Shifting emphasis in pancreatic surgery: Pre-, intra-, and postoperative determinants of outcome
Eshuis, W.J.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 3

THERAPEUTIC DELAY AND SURVIVAL AFTER SURGERY FOR CANCER OF THE PANCREATIC HEAD WITH OR WITHOUT PREOPERATIVE BILIARY DRAINAGE

Wietse J. Eshuis
Niels A. van der Gaag
Erik A.J. Rauws
Casper H.J. van Eijck
Marco J. Bruno
Ernst J. Kuipers
Peter P. Coene
Frank J.G.M. Kubben
Josephus J.G.M. Gerritsen
Jan Willem Greve
Michael F. Gerhards
Ignace H.J.T. de Hingh
Jean H. Klinkenbijl
C. Yung Nio
Steve M.M. de Castro
Olivier R.C. Busch
Thomas M. van Gulik
Patrick M.M. Bossuyt
Dirk J. Gouma

ABSTRACT

Objective: To evaluate the relation between delay in surgery because of preoperative biliary drainage (PBD) and survival in patients scheduled for surgery for pancreatic head cancer.

Background: Patients with obstructive jaundice due to pancreatic head cancer can undergo PBD. The associated delay of surgery can lead to more advanced cancer stages at surgical exploration, affecting resection rate and survival.

Methods: We conducted a multicenter, randomized controlled clinical trial to compare PBD with early surgery (ES) for pancreatic head cancer for complications. We obtained Kaplan-Meier estimates of overall survival for patients with pathology-proven malignancy and compared survival functions of ES and PBD groups using log-rank test statistics. Multivariable Cox regression analyses were performed to evaluate the prognostic role of time to surgery for overall survival.

Results: Mean times from randomization to surgery were 1.2 (0.9-1.5) and 5.1 (4.8-5.5) weeks in the ES and PBD groups, respectively ($P < 0.001$). In the ES group, 60 (67%) of 89 patients underwent resection, versus 53 (58%) of 91 patients in the PBD group ($P = 0.20$). Median survival after randomization was 12.2 (9.1-15.4) months in the ES group versus 12.7 (8.9-16.6) months in the PBD group ($P = 0.91$). A longer time to surgery was significantly associated with slightly lower mortality rate after surgery (hazard ratio 0.90, 95% CI, 0.83-0.97), when taking into account resection, bilirubin, complications, pancreatic adenocarcinoma, tumor-positive lymph nodes, and microscopically residual disease.

Conclusions: In patients with pancreatic head cancer, the delay in surgery associated with PBD does not impair or benefit survival rate.
INTRODUCTION

Patients with a periampullary or pancreatic head tumor generally present with obstructive jaundice. In the absence of radiological signs of locoregional irresectable or metastatic disease, surgical exploration with curative intent is the treatment of choice. Because surgery in jaundiced patients is thought to increase the risk of postoperative complications, preoperative biliary drainage (PBD) is often performed. Routine application of this procedure, which also carries a risk of complications, has been a matter of debate for many years. Recently, we conducted a randomized trial that compared PBD, followed by surgery, with surgery alone. We found that patients allocated to PBD had significantly more overall treatment complications than patients undergoing surgery without PBD. On the basis of these results, we concluded that application of PBD should not be routinely performed.

Preoperative biliary drainage may still be clinically relevant in subsets of patients, such as severely jaundiced patients, patients with ongoing cholangitis, or – in the near future – patients scheduled for neoadjuvant chemoradiation therapy. Preoperative biliary drainage may also be warranted when early surgery (ES) is not feasible because of logistic reasons. Furthermore, PBD allows for referral to a high-volume center.

In the light of these considerations, it is important to evaluate whether the scheduled delay in surgery, required for an effective period of PBD, leads to more advanced cancer stages at exploration. In theory, this could affect the resection rate and eventually lead to reduced survival.

To our knowledge, the study by Smith et al. is the only study that investigated the effects of PBD on survival in patients who underwent pancreatoduodenectomy for pancreatic cancer. The authors found no difference in early survival (up to 6 months after resection) or in long-term survival between stented and nonstented patients. Studies have been performed on the influence of the therapeutic delay on survival in other types of cancer. In rectal cancer, a therapeutic delay from the onset of symptoms until treatment of at least 60 days was shown to be negatively associated with survival. Comparable associations were not found in colonic or lung cancer.

In this study, we investigated the effect of the therapeutic delay on survival of PBD followed by surgery, versus surgery alone, in patients with a malignancy in the pancreatic head region. The data were collected in a randomized clinical trial, supplemented by additional collection of mortality data. In this additional analysis, we evaluated the effect of therapeutic delay conditional on, and in addition to, other documented prognostic factors.
METHODS

STUDY DESIGN

Treatment data were collected in patients who had participated in a randomized, controlled multicenter trial comparing PBD, followed by surgery, with surgery alone (ISRCTN31939699). Details of the trial design have been published elsewhere; here we will summarize the key aspects.

Patients were enrolled in 5 university medical centers and 8 major teaching hospitals. All patients or their legal representatives provided written informed consent for study participation. Included patients were 18 to 85 years of age, had a serum total bilirubin level of 40 to 250 μmol/L (2.3-14.6 mg/dL), and had no evidence of locoregional irresectable or metastatic disease on computed tomography. Within 4 days after computed tomography, patients were randomized to undergo PBD (PBD group) for a period of 4 to 6 weeks, or to proceed to surgery within 1 week (ES group).

Preoperative biliary drainage was performed at endoscopic retrograde cholangiopancreatography (ERCP) by placement of a plastic stent. In case of 2 failed ERCP attempts, percutaneous transhepatic cholangiography was used as rescue option to achieve biliary drainage.

The standard surgical procedure was a pylorus-preserving pancreatoduodenectomy with removal of lymph nodes at the right side of the portal vein. On indication of tumor ingrowth in pylorus or proximal duodenum, a classic Whipple procedure was performed. In case of metastasis or local tumor ingrowth, biopsy samples were taken for histological analysis. Surgical palliation was mostly achieved by creating a hepaticojejunostomy with or without gastroenterostomy and celiac plexus neurolysis. For this analysis, we used and collected additionally data from all patients with histologically proven malignancy. Additional survival data were collected through contacting general physicians, hospitals, or registry databases. Date and cause of death were obtained from general physicians or from hospitals where patients had died during hospital admittance. If details on cause of death could not be provided, date of death was obtained from registry databases.

STATISTICAL ANALYSIS

The main endpoint of the study was overall survival, defined as the time from the date of randomization to the date of death, irrespective of cause. Overall and cancer-

42
specific survival times were evaluated from the time of randomization to the time of death. Kaplan-Meier estimates of survival were obtained. Overall survival was compared between the PBD group and the ES group, using log-rank test statistics, and evaluated for all patients, for patients who underwent resection and for patients with irresectable disease at surgery. Prognostic factors for survival were identified in all patients and in patients who had undergone resection.

We examined the effect of a delay in surgery on survival, conditional on a number of prognostic variables, using multivariable Cox proportional hazards modeling. The following predictors were considered: age, sex, serum total bilirubin level at randomization, need for intraoperative blood transfusion, resection of tumor, and complications related to PBD or surgery. In addition, the following pathological characteristics were considered in patients who had undergone resection: pancreatic adenocarcinoma (vs other malignancies), tumor-positive lymph nodes, and microscopically residual disease.

$P$-values less than 0.05 were considered to indicate statistically significant effects. All statistical analyses were performed using SPSS version 15.0 (Statistical Package for the Social Sciences, Chicago, Illinois).

RESULTS

Between November 2003 and June 2008, 202 patients with obstructive jaundice due to a suspected periampullary malignancy gave informed consent and were included in the randomized trial. Of these 202 patients, 6 patients were excluded from further analysis because they withdrew their informed consent (2) or because their bilirubin levels had not been in accordance with the inclusion criteria before randomization (4). In 185 of the remaining 196 patients, a final diagnosis of histologically proven malignancy was made; these patients were included in this analysis (Table 1).

PATIENT CHARACTERISTICS

The PBD and ES groups consisted of 95 and 90 patients, respectively. At baseline, demographic and clinical characteristics of the 2 study groups were comparable, except for sex and body mass index. Five patients in the ES group underwent PBD, because surgery could not be scheduled in time (3), cholangitis developed (1) or because severe hyperglycemia developed (1). In the PBD group, there were technical failures
in 3 patients: failure of both ERCP and percutaneous transhepatic cholangiography (1), bile duct perforation at ERCP for which an emergency laparotomy was performed (1), and hemorrhage at sphincterotomy, which stopped the procedure (1).

Mean difference between groups in the delay to surgery was 4 weeks: the delay was 1.2 weeks in the ES group (95% confidence interval [CI], 0.9-1.4) versus 5.2 weeks in the PBD group (95% CI, 4.8-5.5). Figure 1 shows the distribution of time from randomization to surgery for the 2 groups. Other treatment characteristics of the 2 study groups were similar. Of the 89 operated patients in the ES group, 29 patients were found to have unresectable disease at surgical exploration (33%), versus 38 of 91 operated patients (42%) in the PBD group ($P = 0.20$). In the PBD group, resection rates of patients with or without PBD-related complications were not different (both 58%, $P = 0.99$).

### Table 1. Demographic and clinical characteristics of 185 patients with histology-proven malignant disease who were randomized to receive PBD or not

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ES ($n = 90$)</th>
<th>PBD ($n = 95$)</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years), mean ± SD</td>
<td>64.6 ± 9.5</td>
<td>64.7 ± 10.3</td>
<td>0.94</td>
</tr>
<tr>
<td>Males – No. (%)</td>
<td>63 (70)</td>
<td>51 (54)</td>
<td>0.02</td>
</tr>
<tr>
<td>Comorbidity – No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19 (21)</td>
<td>14 (15)</td>
<td>0.26</td>
</tr>
<tr>
<td>Cardiovascular disease*</td>
<td>22 (24)</td>
<td>15 (16)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20 (22)</td>
<td>21 (21)</td>
<td>0.99</td>
</tr>
<tr>
<td>COPD</td>
<td>4 (4)</td>
<td>3 (3)</td>
<td>0.72</td>
</tr>
<tr>
<td>Body mass index, mean ± SD†</td>
<td>24.0 ± 3.1</td>
<td>25.2 ± 3.9</td>
<td>0.04</td>
</tr>
<tr>
<td>Duration of symptoms (weeks), med. (IQR)</td>
<td>3 (2-5)</td>
<td>3 (2-5)</td>
<td></td>
</tr>
<tr>
<td>Weight loss (kg), med. (IQR)‡</td>
<td>5 (3-10)</td>
<td>5 (3-7)</td>
<td>0.58</td>
</tr>
<tr>
<td>Karnofsky performance score – No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 80</td>
<td>87 (97)</td>
<td>89 (94)</td>
<td>0.35</td>
</tr>
<tr>
<td>&lt; 80</td>
<td>3 (3)</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>Total serum bilirubin level§</td>
<td>149 ± 54.5</td>
<td>160 ± 57.9</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Treatment variables</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underwent PBD – No. (%)</td>
<td>5 (6)</td>
<td>92 (97)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Time to surgery (weeks), mean (95% CI)</td>
<td>1.2 (0.9-1.5)</td>
<td>5.1 (4.8-5.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Intraoperative blood transfusion – No. (%)</td>
<td>14 (16)</td>
<td>14 (15)</td>
<td>0.95</td>
</tr>
<tr>
<td>Type of surgical treatment – No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resection</td>
<td>60 (67)</td>
<td>53 (56)</td>
<td>0.19</td>
</tr>
</tbody>
</table>
PBD-associated therapeutic delay and survival

| Palliative bypass procedure or exploration | 29 (32) | 38 (40) |
| No surgery | 1 (1) | 4 (4) |
| Overall complications¶ | 35 (39) | 72 (76) | <0.01 |

Pathological variables – No. (%)**

| Irresectable disease | 29 (33) | 38 (42) | 0.20 |
| Characteristics of resected tumors |
| Pancreatic adenocarcinoma | 47 (78) | 30 (57) | 0.15 |
| Ampullary adenocarcinoma | 7 (12) | 12 (23) |
| CBD adenocarcinoma | 4 (7) | 6 (11) |
| Duodenal adenocarcinoma | 1 (2) | 1 (2) |
| Neuroendocrine tumor | 1 (1) | 1 (1) |
| Cystic tumor | - | 3 (6) |
| Tumor-positive lymph nodes (N1) | 39 (65) | 37 (70) | 0.59 |
| Microscopically residual disease (R1) | 16 (27) | 20 (38) | 0.21 |

*Other than hypertension.
†Body mass index is the weight in kilograms divided by the square of the height in meters.
‡Compared with reported weight 1 year earlier.
§To convert values for bilirubin to milligrams per deciliter, multiply by 0.0584.
¶Related to PBD and/or surgery.

**Numbers and percentages shown for 180 patients who underwent surgery and were diagnosed with frozen section (when not resected), or at pathological investigation (after resection).

ES, early surgery; PBD, preoperative biliary drainage; SD, standard deviation; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; CI, confidence interval; CBD, common bile duct

Figure 1. The distribution of time from randomization to surgery in weeks for patients randomized to ES or PBD
Figure 2 shows the resection versus bypass ratio for the 2 groups, plotted against time from randomization to surgery. Overall diagnoses at pathology in resected patients were not different between the ES and PBD groups ($\chi^2$ test including all pathologic entities, $P = 0.15$), but significantly more patients had pancreatic adenocarcinoma in the ES group ($n = 47; 78\%$) than in the PBD group ($n = 30; 57\%$) ($\chi^2$ test of pancreatic adenocarcinoma vs other diagnoses, $P = 0.01$). After resection, tumor-positive lymph nodes (N1) and microscopically residual disease (R1, defined as microscopic tumor involvement of any dissection or resection plane) were found in similar proportions in the 2 study groups.

**SURVIVAL IN PBD AND ES GROUPS**

Two-year follow-up was complete in 177 (96\%) patients. At the last follow up, 32 patients were still alive of whom 2-year follow-up was complete in 24 (75\%), and 153 patients had died.

One patient had died because of unknown reasons. The cause of death in the other patients was disease-related in all but four. These patients died because of cardiac disease (2), recurrence of colonic cancer with metastasis (1), and metastasized amelanotic melanoma (1). Figure 3 shows the Kaplan-Meier overall survival curve for the entire group of 185 patients. Median survival time was 12.7 months (95\% CI, 10.1-15.3).
In the PBD group, 77 had died (81%) versus 76 in the ES group (84%). The Kaplan-Meier overall survival curves for the 2 study groups are shown in Figure 4. Median survival time after randomization in the PBD group was 12.7 months (95% CI, 8.9-16.6), versus 12.2 months (95% CI, 9.1-15.4) in the ES group. Difference between the survival curves was not statistically significant (log-rank test, $P = 0.91$).

**Figure 3.** Kaplan-Meier overall survival curve of 185 patients with a malignancy

**Figure 4.** Kaplan-Meier overall survival curves of patients with a malignancy who were randomized to ES or PBD
PROGNOSTIC FACTORS FOR SURVIVAL IN PATIENTS UNDERGOING SURGICAL TREATMENT

The results of the uni- and multivariable analysis of prognostic factors for overall survival in all operated patients are given in Table 2. Displayed are the hazard ratios and their 95% CIs. In univariable analysis, resection of tumor had a significant protective effect on survival, whereas a higher bilirubin at the time of randomization was associated with worse survival.

Multivariable Cox regression analysis also demonstrated that resection of tumor and high bilirubin at the time of randomization were significant factors for overall survival. In addition, the occurrence of complications related to PBD or surgery was found to be significantly associated with worse survival. Taking other prognostic factors into account, patients with a longer delay between randomization and surgery had a slightly lower mortality (hazard ratio [HR] = 0.91, per increment of 1 week, 95% CI, 0.84-0.99).

Table 2. Uni- and multivariable analysis of predictive factors for overall survival in 180 patients who underwent surgery for a malignancy of the pancreatic head

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Time from randomization to surgery, 1-wk increment</td>
<td>0.98 (0.92-1.05)</td>
<td>0.91 (0.84-0.99)*</td>
</tr>
<tr>
<td>Age, 1-year increment*</td>
<td>1.00 (0.98-1.02)</td>
<td>1.00 (0.98-1.01)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.06 (0.76-1.48)</td>
<td>1.26 (0.87-1.80)</td>
</tr>
<tr>
<td>Bilirubin at randomization (quartiles), 1-quart. increment</td>
<td>1.17 (1.01-1.35)*</td>
<td>1.22 (1.04-1.43)*</td>
</tr>
<tr>
<td>Underwent PBD</td>
<td>0.90 (0.65-1.24)</td>
<td>NA</td>
</tr>
<tr>
<td>Resection of tumor</td>
<td>0.32 (0.23-0.46)**</td>
<td>0.28 (0.20-0.41)**</td>
</tr>
<tr>
<td>Intraoperative blood transfusion</td>
<td>1.10 (0.71-1.71)</td>
<td>1.25 (0.79-1.98)</td>
</tr>
<tr>
<td>Complications related to PBD and/or surgery</td>
<td>1.09 (0.79-1.51)</td>
<td>1.45 (1.01-2.09)**</td>
</tr>
</tbody>
</table>

*At the time of surgery.
**Significant at P < 0.05 level.
***Significant at P < 0.01 level.

HR, hazard ratio; CI, confidence interval; PBD, preoperative biliary drainage; NA, not applicable

SURVIVAL AFTER RESECTION

In the ES group, 60 (67%) of 89 patients underwent resection versus 53 (58%) of 91 patients in the PBD group (P = 0.20). Of resected specimens, 44 (73%) were R0-resections in the ES group, versus 33 (62%) in the PBD group (P = 0.21).
Two-year follow-up was complete in 105 of 113 resected patients (93%). At last follow-up, 82 (73%) patients had died. In the PBD group, 35 (66%) of 53 resected patients had died versus 47 (78%) of 60 resected patients in the ES group. Figure 5 shows the Kaplan-Meier survival curves up to 3 years for patients in the 2 study groups who underwent resection. Median survival times were 21.6 months (95% CI, 10.1-33.2) in the PBD group and 17.8 (95% CI, 11.7-24.0) months in the ES group. The difference in survival was not significant (log-rank test, \( P = 0.25 \)). Median survival times for resected pancreatic and periampullary adenocarcinomas were 15.2 months (95% CI, 10.3-20.2) and 44.7 months (95% CI, 17.3-72.1), respectively (\( P < 0.01 \)).

![Figure 5. Kaplan-Meier overall survival curves of patients with a malignancy who were randomized to ES or PBD and underwent resection of the tumor](image)

**Figure 5.** Kaplan-Meier overall survival curves of patients with a malignancy who were randomized to ES or PBD and underwent resection of the tumor

**PROGNOSTIC FACTORS FOR SURVIVAL AFTER RESECTION**

In univariable analysis of patients who had undergone resection (\( n = 113 \)), the following clinicopathological characteristics were significantly associated with worse overall survival after surgery: high bilirubin at randomization, pancreatic...
adenocarcinoma (compared with other malignancies), the presence of tumor-positive lymph nodes, and microscopically residual disease (Table 3). These variables were entered into a multivariable Cox regression model, alongside age and sex, time from randomization to surgery, and overall complications related to PBD or surgery. Need for intraoperative blood transfusion was not entered into the model because of the low number of events. Multivariable Cox regression analysis showed that time to surgery, total serum bilirubin at randomization, pancreatic adenocarcinoma, tumor-positive lymph nodes, microscopically residual disease, and overall complications related to PBD or surgery were significant factors for overall survival. Taking all other prognostic factors into account, patients with a longer delay to surgery had a slightly lower mortality (HR = 0.85, per increment of 1 week, 95% CI, 0.75-0.96).

Table 3. Uni- and multivariable analysis of predictive factors for overall survival after resection of a malignancy of the pancreatic head in 113 patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Time from randomization to surgery, 1-wk increment</td>
<td>0.92 (0.83-1.01)</td>
<td>0.85 (0.75-0.96)$</td>
</tr>
<tr>
<td>Age, 1-year increment*</td>
<td>1.00 (0.98-1.03)</td>
<td>1.00 (0.97-1.02)</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.06 (0.68-1.66)</td>
<td>1.01 (0.64-1.60)</td>
</tr>
<tr>
<td>Bilirubin at randomization (quartiles), 1-quart. increment</td>
<td>1.29 (1.05-1.57)$</td>
<td>1.26 (1.02-1.54)$</td>
</tr>
<tr>
<td>Intraoperative blood transfusion</td>
<td>1.37 (0.81-2.32)</td>
<td>NA</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma†</td>
<td>2.22 (1.34-3.69)$</td>
<td>1.72 (1.00-2.96)$</td>
</tr>
<tr>
<td>Tumor-positive lymph nodes (N1)</td>
<td>2.63 (1.54-4.49)$</td>
<td>2.04 (1.15-3.62)$</td>
</tr>
<tr>
<td>Microscopically residual disease (R1)</td>
<td>2.93 (1.87-4.59)$</td>
<td>2.11 (1.28-3.50)$</td>
</tr>
<tr>
<td>Complications related to PBD and/or surgery</td>
<td>1.30 (0.82-2.04)</td>
<td>1.97 (1.18-3.27)$</td>
</tr>
</tbody>
</table>

*At the time of surgery.
†Reference category: other malignancies.
‡Significant at P < 0.05 level.
§Significant at P < 0.01 level.

HR, hazard ratio; CI, confidence interval; PBD, preoperative biliary drainage; NA, not applicable
SURVIVAL AFTER PALLIATIVE SURGERY

At last follow-up, 1 patient (2%) with irresectable disease was still alive, 27.6 months after randomization. In Figure 6, the Kaplan-Meier survival curves of the 2 study groups are shown for patients with irresectable disease at surgery (log-rank test, $P = 0.94$). Median survival time for patients with irresectable disease in the PBD group was 7.5 months (95% CI, 4.5-10.5) versus 9.4 months (95% CI, 6.1-12.7) in the ES group.

Figure 6. Kaplan-Meier overall survival curves of patients with a malignancy who were randomized to ES or PBD, and underwent a palliative bypass procedure

DISCUSSION

This is the first randomized study of survival after PBD, followed by surgery compared with surgery alone, in patients with obstructive jaundice due to cancer in the pancreatic head region. The primary aim of this analysis was to investigate whether PBD, and the associated delay in surgery, does impair overall survival rate in patients with a malignant lesion. We found that PBD, with an associated delay in surgery of 4...
weeks, had no effect on overall survival rate, as compared with surgery alone.

The median survival times of the ES and PBD groups, 12.2 and 12.7 months respectively, were comparable. Resection rates were 58% in the PBD group versus 67% in the ES group. Of the resected specimens, 73% were R0 resections in the ES group versus 62% in the PBD group. Both these findings did not reach statistical significance, although they can be considered clinically relevant. Most studies on PBD included only resected patients, to compare postoperative morbidity of pancreatic resection, and did not mention the resection rate in patients with a malignancy. However, the resection rate may be of importance from the perspective of long-term survival in the whole population with potentially resectable tumors. In this study, overall resection rate in operated patients was rather low (63%) but still in accordance with current literature. The difference in resection rates did not lead to different survival rates in the 2 treatment groups.

The median survival times after resection of 21.6 months in the PBD group and 17.8 months in the ES group are irrespective of underlying pathology. The fact that resected patients of the ES group contained significantly more pancreatic adenocarcinomas than the PBD group is likely to have influenced survival times in the 2 study groups. It is well accepted that survival following pancreatoduodenectomy for pancreatic or periampullary tumors is closely related to the histopathological origin and biological behavior of the underlying disease. The median survival times in resected pancreatic adenocarcinoma (15.2 months) and resected periampullary adenocarcinomas (44.7 months) are in line with those in previously published reports. Median survival time in patients who were found to be irresectable at surgery (8.1 months) is in close accordance with previous studies.

We found that in the entire group of patients who underwent surgical treatment, time to surgery was associated with survival, with patients with a longer delay having better survival. Resection of the tumor, high bilirubin levels at randomization, and the occurrence of complications related to PBD or surgery were other prognostic factors for survival rate. In patients who underwent resection, longer delay to surgery was also associated with slightly better survival. Other prognostic factors in resected patients for survival rate were high bilirubin at randomization, pathological diagnosis of pancreatic adenocarcinoma, the presence of tumor-positive lymph nodes, microscopically residual disease, and the occurrence of complications related to PBD or surgery.
The association between longer delay in surgery and better survival in all patients who underwent surgery was not adjusted for pathologic entity, because patients with irresectable disease were also included in this group. This finding may have been influenced by the significantly higher number of pancreatic adenocarcinomas in resected patients of the ES group, leading to earlier resection of these tumors with worse prognosis.

High serum total bilirubin at randomization was also found to be prognostic for overall survival, both in all patients undergoing surgical treatment and in resected patients. This relationship has earlier been identified in periampullary tumors but was not found in pancreatic adenocarcinoma.21-23

Tumor-positive lymph nodes and microscopically residual disease were found to be associated with survival after resection. These associations have been extensively described before for both pancreatic adenocarcinoma and periampullary carcinoma; in pancreatic adenocarcinoma, the achievement of a margin-negative R0 resection has been demonstrated to be the most significant predictor for long-term survival, whereas for periampullary carcinoma positive lymph node status is highly predictive of a dismal outcome.22,24-29

We found that the occurrence of complications related to PBD or surgery is associated with worse survival. Postoperative complications have earlier been recognized as a prognostic factor for long-term survival after resection for pancreatic and periampullary cancer.21-24 Similar findings have been described in oral cancer, colorectal cancer and esophageal cancer.26-32 A possible explanation for this phenomenon is the presence of residual viable tumor cells, especially at anastomotic sites, combined with a systemic inflammatory response leading to the release of proinflammatory cytokines and growth factors and an associated immunosuppression, which may stimulate the growth of these residual tumor cells.31,32

Preoperative biliary drainage was originally performed to improve hepatic function, nutritional status, and immune response, and to reduce the risk of postoperative complications.2-31 The optimal duration of therapeutic biliary drainage to reverse major metabolic abnormalities associated with severe jaundice is unclear.2,5 A short period of drainage does not lead to full recovery, whereas a too extensive period risks stent occlusion and secondary inflammation of the bile duct wall.34,35 In our randomized trial, we aimed for 4 to 6 weeks of biliary drainage. Although early studies showed improved postoperative mortality in jaundiced patients after PBD,
other studies found no beneficial effects of the procedure. In the total patient cohort of this study, we showed that PBD of 4 to 6 weeks leads to more complications than surgery alone and should not be routinely performed. However, the majority of patients with obstructive jaundice referred to our hepatopancreatobiliary department have already undergone biliary drainage, as is the current situation in many other institutions. Apart from the change in referral pattern that is needed for an ES strategy, the difficulty to schedule such a complex operation within a week may hamper the introduction of an ES strategy in daily practice. When ES is not feasible, one may still have to opt for a strategy with PBD. Although this study was not powered to detect differences in survival, the almost identical Kaplan-Meier survival curves of the 2 study groups show that the delay in surgical therapy associated with PBD has no negative effect on survival.

In conclusion, PBD followed by surgery does not impair long-term overall survival in patients with obstructive jaundice due to cancer in the pancreatic head region, as compared with surgery alone. PBD does not offer a survival benefit either. Considering the risk of procedural complications, ES remains the treatment of choice.
REFERENCES


Chapter 3


