

Guidelines for the Application of Surgery and Endoprosthesis in the Palliation of Obstructive Jaundice in Advanced Cancer of the Pancreas

René P. van den Bosch, M.D.,* George P. van der Schelling, M.D.,* Jean H. G. Klinkenbijn, M.D.,* Paul G. H. Mulder, Ph.D.,† Mark van Blankenstein, M.D.,‡ and Johannes Jeekel, M.D., Ph.D.*

From the Department of General Surgery, University Hospital Dijkzigt, the Department of Epidemiology and Biostatistics, Erasmus University,† and the Section of Gastroenterology, Department of Internal Medicine, University Hospital Dijkzigt,‡ Rotterdam, The Netherlands*

Objective

This study was set up to identify patient-related factors favoring the application of either surgery or endoprosthesis in the palliation of obstructive jaundice in subsets of patients with cancer of the head of the pancreas or periaampullary region.

Summary Background Data

In the palliation of obstructive jaundice, surgical biliodigestive anastomosis has traditionally been performed. Surgical biliary bypass is associated with high mortality (15% to 30%) and morbidity rates (20% to 60%) but little recurrent obstructive jaundice (0% to 15%). Biliary drainage with endoscopically placed endoprosthesis has a lower complication rate, but recurrent obstructive jaundice is seen in up to 20% to 50% of patients.

Methods

Patients with advanced cancer of the head of the pancreas or periaampullary region treated at the University Hospital Dijkzigt, Rotterdam, The Netherlands, between 1980 and 1990 were reviewed. In 148 patients, data were compared concerning the morbidity and hospital stay after the palliation of obstructive jaundice with endoscopic endoprosthesis or surgical biliary bypasses. These patients were stratified for long (> 6 months) and short (< 6 months) survival times.

Results

In short-term survivors, the higher late morbidity rates after endoprosthesis were offset by higher early morbidity rates and longer hospital stays after the surgical bypass. In long-term survivors, there was no difference in the hospital stay between the two groups, but the late morbidity rate was significantly higher in the endoprosthesis group.

Conclusions

These data suggest that endoscopic endoprosthesis is the optimal palliation for patients surviving less than 6 months and surgical biliary bypass for those surviving more than 6 months. This policy necessitates the development of prognostic criteria, which were obtained by Cox proportional-hazards survival analysis. Advanced age, male sex, liver metastases, and large diameters of tumors were unfavorable prognostic factors. With these factors, the risk of short- or long-term

survival can be predicted. It is hoped that the application of these data may allow a rational approach toward optimal palliative treatment of this form of malignant obstructive jaundice.

Of the patients with cancer of the head of the pancreas and periampullary region, 70% to 90% have jaundice as a result of biliary obstruction.¹⁻⁴ Biliary obstruction aggravates the patient's already poor clinical condition by causing cholangitis, pruritus, nutritional deficiencies through malabsorption, weight loss, and progressive hepatic failure.⁴⁻⁶ Surgical resection and reconstruction usually provide adequate biliary drainage, but only 10% to 20% of patients can be treated surgically with an intention to cure.^{4,6-8} Thus, in the majority of patients, palliation is the main goal of treatment in terms of relieving pain, cholestasis, and duodenal obstruction.⁹ To relieve obstructive jaundice, surgical biliodigestive anastomosis has traditionally been performed. The associated high mortality (15% to 30%) and morbidity rates (20% to 60%) have led to the introduction of alternative nonsurgical techniques of biliary drainage.^{6,10-13} Internal drainage of the biliary tree was first described by Pereiras et al.⁵ and Burcharth¹⁴ in 1978. Initially, internal drainage was performed by the percutaneous transhepatic route using small-caliber 6- to 7-French endoprosthesis. This procedure was associated with a considerable complication rate. The use of large-caliber, endoscopically placed endoprosthesis reduced the number of complications.¹⁵⁻¹⁹ However, recurrent obstructive jaundice, which is caused by clogging of the endoprosthesis, still is an unsolved problem. In patients with surgical biliary bypasses, obstructive jaundice recurs in 0% to 15% of cases, depending on the used operative technique.^{3,4,6} Obstructive jaundice recurs in up to 20% to 50% of the patients treated with endoprosthesis.²⁰⁻²³ Although endoscopic replacement of an obstructed endoprosthesis is fairly easy, recurrent obstructive jaundice is the major drawback in the use of endoprosthesis.

Several studies have compared endoprosthesis and surgery in the palliation of malignant biliary tree obstruction.^{13,20-25} No consistent differences in morbidity, mortality, and survival rates were found between the two treatment options. However, patients with longer survival times can be expected to experience recurrent obstructive jaundice when treated with endoprosthesis. Hospital readmissions, jaundice, and cholangitis may impair the quality of life. Long-surviving patients may therefore benefit from a surgical biliary bypass. This study was set up to identify patient-related factors favor-

ing the application of surgery or endoprosthesis in the palliation of obstructive jaundice in subsets of patients with cancer of the head of the pancreas or periampullary region.

PATIENTS AND METHODS

The records of all patients admitted to the University Hospital Dijkzigt, Rotterdam, between January 1980 and December 1990 with cancer of the pancreatic head or periampullary region were reviewed. Patients who had not undergone a resection of the tumor because of local unresectability, distant metastases, or inoperability were included in the study. The diagnosis of pancreatic cancer was confirmed by pancreatic biopsy, biopsy of a metastatic lesion with evidence of a primary lesion in the head of the pancreas, or autopsy. Patients with no histologically proven carcinoma but with obvious signs of cancer of the head of the pancreas, who were identified by radiologic imaging techniques and had a supportive clinical course, were also included as were patients who had undergone adjuvant therapy. The eligible patients were divided into four groups: (1) a group with no biliary drainage, (2) a group with surgical biliary bypasses, (3) a group with endoscopic endoprosthesis, and (4) a group of patients in whom only percutaneous transhepatic or nasobiliary drainage was performed. Patients with surgical biliary bypasses who had undergone preoperative biliary drainage with endoprosthesis were included in the group of surgically treated patients. The majority of endoprosthesis were of a 10-French size. In the early years, a 7-French endoprosthesis was sometimes used. A self-expanding stent, which has recently become available, was used in five patients.

Mortality was defined as death within 30 days of the performed procedure. Morbidity in the surgically treated patients manifested itself as postoperative bleeding and leakage from the biliodigestive anastomosis. In the patients treated with endoprosthesis, morbidity consisted of dislocation or obstruction of the endoprosthesis with jaundice and/or cholangitis. In addition, morbidity was divided into early and late morbidity, with early being within 1 week of the performed biliary drainage procedure and late being after more than 1 week. To evaluate the hospitalization in surgically and endoscopically treated patients, we recorded the length of the first hospital admission during which the palliative procedure was performed. The total number of hospital admissions and the total hospitalization time were also recorded. Only hospital admissions for biliary drainage procedures and

Address reprint requests to Professor Dr. J. Jeekel, University Hospital Dijkzigt, Department of General Surgery, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

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its complications were counted; we excluded admissions for chemo- or radiotherapy. The patients were stratified for survival and divided into two groups: (1) one group with a short survival time (< 6 months) and (2) one group with a long survival time (> 6 months). The cutoff point of 6 months approximates the average survival of patients with advanced cancer of the head of the pancreas in this study. The risk of dying within 6 months after the diagnosis was made was calculated with the variables that were found to have a significant influence on survival. These were sex, age, metastases, and the diameter of the tumor at the time of diagnosis. The data on the tumor's diameter at the time of diagnosis were derived from ultrasonography, computed tomography, endoscopic retrograde cholangiopancreatography, or intraoperative observations.

Statistical significance was determined by using the chi square test or Fisher's exact test for cross tables and one-way analysis of variance for normally distributed variables compared between groups. For nongaussian variables, nonparametric tests were used (Mann-Whitney and Kruskal-Wallis). Kaplan-Meier survival curves were compared between groups using the log-rank test. The influence of a number of simultaneous variables on survival was estimated with the Cox proportional-hazards survival analysis. The probability values given are two sided.

RESULTS

The study group consisted of 148 patients with advanced cancer of the head of the pancreas. Of the 148 patients, 113 had undergone a biliary bypass procedure. Surgical biliary bypasses were performed in 44 patients as follows: 34 choledochojejunostomies, 5 choledochooduodenostomies, and 5 cholecystoduodenostomies. Of these 44 patients, 14 had had preoperative biliary drainage by means of a temporary endoprosthesis, a nasobiliary drain, or a percutaneous transhepatic drainage. Endoprostheses were used for biliary drainage in 63 patients, of which 20 cases were preceded by a period of decompressing nasobiliary or percutaneous transhepatic drainage. Nasobiliary or percutaneous transhepatic drainage was the only drainage procedure in six patients.

In 35 patients, no biliary bypass procedure was performed. Of these, 24 patients did not have jaundice or cholestasis, and in 11 patients only, jaundice developed when they were in a terminal stage of their disease.

The patient characteristics for the four groups are listed in Table 1. No significant difference was found in the number of metastases present at the time of diagnosis. The patients in the group treated with endoprostheses were significantly older than the patients in any of the other groups (Student-Newman-Keuls test, $p <$

Table 1. PATIENT CHARACTERISTICS

	≥1 Metastases at Time of Diagnosis		Age (yr) (range)	Male/ Female
	Yes	No		
No biliary bypass (n = 35)	15 (43)	20 (57)	62.0 (36-80)	19/16
Surgical biliary bypass (n = 44)	20 (45)	24 (55)	59.5 (37-88)	23/21
Endoprostheses (n = 63)	19 (30)	44 (70)	66.0 (38-89)*	36/27
External drainage (n = 6)	1 (17)	5 (83)	61.0 (57-71)	5/1

Values in parentheses for metastases data are percentages.
* $p < 0.05$.

0.05). No difference in the diameters of the tumors were found between the patients treated with endoprostheses and surgery. A diameter of the tumor at the time of diagnosis could be obtained in 83% of cases. The diagnosis was histologically confirmed in 120 patients (81%). Twenty-nine patients had complaints of gastric outlet obstruction, 18 of whom underwent a gastroenterostomy for this reason: 6 in the endoprosthesis group, 6 in the surgical group, 5 in the not-drained group, and 1 in the percutaneously drained group. Jaundice occurred at some point in the course of the disease in 124 patients (84%).

Mortality and Morbidity Rates

Of the initial 44 surgical biliary bypasses, 2 cholecystoduodenostomies and 1 choledochojejunostomy failed to function (success rate, 93.2%), resulting in 1 relaparotomy and 2 percutaneous transhepatic drainage procedures. Of the 63 primary endoprostheses that were used in endoscopically treated patients, 3 did not function from the start (success rate after insertion, 95.2%). No significant difference could be found between the 30-day mortality rate after a surgical biliary bypass (13.6%) and the 30-day mortality rate after endoprosthesis insertion (12.7%, $p = 0.88$ by Fisher's exact test). In the patients surviving less than 6 months, the total deaths occurred equally frequently in the patients treated with endoprostheses and those treated with surgical biliary bypasses (Table 2). In these patients with short survival times, early morbidity tended to occur more frequently in the surgically treated patients ($p = 0.05$ by Fisher's exact test). Late morbidity was significantly more frequent in the endoscopically treated patients.

In the group of patients with survival times longer than

Table 2. MORBIDITY IN PATIENTS WITH SURVIVAL SHORTER THAN 6 MONTHS

	Total Morbidity	Early Morbidity (<1 week)	Late Morbidity (>1 week)
Surgery (n = 24)	7 (29)	7 (29)*	0
Endoprotheses (n = 40)	12 (30)	3 (7.5)	9 (23)†

Values in parentheses are percentages.
 * p = 0.05.
 † p < 0.05.

6 months, however, the total morbidity occurred significantly more frequently in the patients treated with endoprotheses (61%) compared with the surgically treated patients (5%, p < 0.05 by Fisher's exact test, Table 3). There was no difference in early morbidity rates between these two groups, but late morbidity occurred significantly more frequently in the endoscopically treated patients (p < 0.05 by Fisher's exact test).

The endoprotheses became obstructed after a mean period of 113 days (range, 4 to 273 days). All patients with recurrent obstructive jaundice were effectively treated by replacing their endoprotheses.

Survival

All patients died during the follow-up. No significant difference (p = 0.29 by the log-rank test) was demonstrated between the survival times of the patients treated with endoprotheses (mean, 6.2 months; median, 4.7 months) and those of the surgically treated patients (mean, 7.8 months; median, 5.5 months). The patients not treated with a biliary bypass had a significantly shorter survival (mean, 4.2 months; median, 2.4 months) compared with the other groups (p < 0.05 by the log-rank test). In patients with biliary drainage by means of a surgical biliary bypass or an endoprosthesis, we analyzed the influence of a number of patient-

Table 3. MORBIDITY IN PATIENTS WITH SURVIVAL LONGER THAN 6 MONTHS

	Total Morbidity	Early Morbidity (<1 week)	Late Morbidity (>1 week)
Surgery (n = 20)	1 (5)	1 (5)	0
Endoprotheses (n = 23)	14 (61)*	0	14 (61)*

Values in parentheses are percentages.
 * p < 0.05.

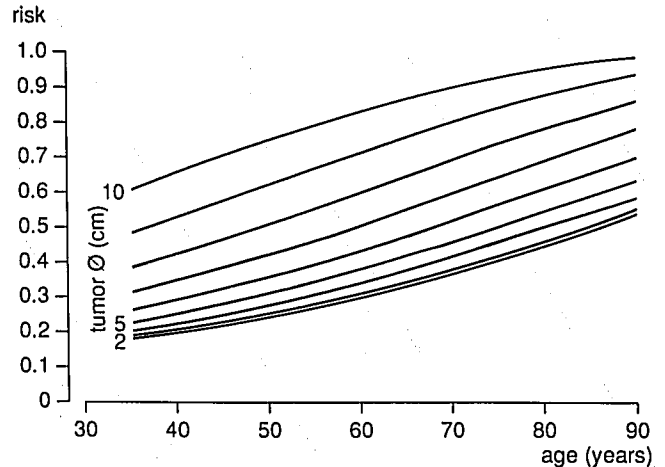


Figure 1. The risk of dying within 6 months after diagnosis as a function of age and the diameter of the tumor in female patients with no liver metastases.

related variables on survival. Survival times were significantly shorter in patients with advanced age, male sex, presence of liver metastases, and large diameters of their tumors at the time of diagnosis (p < 0.05 each by Cox proportional-hazards survival analysis). No influence on survival could be shown for metastases other than to the liver and peritonitis carcinomatosa. Figures 1 to 4 show the predicted risk of dying within 6 months after diagnosis as a function of age, presence of liver metastases (yes or no), sex (male or female), and diameter of the tumor (1 to 10 cm).

Hospital Stay

These results are listed in Tables 4 and 5. In the patients surviving shorter than 6 months and in those sur-

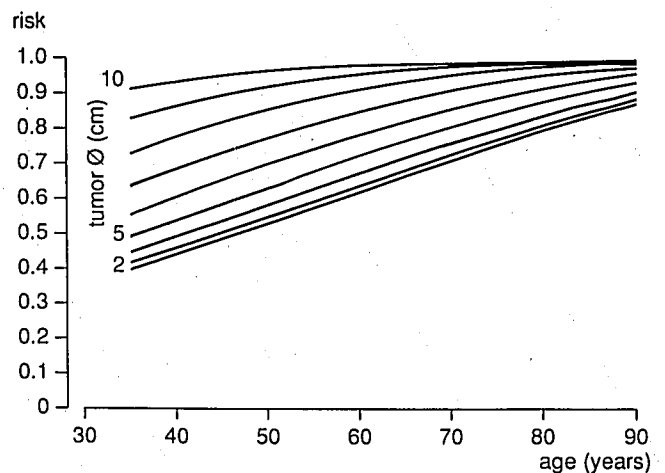


Figure 2. The risk of dying within 6 months after diagnosis as a function of age and the diameter of the tumor in female patients with liver metastases.

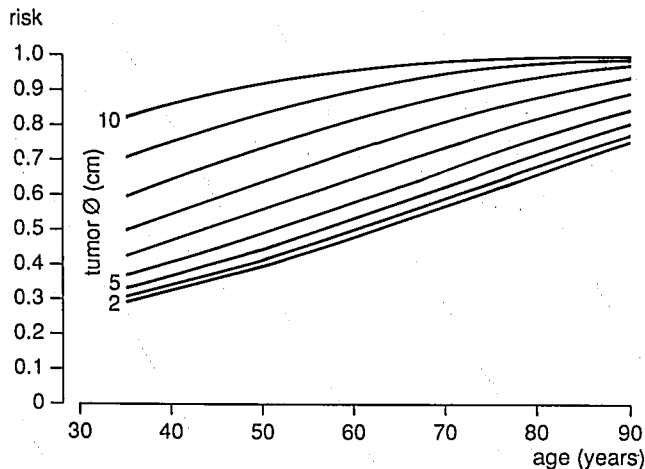


Figure 3. The risk of dying within 6 months after diagnosis as a function of age and the diameter of the tumor in male patients with no liver metastases.

viving longer than 6 months, the first hospital admission was significantly longer in the surgically treated patients compared with that in the patients treated with endoprostheses ($p < 0.05$ by the Mann-Whitney test). In the group of patients with survival times shorter than 6 months, the total hospital stay was significantly shorter for patients treated with endoprostheses ($p < 0.05$, by the Mann-Whitney test). In the group with survival times longer than 6 months, this difference was not detected. No significant difference in the number of hospital admissions was found between the surgically and the endoscopically treated patients in both groups.

DISCUSSION

Because of the high incidence of recurrent obstructive jaundice that is associated with the use of endoprostheses

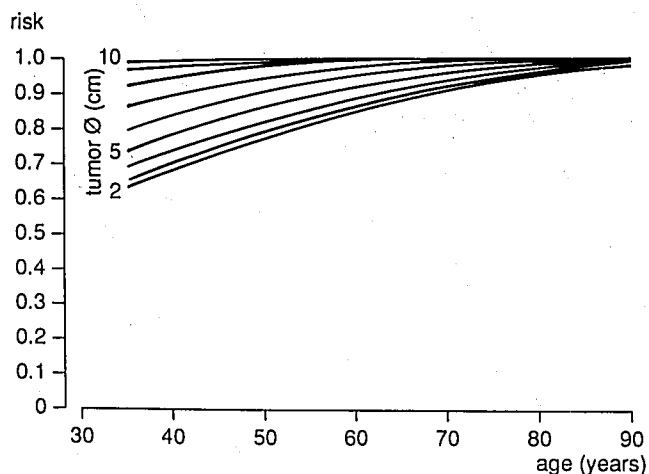


Figure 4. The risk of dying within 6 months after diagnosis as a function of age and the diameter of the tumor in male patients with liver metastases.

Table 4. HOSPITAL STAY PARAMETERS FOR PATIENTS WITH SURVIVAL SHORTER THAN 6 MONTHS

	Initial Hospital Stay (days)	Total Hospital Stay (days)	No. of Admissions
Surgery (n = 24)	42.8 (10-87)	58.8 (12-156)	1.7 (1-4)
Endoprostheses (n = 40)	27.3 (3-66)*	40.3 (12-93)*	2.0 (1-4)

Mean values are given (with range in parentheses).
* $p < 0.05$.

in the palliation of malignant obstructive jaundice, it has been hypothesized that in long-surviving patients treated with endoprostheses the quality of life is impaired as a result of the considerable morbidity and numerous hospital readmissions. Our results show that, in the group of patients surviving longer than 6 months, the patients treated with endoprostheses had morbidity rates up to 61%, significantly higher than those in the patients treated with surgical biliary bypasses (5%). In patients surviving shorter than 6 months, a difference in morbidity was not found because early surgical morbidity compensated for the late morbidity in the endoprostheses group.

The 30-day mortality rate in our study was 13.6% in the surgically treated patients and 12.7% in the endoscopically treated patients. High perioperative mortality rates (15% to 30%) have been described in the literature,^{6,10-13} although recently, considerable improvement in mortality rates after surgical biliary bypasses have been reported.²⁶⁻²⁹ Although 30-day mortality rates of 0% to 24% after endoscopic biliary drainage have been reported,^{12,13,20-22,24,25} the high 30-day mortality rate in the endoscopically treated patients in this study is partially explained by the older age of these patients.

Table 5. HOSPITAL STAY PARAMETERS FOR PATIENTS WITH SURVIVAL LONGER THAN 6 MONTHS

	Initial Hospital Stay (days)	Total Hospital Stay (days)	No. of Admissions
Surgery (n = 20)	27.3 (14-50)	53.5 (17-151)	2.8 (1-6)
Endoprostheses (n = 23)	20.0 (5-37)*	56.1 (13-113)	3.0 (1-8)

Mean values are given (with range in parentheses).
* $p < 0.05$.

The hospital stay in patients with a survival time shorter than 6 months was significantly shorter in patients treated with endoprotheses. However, in patients with survival times longer than 6 months, this difference disappeared as a result of the frequent readmissions for recurrent obstructive jaundice.

We did not find a difference in survival between the endoscopically treated and the surgically treated groups. The patients who did not need a biliary drainage procedure had a shorter survival time mainly because a substantial proportion of these patients presented in a late stage of their disease, which was caused by the absence of jaundice as a presenting sign.

Previous studies that have compared endoscopically inserted endoprotheses and surgical biliary bypasses did not find a difference in survival, mortality, or morbidity rates.^{13,21,22,24,25} Shepherd et al.²² and Brandabur et al.²⁴ reported shorter initial and total hospital stays in patients treated with endoprotheses, whereas other studies did not find a difference in the hospital stay. None of these studies differentiated between short- and long-surviving patients.

We conclude that, in patients with survival time shorter than 6 months, endoscopic biliary drainage is more favorable because it will lead to a shorter hospitalization. In patients with survival times longer than 6 months, however, surgical biliary bypass will eventually produce significantly less morbidity and is therefore superior to endoprotheses in the palliation of malignant obstructive jaundice in these patients.

To apply these conclusions, the surgeon should be able to estimate the chance of long or short survival times for the individual patient with unresectable cancer of the head of the pancreas. The factors that we found to be significant influences on the survival time were sex, age, the diameter of the tumor, and liver metastases. Several other studies have shown that these are important prognostic factors in patients with advanced cancer of the pancreas.³⁰⁻³² Figures 1 to 4 show the calculated risk of dying within 6 months after the diagnosis is made for patients with every combination of factors. Obviously, male patients with liver metastases have a small chance of surviving longer than 6 months, with any diameter of their tumor or at any age. This applies to a lesser extent to female patients with liver metastases. Endoprotheses seem to be most efficient in the palliation of obstructive jaundice in these patients. In the patients with no liver metastases and small diameters of their tumors, the chance of surviving longer than 6 months is relatively good, especially in young women. The results of this study indicate that these patients could benefit from a surgical biliary bypass. For patients with a prognosis somewhere in the middle of the survival curve, the policy is less clear. Other parameters, such as the physical per-

formance level, should be taken into consideration for the individual patient. Furthermore, if a patient is found to have an unresectable tumor at laparotomy, the presence of good prognostic factors should prompt the surgeon to perform a biliodigestive anastomosis.

The quality of endoscopic biliary drainage is likely to improve in the future. Newly designed endoprotheses and self-expanding stents may be associated with less long-term complications.³³ Clogged endoprotheses can often be exchanged as an outpatient procedure. The impact of these developments, however, is yet to be evaluated.

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