into the operative procedure. From 10/1988 to 12/1991 (Dep. of Surgery, University of Hamburg) and from 1/1992 to 3/1998 (University of Kiel) 245 patients were referred for treatment for a malignant tumor in the head of the pancreas. 137 patients were irresectable due to distant tumor spread or extensive infiltration of the mesentery. In 108 patients a prospective observation study with goal to evaluate the influence of extended lymph node dissection was initiated. This study was restricted to 72 patients, in whom the diagnosis of a ductal adenocarcinoma of the pancreatic head was established by two different experts in pancreatic pathology, because in 36 patients other neoplasms, such as neuroendocrine or ampullary carcinomas were diagnosed.

Standard surgical techniques

In 26 patients partial pancreaticoduodenectomy was combined with a regional lymphadenectomy (RLA) whereas in 46 patients an extended radical retroperitoneal lymphadenectomy was performed. Regional lymph node dissection included removal of all lymph nodes along the hepatoduodenal ligament, the celiac trunk, the first 3 cm of the splenic artery, the right side of the superior mesenteric artery and the ventral surface of the vena cava and the renal veins. During extended retroperitoneal lymphadenectomy all lymphatic, mesenteric artery and along the aorta between the inferior mesenteric artery and the diaphragma was additionally resected. The specific details of both groups (RLA vs. ELA) regarding age distribution, operation time, blood loss, hospital mortality and histopathological staging according to the UICC 1997 are given in Tables 1 and 2.

Patients were not prospectively randomized into two groups regional...
versus extended lymphadenectomy. The individual patient was assigned to one of the two groups after weighing the patient's general stage [10] and life expectancy and after informed consent about potential quality of life interferences, especially diarrhea. Patients were informed, that extensive retroperitoneal tissue clearance will induce diarrhea with a nearly 100% probability.

Table 1: Stage distribution according to the UICC in correlation to the type of operation performed: partial duodenopancreatectomy with regional (PDP+RLA) vs. extended retroperitoneal (PDP+ELA) lymphadenectomy

<table>
<thead>
<tr>
<th>UICC stage</th>
<th>R stages (all)</th>
<th>R 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDP + RLA</td>
<td>PDP + ELA</td>
<td></td>
</tr>
<tr>
<td>n = 26</td>
<td>n = 46</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>III</td>
<td>9</td>
<td>20</td>
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<tr>
<td>IVa</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>IVb</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2: Specific data correlated to the type of operation: partial duodenopancreatectomy with regional (PDP+RLA) vs. extended retroperitoneal lymphadenectomy (PDP+ELA)

<table>
<thead>
<tr>
<th>Data category</th>
<th>PDP + RLA (n = 26)</th>
<th>PDP + ELA (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>65.5 y</td>
<td>57.4 y</td>
</tr>
<tr>
<td>Mean op-time</td>
<td>5'58 min</td>
<td>7'31 min</td>
</tr>
<tr>
<td>Mean blood units</td>
<td>4.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Mean analysed LN</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>3.8%</td>
<td>6.5%</td>
</tr>
</tbody>
</table>

**Results**

Data related to the stage of the disease and to the type of lymph node dissection are summarized in Table 1 for all patients and for R0-resected patients. Specific data according to operation time, intraoperative blood loss, patient's age and number of lymph nodes investigated in correlation to the dissection technique are given in Table 2.

**RLA vs. ELA:** As shown in Table 2 in patients after regional lymphadenectomy (RLA; n=26) an average of 14 lymph nodes was histologically examined in contrast to 24 lymph nodes in the group of patients with extended retroperitoneal lymph node dissection (ELA; n=46). In 4 patients positive paraaortic lymph nodes were found, but these patients had positive lymph nodes in the regional compartments too, so that there was no development of skip metastases in distant lymph node compartments.

Mortality was 3.8% (n=1) in the RLA group, and 6.5% (n=3) in the ELA group. For all resected patients mortality was 5.5% (n=4). 76% of patients after extended retroperitoneal tissue clearance suffered from diarrhea.

Analyzing long-term survival on the basis of R0-resected patients (n=58; RLA: n=18; ELA: n=40) this study showed no significant difference between patients with RLA and patients with ELA (Fig. 1).

With increasing numbers of patients there might be the chance that for a subgroup of patients extended retroperitoneal tissue clearance will be beneficial, because at time the probability is that 6 years after resection all patients will be dead after RLA, whereas after ELA 17.8% of the patients should survive more than 6 years.

![Figure 1: Cumulative survival of R0-resected patients (n=58) correlated to the type of lymphadenectomy: RLA vs. ELA](image-url)
adenocarcinoma of the head of the pancreas (n=40) (Fig. 2). *N*-stages: 5-year survival of node negative patients (n=20) was 46.9% compared to 22% for patients in N1 stage (n=38). The difference between the number of patients in stage I/II (n=18) and the N0 group (n=20) is due to two patients with T4 N0 M0 carcinomas (Fig. 3).

**Grading:** In this study tumor grading had a significant (p=0.0022) prognostic influence. None of the 12 patients with a poorly differentiated adenocarcinoma of the head of the pancreas survived the first year whereas 1-year survival was 55% for patients with well (n=11) or moderately n=35) differentiated tumors (Fig. 4).

**Portal and/or mesenteric vein involvement:** In 27% of the 72 patients (n=20; RLA: n=3; ELA: n=17) a segment of the portal and/or mesenteric vein was resected due to histologically proven or macroscopically suspected tumor infiltration. At least tumor infiltration was confirmed by microscopic findings in 16 patients. In 4 cases an inflammatory reaction of the vein was misassessed by the surgeon as tumor infiltration.

To analyze the prognostic influence of portal or mesenteric vein involvement only R0-resected patients (n=15) were investigated. All patients with microscopically proven tumor infiltration died within 10 months (Fig. 5). Only one patient of the 4 patients, in whom no tumor infiltration was found histologically, survived more than 10 months. This patient has a stage I disease with a massive inflammatory reaction around the tumor at the portal vein which was misjudged as tumor involvement. The three other patients were stage III in one and stage IV in two cases with an unfavourable prognosis in any case.

The 5% hospital lethality was in the same range as the 5.5% lethality of the whole series.

**R1/R2-resections:** 12 of 72 patients (=16.7%) were classified as R1 (n=8) or R2 (n=4) resection. Two of them died during their hospital stay, resulting in a specific mortality of 16.6%. Survival analysis showed no difference between R1 or R2-resected patients, they all died within 17 months. The seriously increased mortality of R1/R2-resected patients rises the question for better selection criteria, if possible.

**Discussion**

More radical operative procedures have been developed to improve survival of patients suffering from ductal adenocarcinoma of the head of the pancreas [3,9,19]. Although resection of involved portal segments or radical retroperitoneal tissue clearance can be performed with low mortality (< 5%) [4,6,17-20], these procedures are not widely accepted. Currently it is still controversial whether extended radical surgery can improve long-term survival in this carcinoma with its particularly poor prognosis [21-24]. The main subjects of the controversial discussion concern the standardization of the surgical approach, the extent of lymph node dissection, the indication to resect portal or mesenteric vein segments, the definition of R0 resections and the indication of adjuvant treatment modalities [8,9,17,25-29]. Consequently this study was standardized in as many aspects as possible:

The series was restricted to patients with ductal adenocarcinomas of the head of the pancreas, all operations
were performed by or in presence of the same two surgeons (BK;DH-B), all specimens were reviewed by the same two pathologists (GK; JL).

This study showed the somewhat unexpected result [9,30,31,32] that no significant difference in long-term survival rates of patients subjected to partial pancreaticoduodenectomy with regional (PDP+RLA) versus extended (PDP+ELA) lymphadenectomy could be demonstrated. Considering the high percentage of stage III and IV patients in both groups (ELA=77.5%; RLA=50%), with both operative procedures acceptable 5-year survival rates of 17.6% (ELA) and 35% (RLA) were achieved.

Because our study could not demonstrate any effect on long-term survival in regard to the extent of lymph node dissection, the two groups were analyzed as one for further investigations of prognostic parameters. For stage I and II patients (n=18) an excellent overall 5-year survival of 63% was achieved, 9 of these patients had a PDP+RLA and 9 patients a PDP+ELA. 5-year survival rates differed with 50% for the RLA-group and 74.1% for the ELA-group. Due to the small numbers of the subgroups it remains to be seen whether this difference is due to the more radical operation or the better pathologic staging caused by an increased number of investigated lymph nodes.

Comparing patients with G1/G2 tumors with patients after resection of G3 tumors a significant (p=0.0022) prognostic influence was shown by our study. Similar results are published by other authors with the exception of Cameron et al [7], who found tumor differentiation to be of no predictive value.

In patients without nodal involvement (n=20) a 5-year survival of 46.9% was found. Similar results are published by other series [6,7,33]. Nagakawa et al [30,31] published a 71.4% 5-year survival rate for node negative cases after extensive retroperitoneal tissue clearance. It is still open for discussion whether this result is due to the type of surgery or due to an extensive histologic evaluation eliminating all cases even with micrometastatic lymph node involvement from this group. Our study shows comparable results for the subgroup of 9 stage I/II patients after curative resection and ELA (5-year survival = 74.1%).

Nodal involvement is correlated with a poor prognosis and 5-year survival rates below 5% [6,27,33]. A 5-year survival of 15% in our study for N1 stage patients is comparable to the 5-year survival of 17.8% published by Nagakawa et al [30,31] in node positive patients after extended retroperitoneal lymphadenectomy. However, the similar results of our study were achieved independently of the extent of lymph node dissection.

Portal or mesenteric vein infiltration by an adeno-carcinoma of the head of the pancreas in most series represents a strong negative prognostic factor [29,34]. Our current study demonstrates comparable findings, in which the worst prognosis was significantly associated with a histologically proven tumor infiltration of the portal/mesenteric vein. However, since mortality rates did not increase in the group of 20 patients in whom segments of the portal and/or mesenteric vein were resected (5%), we will proceed intraoperatively with segmental resection in order to achieve a R0 resection. Most authors report similar experiences and consequences. Only Ishikawa et al published a 59% 3-year survival rate for patients with semicircular and short (<1.2 cm) portal vein stenoses and a 29% 3-year survival rate for patients with longer and circular involvement of venous structures [35].

Consequences: In patients with supposed or already proven adenocarcinoma of the head of the pancreas which seems to be resectable, paraaortic lymph nodes are investigated at the beginning of the operation by frozen section. If tumor involvement is found, a partial pancreaticoduodenectomy is performed with regional lymphadenectomy restricted to the right side of the mesenteric vein (RLA), in order to avoid long-term diarrhea.

In case of negative paraaortic lymph node findings by frozen section the operation proceeds with an extended retroperitoneal tissue clearance (ELA), if the patient has given full informed consent to the higher perioperative risks, the still unproven beneficial effect and the potential negative impact on quality of life associated with the more extensive retroperitoneal lymph node removal.

References

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