Genes and surgery in pancreatic cancer
van Heek, N.T.

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The need for a prophylactic gastrojejunostomy for unresectable periampullary cancer

A prospective randomized multi-center trial with special focus on assessment of quality of life

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Background
Several studies including one randomized trial propagate to perform a prophylactic gastrojejunostomy routinely in patients with periampullary cancer found to be unresectable during laparotomy. Others suggest an increase of postoperative complications. Controversy still exists in general surgical practice if a double bypass should be performed routinely in these patients. The aim of the study was to evaluate the effect of a prophylactic gastrojejunostomy on the development of gastric outlet obstruction and quality of life in patients with unresectable periampullary cancer found during explorative laparotomy.

Methods
Between December 1998 and March 2002, patients with a periampullary carcinoma who were found to be unresectable during exploration were randomized to receive a double bypass (hepaticojejunostomy and a retrocolic gastrojejunostomy) or a single bypass (hepaticojejunostomy). Randomization was stratified for center and presence of metastases. Patients with gastrointestinal obstruction and patients treated endoscopically for more than 3 months were excluded. Primary endpoints were development of clinical gastric outlet obstruction and surgical intervention for gastric outlet obstruction. Secondary endpoints were mortality, morbidity, hospital stay, survival and quality of life, measured prospectively by the EORTC-C30 and Pan26 questionnaires. It was decided to perform an interim analysis after inclusion of 50% of the patients (n=70).

Results
Five of the 70 patients randomized were lost to follow-up. From the remaining 65 patients, 36 patients underwent a double, and 29 a single bypass. There were no differences in patient demographics, preoperative symptoms and surgical findings between the groups. Clinical symptoms of gastric outlet obstruction (GOO) were found in two of the 36 patients (5.5%) with a double bypass, and in 12 of the 29 patients (41.4%) with a single bypass (p=0.001). In the double bypass group one patient (2.8%) and in the single bypass group 6 patients (20.7%) required (re-) gastrojejunostomy during follow-up (p=0.04). The absolute risk reduction (ARR) for re-operation in the double bypass group was 18%, and the numbers needed to treat (NNT) was 6. Postoperative morbidity rates, including delayed gastric emptying, were 31% in the double versus 28% in the single bypass group (p=0.12). Median postoperative length of stay was 11 (4-76) days in the double versus 9 (6-20) days in the single bypass group (p=0.06); median survival was 7.2 months in the double versus 8.4 months in the single bypass group (p=0.15). No differences were found in the quality of life between both groups. After surgery most quality of life scores deteriorated temporarily and were restored to their baseline score (t=-1) within four months.

Conclusions
Prophylactic gastrojejunostomy significantly decreases the incidence of gastric outlet obstruction without increasing complication rates. There were no differences in quality of life between the two groups. Together with the previous randomized trial from the Hopkins group this study provides sufficient evidence to state that a double bypass consisting of a hepaticojejunostomy and a prophylactic gastrojejunostomy is preferable to a single bypass consisting of only a hepaticojejunostomy in patients undergoing surgical palliation for unresectable periampullary carcinoma. Therefore, the trial was stopped earlier than planned.
INTRODUCTION

Of the patients with periampullary tumors who undergo exploratory surgery with the intention to perform a pancreaticoduodenectomy, 25% to 75% are found to have unresectable disease. Appropriate palliation of the main symptoms obstructive jaundice, duodenal obstruction and pain, is of major importance in these patients.

Since 70% of the patients with periampullary carcinoma presents with jaundice, adequate biliary drainage is essential for palliation. Non-surgical options include the percutaneous or endoscopic insertion of endoprostheses. Surgical options include internal drainage by means of a biliodigestive bypass, which is suggested to be treatment of choice in patients in a reasonable to good physical condition and a life expectancy of at least 3 to 6 months. However, especially after relatively long survival, 10% - 20% of patients develop gastroduodenal obstruction after a biliary-digestive bypass alone, as demonstrated by retrospective reviews of surgical series. In a recent prospective randomized study it was even shown that patients with metastases found during explorative laparotomy in patients scheduled for resection should preferably be treated with a surgical bypass instead of stenting. In order to prevent gastroduodenal obstruction, a prophylactic gastroenterostomy has been advised during the same surgical procedure. In a prospective randomized controlled trial from the Johns Hopkins group published shortly after starting the present trial, it was concluded that a gastrojejunostomy should be performed routinely when a patient is undergoing surgical palliation for unresectable periampullary carcinoma.

However, it can be questioned whether results from one center of excellence in a selected group of patients can be generalized. Others showed disadvantages of adding a gastrojejunostomy to the operation. In a study from the Netherlands it was shown that a double bypass did increase morbidity and even mortality. Another well known complication after prophylactic gastrojejunostomy is delayed gastric emptying, varying from 2% to 14%, which might increase the complication rate after a double bypass. Therefore a double bypass is not yet generally accepted as standard treatment.

Quality of life (QoL) was not addressed from a patient perspective by means of questionnaires in the trial from Hopkins. Health-related QoL may be informative especially in trials of advanced-stage cancer comparing different palliative treatments with limited effects on survival gain and tumor response. There is accumulating evidence to suggest that QoL scores have prognostic value. We have therefore conducted this randomized study with special focus on assessment of QoL. The aim was to evaluate the effect of a prophylactic gastrojejunostomy in patients undergoing bilioldigestive anastomosis for unresectable periampullary carcinoma in a multi-center trial. Because the results from the previous mentioned randomized controlled trial from the Hopkins group were published shortly after the start of the present study, it was decided to perform an interim analysis after the inclusion of 50% of the patients (n=70).
Patients

Patients with unresectable disease found during surgical exploration with the intention to perform a resection in the Academic Medical Center Amsterdam, the University Hospital Dijkzigt in Rotterdam, and two general Dutch hospitals between December 1998 and March 2002, were considered for inclusion in this trial. After perioperative finding of metastases or ingrowth in major visceral vessels they were randomized for a double bypass (hepaticojejunostomy and a retrocolic gastrojejunostomy) or a single bypass (hepaticojejunostomy alone). Randomization was centralized in the Academic Medical Center Amsterdam, with stratification for center and the presence of metastases.

The primary endpoint was signs and symptoms of GOO and surgical intervention for GOO. Secondary endpoints were mortality, morbidity including postoperative delayed gastric emptying, hospital stay, survival and QoL. Inclusion criteria were unresectable periampullary cancer and biliary obstruction during explorative laparotomy. Exclusion criteria were upper gastrointestinal surgery in history, endoscopic treatment for longer than 3 months, presentation with gastric or duodenal obstruction, no cytological or histological prove of malignancy, and tumor-positive ascites. This study was approved by the Medical Ethical Committees of the Academic Medical Center Amsterdam and by the three other centers involved. Patients with a periampullary tumor who were scheduled to undergo an exploratory laparotomy with the intention to perform a pancreaticoduodenectomy were asked written informed consent in the four participating centers.

The sample size was calculated based on data from the literature. Between 20% and 30% of the patients will develop GOO after biliodigestive bypass for unresectable periampullary cancer, whereas approximately 7% of the patients that receive a biliodigestive bypass and a prophylactic gastrojejunostomy for unresectable periampullary cancer will develop GOO as reported previously. With an $\alpha=0.05$ and a power of $0.8 (\beta=0.2)$, the number of patients needed for each group is 62. Assuming a drop out of 10%, the sample size is 140. Because the randomized controlled trial of the Hopkins group was published shortly after the start of this study demonstrating a significant lower incidence of late GOO in patients with a prophylactic gastrojejunostomy, there was an extensive discussion among the participating centers if the trial should be continued. It was decided to continue but to perform an interim analysis at 50% inclusion of the patients (n=70) in order to decide whether continuing inclusion was justifiable.

Definitions

The term periampullary tumors used in this study comprised pancreatic carcinoma, bile duct carcinoma, and ampullary carcinoma. Unresectable cancer was defined as pathologically proven local invasion of major visceral vessels or metastases shown during explorative surgery. Biliary
obstruction was defined as clinical jaundice with impaired liver function (>2x normal range). Gastric outlet obstruction (GOO) was defined as clinical symptoms of obstruction, like nausea and vomiting, in combination with radiological or endoscopic proof of gastric retention or stenosis. Delayed gastric emptying was defined as stomach drainage for longer than 10 days postoperatively or intolerance for normal food intake for longer than two weeks postoperatively, as reported previously.¹⁹

Surgical procedure
Patients were randomized during surgery after the surgeon found local unresectability or metastases without the presence of imminent duodenal obstruction. Patients received either a retrocolic gastrojejunostomy or no gastrojejunostomy. A hepaticojejunostomy, cholecystectomy and chemical splanchnicectomy with 50% ethanol were performed routinely. Feeding jejunostomies were only used in a few patients (<10%) with severe malnutrition. Histological confirmation of the diagnosis was obtained in all patients. Postoperative chemo- and / or radiotherapy was employed selectively based on the recommendations of a multidisciplinary team from the different hospitals and the patient’s preference.

Data collection
Data were collected prospectively on all patients, including demographics, history, physical examination, surgical findings, and out-patient clinical information. Data collection and follow-up were completed through December 2002 on all patients, based on forms filled in during regularly scheduled visits at the outpatient clinic and interviews by telephone with the general physician or the patient’s family.

Quality of life
For prospective measurement of QoL, the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ-C30, version 2.0, EORTC Study Group on Quality of Life, Brussels, Belgium)²⁰ and the pancreatic cancer module (QLQ-PAN26)²¹ were used. The validated EORTC QLQ-C30 questionnaire is developed to assess the health-related QoL of cancer patients participating in international clinical trials.²¹ It comprises 30 items relating to symptoms, physical status, working ability, and emotional, cognitive, and social functioning, as well as a global quality of life scale. The validity has been shown previously.²⁰ ²² ²⁴ The QLQ-PAN26 is a disease specific module designed to administer together with the general QLQ-C30. It can be used for patients at all disease stages undergoing surgical resection, palliative surgical intervention, endoscopic palliation or palliative chemotherapy.²⁵ This model comprises 26 questions assessing pain, dietary changes, altered bowel habit, related emotional problems, and other symptoms (cachexia, indigestion, flatulence, dry mouth, taste changes). These two questionnaires were prospectively assessed at
different time points during the study. Baseline measurement (t = -1) was performed after admission in the hospital on the day before surgery. The first postoperative questionnaire was filled in on the day of discharge (t = 0). Following questionnaires were sent monthly to the patients at home and returned by mail (t = 1, 2, 3, ...).

A hypothesis was formulated concerning the scales most likely to reveal an effect of two major endpoints GOO and DGE, and most likely to show a potential difference between both groups. We assumed that the global health status, the physical and emotional functioning and the pain score of the QLQ-C30, together with all gastrointestinal symptom scales of both the QLQ-C30 and the QLQ-Pan26 would give appropriate information. For this last purpose an overall digestive symptoms scale including the following scales was created including nausea and vomiting, appetite loss, constipation, and diarrhoea from the QLQ-C30, as well as digestive, altered bowel habits, flatulence, and gastrointestinal symptoms from the QLQ-Pan26.

Statistical analysis
Statistics were performed using the SPSS Base 11.0 for Windows Statistical Software Package (SPSS, Chicago, IL). All results are given as mean (SD) or median and ranges. Differences between the two groups were compared using the Fisher's exact test, and differences between means were compared using the Student’s t test. Length of survival in the two groups was compared using the log-rank test. Statistical significance was set at p < 0.05.

Standard scoring algorithms were followed for QLQ-C30 and QLQ-Pan26. We performed two different analyses. In the first analysis we used the available data only without imputing missing data. In the second analysis we adopted an imputation technique carrying the last QoL value forward to the next occasion. All scores were linearly converted to a scale of 0-100. The non-imputed QoL scales were presented graphically for the postoperative phase up to 12 months after date of surgery. To investigate whether QoL differed for both groups shortly before death, an analysis was performed as presented in the studies by Morris, in which death was considered time point 0 and the questionnaires before death were renamed as last before death, second last before death and so on. The mean score, SD and comparison of the two groups were calculated for each scale at each time point.

Study population
Of the 70 patients randomized at time of the interim analysis, pathology was revised in two patients and three patients were lost to follow-up. In one patient definite pathology revealed a benign tumor. In the other patient revision of the frozen section from a liver biopsy taken during explorative laparotomy revealed active inflammation in stead of adenocarcinoma, and a pylorus preserving
pancreaticoduodenectomy (PPPD) was performed subsequently. From the remaining 65 patients, 36 patients (55%) were treated by a double bypass and 29 patients (45%) by a single bypass. The two groups were comparable for patient demographics, pre- and peroperative findings, but not for gender (Table 1). More men than women received a double bypass for unresectable periampullary cancer, while it appeared to be the opposite in the single bypass group (p=0.026). The mean age in both groups was not different, obstructive jaundice was the most common preoperative symptom with 78% in the double bypass group, and 79% in the single bypass group.

Table 1 Patient demographics and preoperative and peroperative findings

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Double bypass n = 36</th>
<th>Single bypass n = 29</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academic centers (n=2)</td>
<td>28 (78%)</td>
<td>24 (83%)</td>
<td>0.44</td>
</tr>
<tr>
<td>General centers (n=2)</td>
<td>8 (22%)</td>
<td>5 (17%)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>63 ± 9</td>
<td>65 ± 8</td>
<td>0.28</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (67%)</td>
<td>11 (38%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Female</td>
<td>12 (33%)</td>
<td>18 (62%)</td>
<td></td>
</tr>
<tr>
<td>Preoperative symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea / vomiting *</td>
<td>10 (28%)</td>
<td>7 (24%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>18 (50%)</td>
<td>15 (52%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Weight loss</td>
<td>24 (67%)</td>
<td>17 (59%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic head</td>
<td>32 (89%)</td>
<td>25 (86%)</td>
<td>0.74</td>
</tr>
<tr>
<td>Distal common bile duct</td>
<td>4 (11%)</td>
<td>2 (7%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Ampulla</td>
<td>-</td>
<td>2 (7%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Unresectability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local vascular invasion</td>
<td>19 (53%)</td>
<td>15 (52%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Metastases</td>
<td>16 (44%)</td>
<td>13 (45%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Both</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

* Preoperative symptoms of nausea and vomiting were not caused by gastric outlet obstruction

Based on preoperative evaluation and surgical findings, the head of the pancreas was the predominant site of origin of the tumor: 89% of the tumors in the double, and 86% of the tumors in the single bypass group. Since randomization took place for the presence of metastases, the reason for unresectability was equally divided among both groups (table 1).

Short-term outcome
Mortality, morbidity and length of hospital stay for both treatment groups are listed in table 2. There were no perioperative deaths. A 72 year old man died in the hospital 24 days after the double bypass procedure. He had been suffering for three weeks from a iatrogenic bleeding and subsequent intra-abdominal abscesses after a staging laparoscopy before exploration and a bypass procedure were performed.
Table 2  Short-term outcome, length of hospital stay, and adjuvant therapy

<table>
<thead>
<tr>
<th></th>
<th>Double bypass n = 36</th>
<th>Single bypass n = 29</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital</td>
<td>1 (3%)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Morbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any complication</td>
<td>11 (31%)</td>
<td>8 (28%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Wound infection</td>
<td>3 (8%)</td>
<td>1 (3%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Biliary anastomotic leakage</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>GI leakage</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Cardiac</td>
<td>4 (11%)</td>
<td>2 (7%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Intra-abdominal bleeding</td>
<td>0</td>
<td>1 (3%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>6 (17%)</td>
<td>1 (3%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median</td>
<td>411 (4-76)</td>
<td>9 (6-20)</td>
<td>0.06</td>
</tr>
<tr>
<td>range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo- and radiotherapy</td>
<td>14 (39%)</td>
<td>12 (41%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>4 (11%)</td>
<td>3 (10%)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>1 (3%)</td>
<td>1 (4%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>17 (47%)</td>
<td>13 (45%)</td>
<td></td>
</tr>
</tbody>
</table>

At least one complication was found in 11 patients (31%) after double bypass and in 8 patients (28%) after single bypass. Delayed gastric emptying was the most frequent complication (17%) after double bypass, but only seen in one patient (3%) after single bypass (p=0.12). The incidence of biliary and gastrojejunai anastomotic leak was the same in both groups. The median postoperative length of stay in hospital was 11 (4-76) days in the double bypass group, and 9 (6-20) days in the single bypass group (p=0.06).

Figure 1  Kaplan-Meier survival curve for all included patients (n=65) with periampullary carcinoma found to be unresectable during explorative laparotomy. A double bypass was performed in 36 patients with a median survival of 7.2 (1-19) months, and a single bypass was performed in 29 patients with a mean survival of 8.5 (3-20) months (p=ns).
Survival and long-term outcome
There was no significant difference in the median survival between the double and the single bypass group: 7.2 and 8.4 months, respectively (p=0.15) (figure 1).

During follow-up clinical gastric outlet obstruction (GOO) was diagnosed in two of the 36 patients (5.5%) after double bypass, and in 12 of the 29 patients (41.4%) after single bypass (p=0.001). After double bypass one patient with GOO (2.8%) underwent relaparotomy and revision of the gastrojejunostomy. After single bypass 6 of the 12 patients with GOO (20.7%) underwent relaparotomy and a gastrojejunostomy was performed (p=0.04). The median time interval between initial exploration and late gastrojejunostomy was 3.5 months. Absolute risk reduction (ARR) for re-operation by performing a double bypass was 18%, and the numbers needed to treat (NNT) was 6.

Quality of life
Compliance with questionnaire completion was comparable in the double and the single bypass group. The compliance rate in both groups was over 90% in the first 4 months after surgery and decreased to 75% in the last two months of the terminal phase. Outcomes of QoL assessment were independent of the analysis used. The QoL

Figures 2A-E QoL graphs representing the 12 months after surgery of the patients randomized to receive a double or a single bypass. Left side of graph represents time of operation. The non-imputed data of the following subscales are presented:
- (A) Global health status
- (B) Physical functioning
- (C) Emotional functioning
- (D) Pain
- (E) Digestive symptoms

Error bars show 95.0% CI of mean
Lines show means
scales based on non-imputed data are shown in figures 2A-E by means of a graph with error bar (confidence interval for mean 95%) for each scale. Overall, no major differences were seen in QoL between the two surgical treatment groups. Patients in both groups showed a similar course in the scores for all scales and did not differ from each other significantly at most points in time. On the day of discharge (t=0), both groups showed a significant decrease in all functional scales except the physical functioning compared to the preoperative status. The symptom variables pain and digestive symptoms were significantly more pronounced after both surgical procedures. Overall, the QoL scores were stable over the course of the study for patients in both groups. All scales came back to their original baseline score (t=-1) within 4 months and remained so throughout follow-up.

In figures 3A-E the terminal phase of the last 6 months is represented in a graph for the five subscales of QoL in both groups. The time of death is on the right side of the graph. No differences in QoL were seen in the months before death between the two groups. In both groups the global health status and emotional functioning score decreased rapidly during the last 2 months before death.

**Figures 3A-E** QoL graphs representing the terminal phase (6 months before death) of the patients randomized to receive a double or a single bypass. Right side of the graph represents death. The non-imputed data of the following subscales are presented:

- (A) Global health status
- (B) Physical functioning
- (C) Emotional functioning
- (D) Pain
- (E) Digestive symptoms

Error bars show 95.0% CI of mean
Lines show means
Table 3 Long-term outcome and survival

<table>
<thead>
<tr>
<th></th>
<th>Double bypass n = 36</th>
<th>Single bypass n = 29</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric outlet obstruction</td>
<td>2 (6%)</td>
<td>12 (41%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Clinical re-operation needed</td>
<td>1 (3%)</td>
<td>6 (21%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Survival (months) median</td>
<td>7.2</td>
<td>8.4</td>
<td>0.15</td>
</tr>
</tbody>
</table>

DISCUSSION

The outcome of this prospective randomized controlled trial gives further support to the strategy to routinely perform a retrocolic gastrojejunostomy in patients undergoing a palliative bilidigestive bypass for unresectable periampullary cancer found during explorative laparotomy. Prophylactic gastrojejunostomy added to a hepaticojejunostomy significantly decreases the incidence of late GOO and relaparotomies without increasing the incidence of postoperative complications. Patients do not report differences in QoL after receiving a double or a single bypass. Hospital stay was slightly longer for the patients with a double bypass (11 days) than for the patients with a single bypass (9 days), although not statistically significant (p=0.06). We can conclude from this study that patients who are found to have an unresectable tumor at laparotomy for periampullary cancer are preferably treated by a hepaticojejunostomy and prophylactic gastrojejunostomy compared to a hepaticojejunostomy alone.

In patients with unresectable periampullary cancer palliation of obstructive jaundice, duodenal obstruction and pain is of primary importance, preferably with a short hospital stay, maximal survival, and optimal QoL.5,6 Palliation of obstructive jaundice by nonsurgical techniques is the treatment of choice when unresectable cancer is already found during diagnostic work-up, in particular in patients with an expected short survival. Endoscopic and percutaneous biliary stenting are successful modalities, although recurrent cholangitis due to stent occlusion is a well known problem despite all efforts to prevent this very common complication.29,30 Fit patients will benefit from palliative surgery that allows long-lasting biliary drainage,5,33 and biliary bypass procedures can be undertaken nowadays with acceptable rates of morbidity and mortality.34,36 In a trial on diagnostic laparoscopy, performed before the present study, surgical palliation proved to be superior to stenting in patients with an unresectable tumor found during laparotomy with the intention to perform a resection.10 To add a "prophylactic" gastrojejunostomy to the biliary bypass procedure is based on the relatively high incidence of GOO that has been reported during follow-up.37,38 The reluctance to perform a prophylactic gastroenterostomy routinely is based on the occurrence of additional postoperative complications; DGE and gastrointestinal bleeding have been
reported.\textsuperscript{39-40} In the principle of "non nocere" surgery should have a minimal risk of postoperative complications especially in these patients with palliative treatment.

Earlier studies on surgical gastroenterostomy reported postoperative morbidity and mortality rates from 5 to 41\% and 11\% to 33\% respectively.\textsuperscript{14} In one study it was stated that the need for a gastrojejunostomy due to GOO was associated with a poor outcome and had little role in the management of patients with pancreatic cancer.\textsuperscript{39} However, death was their only endpoint.\textsuperscript{39} In a more recent study it has been suggested that patients with unresectable periampullary cancer do not survive long enough to develop a gastrointestinal obstruction and there would be no need for a prophylactic gastrojejunostomy.\textsuperscript{41} In a retrospective study from the Memorial Sloan Kettering Cancer Center the perioperative morbidity rate increased significantly without prolonging survival by the addition of a prophylactic gastric bypass.\textsuperscript{45}

More recently, proponents of the prophylactic gastrojejunostomy observed that the concomitant biliary and gastric bypass did not increase the operative morbidity and mortality.\textsuperscript{11,34,36,43-45} Also mortality of subsequent gastric bypass added to initial single bypass could be as high as 25\%, whereas the incidence of subsequent GOO in those without gastric bypass was 10\%.\textsuperscript{46} The Johns Hopkins group was the first to show the benefits of a routinely performed prophylactic gastrojejunostomy in a randomized trial,\textsuperscript{11} but controversy still exists in general surgical practice. The fact that the study was performed in a highly specialized referral center in the United States is probably a reason to doubt whether the findings in a selected group of referred patients can be generalized.\textsuperscript{3} The relatively high incidence of patients with tumors located in the uncinate process could also influence the occurrence of GOO because of their location related to the duodenum. In the present multi-center trial 42\% suffered from symptoms of GOO and 21\% of the patients after a single bypass and 3\% of the patients after a double bypass had to undergo a gastrojejunostomy in a later phase of their life. It would have been ideal to let an independent observer decide whether the patient needed a re-laparotomy for GOO, however, this was not feasible, and the decision was made by the local surgeons. Although late GOO could be the result of functional disturbance rather than an organic obstruction, functional outcome is the most important outcome in patients undergoing palliative surgery for periampullary cancer. Six patients needed a double bypass in order to prevent one patient from undergoing a re-operation (ARR=18\% and NNT=6). Operative morbidity and mortality were not significantly different. The limited, not significant differences in survival were probably due to the male / female ratio, a well known risk factor.\textsuperscript{47}

As discussed earlier, we decided immediately after the start of this study to perform an interim analysis after inclusion of 50\% of the patients (n=70) because of the publication of the first randomized trial from the Johns Hopkins Hospital.\textsuperscript{11} At that time (1999) there was even a discussion if this second trial should be performed or stopped immediately. There was agreement to continue,
to perform an interim analysis, and to stop if a significant difference was found in the primary endpoint (GOO) towards the same direction as the Hopkins trial. Because the outcome of this interim analysis was comparable with the outcome of that trial, the participating centers decided to discontinue the trial accordingly.

A statistician (Prof. dr. P.M. Bossuyt, head of the department of Clinical Epidemiology) was consulted to discuss the proposal of stopping the trial. Regarding the decision in 1999 to perform a interim analysis and the significant difference in primary endpoint comparable to the first randomized trial, he considered stopping the trial justified, realizing that this would reduce the "strength" of the trial and could introduce a type II error. An important aspect of palliative surgery is the quality of the remaining life. Only limited data are available with respect to QoL assessment in patients after surgical palliation for unresectable periampullary cancer. No prospective study has been performed as yet in which QoL was estimated in patients who were treated by two different surgical palliative strategies using a standardized questionnaire. Health-related QoL assessment seeks to measure the impact of the disease process on the physical, psychological and social aspects of the person's life and feeling of well-being.

The EORT QLQ-C30 was used as a valid and reliable instrument for assessing overall QoL in cancer patients, and the QLQ-Pan26 as a disease specific questionnaire. A definite conclusion from this trial is that no major differences were found in the various subscales of QoL between patients after a double bypass and after a single bypass. Both groups showed a temporary decrease in global health status and emotional functioning, and a temporary postoperative increase in pain and digestive symptoms. In the terminal phase two months before death a decrease on most QoL scales was seen as could be expected, but no differences were found between the two groups either. Recovery after both types of surgery was the same. It might be that a negative effect of GOO in the single bypass group is compensated by a relatively early surgical intervention and that other aspects (end stage of disease) influenced QoL more than symptoms.

There are some well-known difficulties associated with the analysis of QoL data in a progressive disease, mostly because of the multidimensional and longitudinal nature of QoL data. In many trials like this one, analysis is complex due to attrition caused by the reduction of patients numbers through death and missing data values due to patient non-compliance at the end stage of the disease. In our study many data were missing in the postoperative follow-up of 12 months due to attrition, because the median survival was 8 months. We chose to report the available non-imputed data and not the imputed non-ignorable missing data, because both analyses revealed the same outcome. Our strategy probably reports an overestimation of QoL towards the end of life, since a number of patients were too weak to fill in the questionnaires at that point. Mentioned restrictions however, are not of great importance for the QoL assessment of both groups, because the aim was to identify differences between two palliative treatments.
In conclusion, this prospective randomized controlled trial confirms that in patients with periampullary cancer found to be unresectable during explorative laparotomy with the intention to perform a resection, a double bypass consisting of a hepaticojejunostomy and a prophylactic gastrojejunostomy is preferable to a single bypass consisting of only a hepaticojejunostomy. The need for re-operation for GOO was significantly reduced without increasing complication rates. The early postoperative decreased quality of life was not additionally jeopardized by the extra bypass. Therefore the trial was stopped earlier than planned.

REFERENCES


