

# Morbidity and Mortality After Radical and Palliative Pancreatic Cancer Surgery

## Risk Factors Influencing the Short-Term Results

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### Objective

To analyze the morbidity and mortality after radical and palliative pancreatic cancer surgery in Norway, especially the risk factors.

### Summary Background Data

A prospective multicenter study between 1984-1987 including only histologically or cytologically verified adenocarcinoma of the pancreas (N = 442) or the papilla of Vater (N = 30); 84 patients (19%) with pancreatic carcinoma and 24 patients (80%) with papilla carcinoma underwent radical operations. A palliative procedure was performed in 252 patients (53%).

### Methods

Clinical data, surgical procedures and the following morbidity and mortality were recorded on standardized forms. The risk factors were analyzed by a logistic multiple regression model.

### Results

The morbidity, reoperation, and mortality rates were 43, 18, and 11% after radical surgery and 23, 4, and 14% after palliative surgery. Karnofsky's index was the sole independent risk factor for death after radical surgery. Splenectomy, age, and TNM stage influenced morbidity. Diabetes, Karnofsky's index, and liver metastases were risk factors in palliative surgery.

### Conclusions

The morbidity and mortality risks were comparable between total pancreatectomy and a Whipple's procedure and between biliary and a double bypass. Preoperative biliary drainage had no impact on the risks and may be abandoned. High age is a relative and a low Karnofsky's index an absolute contraindication for radical surgery. Nonsurgical palliation of jaundice should be considered according to the presence of independent risk factors.

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Since Whipple and his colleagues in 1935 introduced radical en bloc resection of the head of pancreas and duodenum,<sup>1</sup> much debate has surrounded the application of pancreatoduodenectomy versus a palliative pro-

cedure in patients with resectable pancreatic carcinoma in relation to long-term survival.<sup>2,3-6</sup> In addition, much debate has focused on the surgical techniques and procedures, especially on pancreatic resection ad modum

**Table 1. DISTRIBUTION OF PATIENTS WITH CARCINOMA OF THE PANCREAS ACCORDING TO TNM STAGE AND TREATMENT GROUP**

| Group               | TNM Stage    |               |               |               |               |                 |                |                  |                |                  |
|---------------------|--------------|---------------|---------------|---------------|---------------|-----------------|----------------|------------------|----------------|------------------|
|                     | I<br>N = 57* | II<br>N = 49* | III<br>N = 79 | IV<br>N = 193 | I-II<br>N = 1 | I-III<br>N = 12 | I-IV<br>N = 18 | II-III<br>N = 30 | II-IV<br>N = 3 | Total<br>N = 442 |
| Radical operated    |              |               |               |               |               |                 |                |                  |                |                  |
| No. of patients     | 46           | 6             | 27            | 3             | —             | 1               | —              | 1                | —              | 84               |
| Male                |              |               |               |               |               |                 |                |                  |                | 47               |
| Female              |              |               |               |               |               |                 |                |                  |                | 37               |
| Age (yr)            |              |               |               |               |               |                 |                |                  |                |                  |
| Mean                |              |               |               |               |               |                 |                |                  |                | 64.1             |
| Median              |              |               |               |               |               |                 |                |                  |                | 65               |
| Min.                |              |               |               |               |               |                 |                |                  |                | 40               |
| Max.                |              |               |               |               |               |                 |                |                  |                | 81               |
| Palliative operated |              |               |               |               |               |                 |                |                  |                |                  |
| No. of patients     | 9            | 41            | 52            | 125           | 1             | 1               | 2              | 15               | 1              | 247              |
| Male                |              |               |               |               |               |                 |                |                  |                | 127              |
| Female              |              |               |               |               |               |                 |                |                  |                | 120              |
| Age (yr)            |              |               |               |               |               |                 |                |                  |                |                  |
| Mean                |              |               |               |               |               |                 |                |                  |                | 67.6             |
| Median              |              |               |               |               |               |                 |                |                  |                | 68               |
| Min.                |              |               |               |               |               |                 |                |                  |                | 37               |
| Max.                |              |               |               |               |               |                 |                |                  |                | 92               |
| Not operated        |              |               |               |               |               |                 |                |                  |                |                  |
| No. of patients     | —            | 1             | —             | 63            | —             | 10              | 16             | 14               | 2              | 106              |
| Male                |              |               |               |               |               |                 |                |                  |                | 54               |
| Female              |              |               |               |               |               |                 |                |                  |                | 52               |
| Age (yr)            |              |               |               |               |               |                 |                |                  |                |                  |
| Mean                |              |               |               |               |               |                 |                |                  |                | 71               |
| Median              |              |               |               |               |               |                 |                |                  |                | 71               |
| Min.                |              |               |               |               |               |                 |                |                  |                | 30               |
| Max.                |              |               |               |               |               |                 |                |                  |                | 88               |

\* Including distal resections.

Whipple versus total pancreatectomy<sup>7-21</sup> and between palliative surgical procedures, i.e., biliary-versus double bypass<sup>22-25</sup> in relation to postoperative morbidity, mortality, and long-term survival. Much debate has also surrounded the value of preoperative biliary drainage in jaundiced patients in relation to postoperative morbidity and mortality.<sup>11,26-32</sup> Regarding the dismal long-term prognosis for patients with pancreatic carcinoma even for radical resected cases, factors influencing the postoperative morbidity and mortality rates after both radical and palliative surgery are of greatest importance, especially as nonsurgical permanent biliary drainage by endoprosthesis is an alternative to palliative surgery.<sup>33-37</sup>

This study analyzed the postoperative morbidity and mortality after radical and palliative pancreatic cancer surgery in Norway, especially the risk factors influencing postoperative morbidity and mortality.

## PATIENTS AND METHODS

Thirty-eight Norwegian hospitals, which included 7 university and 23 county and district hospitals, participated in the trial. After preliminary investigations, eight local hospitals referred their patients to larger hospitals for diagnosis and treatment. Data regarding the case history, diagnosis and resectability assessment, macroscopic and microscopic examinations, surgical procedure, and postoperative follow-up were recorded on standardized forms that were regularly submitted to the study headquarters for computation. The Norwegian Pancreatic Cancer Trial comprises two randomized studies partly presented elsewhere<sup>38</sup>; 442 patients with pancreatic carcinoma and 30 patients with carcinoma of the

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**Table 2. DISTRIBUTION OF PATIENTS WITH CARCINOMA OF THE PAPANILLA OF VATER ACCORDING TO TNM STAGE AND TREATMENT GROUP**

| Group               | TNM Stage   |             |              |             | Total<br>N = 30 |
|---------------------|-------------|-------------|--------------|-------------|-----------------|
|                     | I<br>N = 14 | II<br>N = 9 | III<br>N = 3 | IV<br>N = 4 |                 |
| Radical operated    |             |             |              |             |                 |
| No. of patients     | 13          | 8           | 3            | —           | 24              |
| Male                |             |             |              |             | 12              |
| Female              |             |             |              |             | 12              |
| Age (yr)            |             |             |              |             |                 |
| Mean                |             |             |              |             | 64.8            |
| Median              |             |             |              |             | 67              |
| Min.                |             |             |              |             | 36              |
| Max.                |             |             |              |             | 81              |
| Palliative operated |             |             |              |             |                 |
| No. of patients     | 1           | 1           | —            | 3           | 5               |
| Male                |             |             |              |             | 3               |
| Female              |             |             |              |             | 2               |
| Age (yr)            |             |             |              |             |                 |
| Mean                |             |             |              |             | 70.4            |
| Median              |             |             |              |             | 78              |
| Min.                |             |             |              |             | 49              |
| Max.                |             |             |              |             | 88              |
| Not operated        |             |             |              |             |                 |
| No. of patients     | —           | —           | —            | 1           | 1               |
| Female              |             |             |              |             | 1               |
| Age (yr)            |             |             |              |             | 76              |

papilla of Vater were accrued between April 1984 and April 1987.

The presenting symptoms, signs, and diagnosis related to stage and tumor site of these patients; and the results of tests in diagnosing resectable carcinoma and factors influencing resectability in stage I carcinomas have been published.<sup>39,40</sup>

### Eligibility for the Trial

Only patients with histologically or cytologically verified adenocarcinoma of the exocrine pancreas or the papilla of Vater were included in the trial. Patients with pancreatic tumor and liver metastasis who had not been operated on were included after histologic or cytologic verification of the metastasis. Patients with endocrine tumor, cholangiocarcinoma, metastatic pancreatic tumor, cystadenocarcinoma, and histologically or cytologically unverified primary pancreatic tumor were excluded.

### Staging

The tumor node metastasis (TNM) clinical classification for carcinoma of the pancreas or the papilla of Vater

was used.<sup>41</sup> Carcinoma of the papilla of Vater, in our previous reports from the trial<sup>38-40</sup> classified in assembly with the proposed TNM classification of pancreatic carcinoma,<sup>42</sup> in this study was reclassified based on the registration forms according to the approved UICC TNM clinical classification for this tumor site.<sup>41</sup>

### Preoperative Biliary Drainage

Each hospital followed their ordinary routine regarding drainage of bile preoperatively and no instructions were given in the trial on this issue.

### STUDY DESIGN AND STATISTICAL METHODS

The quality of life was assessed according to Karnofsky's index.<sup>43</sup> Differences between treatment groups were compared by X<sup>2</sup> analysis or Fisher exact test when appropriate. A two-tailed test with a p value < 0.05 was regarded as statistically significant, values of marginal statistical significance were stated as p = 0.05-0.10. Pre- and intraoperative variables which may be related to postoperative morbidity and mortality were analyzed using first a forward stepwise logistic regression analysis and further analyzed by a backward stepwise logistic multiple regression model of radical and palliative operated patients separately. Separate analyses were performed with morbidity and mortality as dependent variables, respectively; in addition as a factor, radical versus palliative surgery was studied in separate analyses. Age, Karnofsky's index, and tumor size were used as continuous variables. A significance level of 0.05 for each comparison initially was applied in the analyses.<sup>44</sup> The final regression model should fulfill the following three requirements: (1) The model should fit the observed data adequately, i.e., give a test for goodness of fit with p > 0.05;<sup>45</sup> (2) The final model should explain the effect of individual variables influencing morbidity and mortality in the simplest way;<sup>46</sup> (3) To adjust for multiple significance

**Table 3. DISTRIBUTION OF PATIENTS WITH A DISTAL RESECTION FOR PANCREATIC CARCINOMA ACCORDING TO TNM STAGE AND TUMOR SITE**

| TNM Stage | Tumor Site | No. of Patients | Radical Resection |
|-----------|------------|-----------------|-------------------|
| I         | Tail       | 2               | Yes               |
| II        | Tail       | 1               | Yes               |
| III       | Tail       | 1               | No                |
| IV        | Body       | 1               | No                |

**Table 4. SURGICAL PROCEDURES AND POSTOPERATIVE COMPLICATIONS, REOPERATIONS AND MORTALITY IN 365 PATIENTS WITH CARCINOMA OF THE PANCREAS OR PAPANILLA OF VATER**

| Surgical Procedure                    | No. of Patients |              |             |                          |
|---------------------------------------|-----------------|--------------|-------------|--------------------------|
|                                       | Operated        | Complication | Reoperation | Postoperative Mortality* |
| Total pancreatectomy                  | 6 (2)           | 2 (33)       | 2 (33)      | 0                        |
| Total pancreatectomy with splenectomy | 22 (6)          | 14 (64)      | 4 (18)      | 5 (23)                   |
| Whipple's operation                   | 78 (21)         | 27/76 (36)   | 13/76 (17)  | 7 (9)                    |
| Whipple's operation with splenectomy  | 2 (0.5)         | 2 (100)      | 0           | 0                        |
| Exploratory laparotomy                | 58 (16)         | 11/56 (20)   | 2/55 (4)    | 11 (19)                  |
| Biliary-bypass                        | 108 (30)        | 25/107 (23)  | 3/106 (3)   | 16 (15)                  |
| Biliary and duodenal bypass           | 86 (24)         | 21/83 (25)   | 5/82 (6)    | 8 (9)                    |
| Distal resection                      | 5 (1)           | 1 (20)       | 0           | 0                        |
| Total                                 | 365             |              |             |                          |

\* Death within 30 days after operation.

testing the significance level  $\alpha = 0.05$  for each comparison was reduced according to Bonferroni's adjustment<sup>47</sup> and the analyses were also repeated with 0.01 as an end point for each comparison to reduce the overall probability of type I error. The computations were performed using the BMDP (BMDP Statistical Software, Los Angeles, CA) statistical program package implemented on the Univac 1100 (Sperry Univac, Salt Lake City, UT) computer of the University of Bergen.<sup>45</sup>

### Treatment Groups

The distribution of all patients according to TNM stage and treatment group are given in Table 1–3. In all 365 patients (77%) were operated on. A radical surgical procedure was performed in 108 patients (23%), in 24 patients (80%) with carcinoma of the papilla of Vater, and in 84 (19%) with pancreatic carcinoma. A palliative operation was performed in 252 patients (53%), a distal pancreatic resection in 5 (1%). Of pancreatic head tumors, 78 of 365 (21%) patients underwent radical resections. Six of 66 tumors of the body (9%) were radical resected, 3 of 11 (27%) tumors of the tail had a "radical" distal resection.

## RESULTS

### Postoperative Morbidity, Reoperations, and Mortality

After radical surgery, the rates of postoperative morbidity, reoperations and mortality were 43%, 18%, and 11%, respectively. After palliative surgery, the corresponding rates were 23%, 4%, and 14%, respectively. The

rates of morbidity and reoperations were higher after radical compared with palliative surgery ( $p < 0.0004$  and  $< 0.00004$ ), respectively, but the mortality rate was comparable between a radical and a palliative surgical procedure ( $p = 0.58$ ) (Table 5). Total pancreatectomy and a Whipple procedure had comparable rates of morbidity, mortality, and reoperations ( $p = 0.10$ , 0.3 and 0.8). Splenectomy performed in a radical procedure increased the morbidity rate ( $p = 0.01$ ) (Table 5). A palliative biliary- and biliary and concomitant duodenal bypass had comparable postoperative morbidity rates ( $p = 0.9$ ) and mortality rates ( $p = 0.3$ ) (Table 4).

### Hospital Groups and Postoperative Morbidity, Reoperations, and Mortality

Both after radical and palliative surgery, the rates of postoperative morbidity, mortality, and reoperations were comparable between the university, county, and district hospital groups. Details are given in Table 6.

### Preoperative Biliary Drainage and Postoperative Morbidity and Mortality

Of 108 patients who underwent radical resection, preoperative biliary drainage (PBD) was used in 35 (32%). Details are given in Table 7. Patients who underwent radical resections were retrospectively grouped according to PBD versus no PBD and were regarded comparable according to other risk factors, e.g., age, Karnofsky's index, TNM stage, tumor site, hospital group, surgical procedure, antibiotic- and thrombose prophylaxis. This preliminary retrospective comparison did not reveal pre-

**Table 5. COMPARISON OF POSTOPERATIVE COMPLICATIONS, REOPERATIONS AND POSTOPERATIVE MORTALITY ACCORDING TO TYPE OF SURGICAL PROCEDURE IN PATIENTS WITH CARCINOMA OF THE PANCREAS OR PAPANICOLAOU PAPILLA OF VATER**

| Group   |         | No. of Patients (%) |             |             | p value    |
|---|---------|---------------------|-------------|-------------|------------|
|   |         | Complication        | Reoperation | Mortality # |            |
| Radical versus palliative surgery   | N = 108 | 45/106 (43)         | 19/106 (18) | 12/108 (11) | <0.0004*   |
| Total pancreatectomy versus Whipple's operation                             | N = 252 | 57/246 (23)         | 10/243 (4)  | 35/252 (14) | <0.00004** |
| Radical surgery with splenectomy versus radical surgery without splenectomy | N = 28  | 16/28 (57)          | 6/28 (21)   | 5/28 (18)   | 0.58***    |
|   | N = 80  | 29/78 (37)          | 13/78 (17)  | 7/80 (9)    | 0.10*      |
|   | N = 84  | 29/78 (37)          | 13/78 (17)  | 7/80 (9)    | 0.78**     |
|   | N = 24  | 16/24 (67)          | 4/24 (17)   | 5/24 (21)   | 0.33***    |
|   | N = 84  | 29/82 (35)          | 15/82 (18)  | 7/84 (8)    | 0.012*     |
|   |         |                     |             |             | 0.9**      |
|   |         |                     |             |             | 0.17***    |

# Death within 30 days after operation.

X2 = Test between \* complications; \*\* reoperations; \*\*\* mortality. Distal resections not included in the analysis.

operative biliary drainage to influence the postoperative morbidity or mortality rate after radical surgery (Table 8).

### Types of Complications and Related Causes of Death

After radical surgery, the "general" complications (cardial, pulmonary and thromboembolic) were frequent and found in 17% of the patients, with a corresponding mortality rate of 28%. Infections were found in 16 of 105 radical operated patients (15%), in 9 of 82 patients (11%) with preserved spleen versus 7 of 24 (30%) splenectomized patients ( $p = 0.06$ ).

After palliative surgery, the "general" complications were found in 9% of patients, corresponding mortality

65%. Postoperative infections were found in 19 of 240 patients (8%) (Table 9).

### Other Types of Complications

One radical and one palliative operated patient, both without PBD were reported with postoperative renal insufficiency. Gastric retention was found after radical surgery in three patients and a minor bleeding ulcer was found in one patient. Acute pancreatitis developed in three patients after a palliative procedure.

### Diabetes Mellitus

Preoperative diabetes was found in 9 of 106 radical operated patients (9%). Insulin-dependent diabetes after

**Table 6. HOSPITAL GROUP AND POSTOPERATIVE COMPLICATIONS, REOPERATIONS AND POSTOPERATIVE MORTALITY**

| Group              |         | No. of Patients           |                        |                          | p value* |
|--------------------|---------|---------------------------|------------------------|--------------------------|----------|
|                    |         | University Hospital N = 7 | County Hospital N = 10 | District Hospital N = 13 |          |
| Radical surgery    | N = 108 | N = 53                    | N = 28                 | N = 27                   |          |
| Complication       |         | 27 (51)                   | 9 (32)                 | 9 (33)                   | 0.16     |
| Reoperation        |         | 13 (25)                   | 2 (7)                  | 4 (15)                   | 0.14     |
| Mortality          |         | 4 (8)                     | 3 (11)                 | 5 (19)                   | 0.33     |
| Palliative surgery | N = 252 | N = 102                   | N = 53                 | N = 97                   |          |
| Complication       |         | 25 (25)                   | 11 (21)                | 21 (22)                  | 0.83     |
| Reoperation        |         | 6 (6)                     | 0                      | 4 (4)                    | 0.20     |
| Mortality          |         | 12 (12)                   | 7 (13)                 | 16 (17)                  | 0.62     |

\* X2 test.

**Table 7. DETAILS OF PREOPERATIVE BILIARY DRAINAGE AND S-BILIRUBIN BEFORE RADICAL SURGERY**

|  | Radical Surgery                         |                       |
|--|---|-----------------------|
|  | Preoperative Biliary Drainage<br>N = 35 | No Drainage<br>N = 73 |
| Preoperative biliary drainage (days)                     |   |                       |
| Mean   | 15.7                                    |                       |
| Median   | 14                                      |                       |
| Min.   | 2                                       |                       |
| Max.   | 41                                      |                       |
| Endoscopic (EBD) biliary drainage (days)                 | N = 14                                  |                       |
| Mean   | 21.6                                    |                       |
| Median   | 20                                      |                       |
| Min.   | 7                                       |                       |
| Max.   | 41                                      |                       |
| Percutaneous (PTBD) transhepatic biliary drainage (days) | N = 21                                  |                       |
| Mean   | 11.7                                    |                       |
| Median   | 12                                      |                       |
| Min.   | 2                                       |                       |
| Max.   | 28                                      |                       |
| s-bilirubin at operation (µmol/L)                        |   |                       |
| EBD + PTBD   |   |                       |
| Mean   | 96.5                                    | 144.3                 |
| Median   | 75                                      | 116                   |
| Min.   | 13                                      | 5                     |
| Max.   | 391                                     | 517                   |
| EBD  |   |                       |
| Mean   | 48.2                                    |                       |
| Median   | 38.5                                    |                       |
| Min.   | 13                                      |                       |
| Max.   | 130                                     |                       |
| PTBD   |   |                       |
| Mean   | 128.7                                   |                       |
| Median   | 99                                      |                       |
| Min.   | 16                                      |                       |
| Max.   | 391                                     |                       |

a Whipple procedure was found in 4 of 66 patients (6%). Two of these patients had preoperative diabetes.

**Risk Factors for Postoperative Morbidity and Mortality**

*Radical Surgery: Morbidity*

The final logistic regression model, which fit the data well (p = 0.8–1.0 for goodness of fit), revealed only splenectomy significantly to increase the morbidity rate. Increasing age and TNM stage may have a marginal effect. The university hospital group may have the lowest risk for complications (Tables 10, 11).

*Radical Surgery: Mortality*

In the final model (p = 0.3 and 0.4 for goodness of fit) only Karnofsky’s index true independently influenced postoperative mortality, a higher index reduced the mortality risk. Preoperative biliary drainage (PBD), number of days with PBD, or s-bilirubin at operation were not found to be significant prognostic factors for postoperative morbidity and mortality in the multivariate analyses (Table 12).

*Palliative Operations: Morbidity*

The final model, which fit the data well (p = 1.0 for goodness of fit), revealed only preoperative diabetes significantly to increase the risk for complications. Marginally tumor extension into large vessels may increase the risk for complications for tumors of the head and the body, and irrespective of present tumor invasion, the risk for complications may be highest for tumors of the papilla and the head (Table 13).

*Palliative Operations: Mortality*

Preoperative diabetes, Karnofsky’s index, and liver-metastasis independently significantly influenced postoperative mortality (p = 0.2–0.9 for goodness of fit). Both diabetes and present liver metastasis increased the mortality risk while a high Karnofsky’s index lowered the risk (Table 14).

**Risk for Postoperative Morbidity and Mortality According to Surgical Procedures**

Including in the logistic regression models as variables, total pancreatectomy versus Whipple procedure and biliary versus biliary and duodenal bypass versus exploratory laparotomy, the analyses revealed no independent effect on morbidity and mortality from the type of radical or palliative surgical procedure performed. Including in the model as a variable, a radical surgical pro-

**Table 8. POSTOPERATIVE MORBIDITY AND MORTALITY AFTER RADICAL SURGERY ACCORDING TO PREOPERATIVE BILIARY DRAINAGE VERSUS NO DRAINAGE**

| Group           | No. of Patients               |             | p Value* | Total       |
|-----------------|-------------------------------|-------------|----------|-------------|
|                 | Preoperative Biliary Drainage | No Drainage |          |             |
| Radical surgery | N = 35                        | N = 73      |          | N = 108     |
| Morbidity       | 16/35 (46)                    | 29/71 (41)  | 0.79     | 45/106 (43) |
| Mortality       | 3/35 (9)                      | 9/73 (12)   | 0.80     | 12/108 (11) |

\* X2 test.

**Table 9. TYPES OF POSTOPERATIVE COMPLICATIONS AND RELATED MORTALITY AFTER RADICAL AND PALLIATIVE SURGERY FOR CARCINOMA OF THE PANCREAS OR PAPANILLA OF VATER**

| Type of Complication      | No. of Patients         |           |      |                            |             |      |
|---------------------------|-------------------------|-----------|------|----------------------------|-------------|------|
|                           | Radical Surgery N = 108 |           |      | Palliative Surgery N = 252 |             |      |
|                           | Complication            | Mortality | (%)* | Complication               | Mortality   | (%)* |
| Intestinal obstruction    | 3/105 (3)               | —         |      | 1/241 (0.4)                | —           |      |
| Hemorrhage                | 16/105 (15)             | 5/104 (5) | (31) | 9/241 (4)                  | 4/234 (2)   | (44) |
| Anastomotic insufficiency |                         |           |      |                            |             |      |
| Biliary                   | 4/105 (4)               | 1/104 (1) | (25) | —                          | —           |      |
| Pancreatic                | 2/81 (3)                | 1/80 (1)  | (50) | —                          | —           |      |
| Gastrointestinal          | 3/105 (3)               | 1/104 (1) | (33) | 1/96 (1)                   | —           |      |
| Intra-abdominal abscess   | 8/105 (8)               | 3/104 (3) | (38) | 4/240 (2)                  | —           |      |
| Fistula                   | 4/104 (4)               | —         |      | 3/240 (1)                  | 1/233 (0.4) | (33) |
| Wound infection           | 4/105 (4)               | 2/104 (2) | (50) | 4/240 (2)                  | —           |      |
| Wound dehiscence          | —                       | —         |      | 4/240 (2)                  | —           |      |
| Septicemia                | 4/105 (4)               | 3/104 (3) | (75) | 11/240 (5)                 | 3/233 (1)   | (30) |
| General†                  | 18/105 (17)             | 5/104 (5) | (28) | 22/240 (9)                 | 13/233 (6)  | (65) |
| Others                    | 15/102 (15)             | 5/101 (5) | (33) | 15/240 (6)                 | 7/233 (3)   | (50) |

\* % of patients with complication.  
 † Cardial, pulmonary, thromboembolism.

cedure versus a palliative procedure, the analysis revealed a radical surgical procedure to independently significantly increase the risk for complications, i.e., almost triple the risk, but radical surgery did not independently carry a higher risk for postoperative mortality than a palliative procedure (Table 15). A summary of the risk

factors revealed according to different significance levels ( $\alpha = 0.05$  and  $0.01$ ) used for the multiple comparisons in the analyses are given in Table 16.

**DISCUSSION**

**Radical Versus Palliative Surgery**

The postoperative morbidity rate after radical resections, previously 50–60%,<sup>9,11,48–53</sup> has declined during the two last decades and is between 30–45%,<sup>16,17,19,54–56</sup> consistent with a morbidity rate of 43% in the present study. The mortality rate has also declined in the same period, from approximately 20–30%,<sup>9,4,50–53</sup> to about 10% or even lower,<sup>16,19,55,57</sup> consistent with a mortality

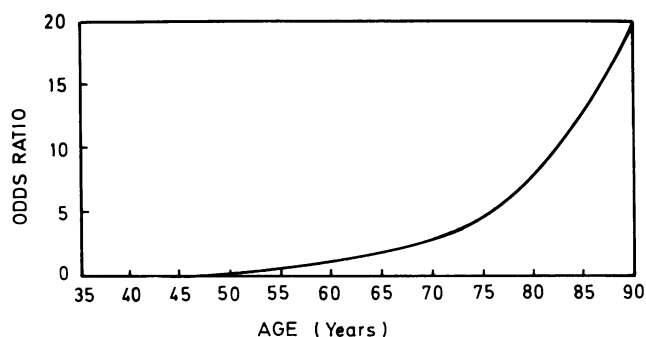
**Table 10. PRE- AND INTRAOPERATIVE RISK FACTORS ANALYZED BY THE LOGISTIC REGRESSION MODEL FOR POSTOPERATIVE MORBIDITY AND MORTALITY**

|                   |  |
|-------------------|--|
| Hospital group    | Days with preoperative biliary drainage s-bilirubin before operation |
| Age               |  |
| Sex               |  |
| Presenting        | Metastasis   |
| Jaundice          | Liver  |
| Abdominal pain    | Peritoneal   |
| Weight loss       | Regional lymph nodes   |
| Patient's delay   | Tumor extension  |
| Doctor's delay    | Neighboring organs   |
| Diagnostic delay  | Large vessels  |
| Preoperative      | Duodenum   |
| Jaundice          | Outside capsule  |
| Diabetes          | Tumor  |
| Karnofsky's index | Size   |
| Biliary drainage  | Site   |
| Prophylaxis       | Surgical procedure   |
| Antibiotic        | Splenectomy  |
| Thrombose         | TNM stage  |

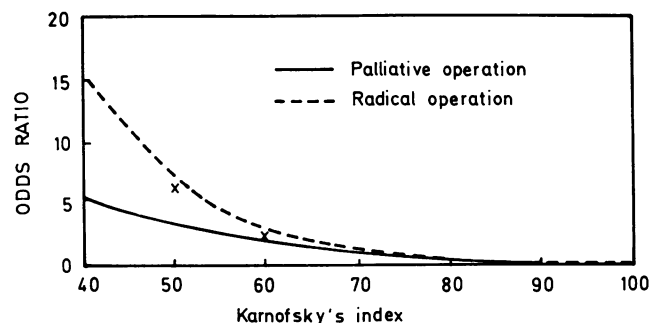
**Table 11. SUMMARY OF LOGISTIC REGRESSION ANALYSIS OF RISK FACTORS FOR POSTOPERATIVE MORBIDITY AFTER RADICAL RESECTIONS IN PATIENTS WITH CARCINOMA OF THE PANCREAS OR PAPANILLA OF VATER (N = 87)**

| Variable    | Coef-<br>ficient | SE    | p<br>Value | Category | Odds<br>Ratio | 95%<br>CI |
|-------------|------------------|-------|------------|----------|---------------|-----------|
| Splenectomy | -1.521           | 0.583 | 0.0059     | yes      | 1             |           |
|             |                  |       |            | no       | 0.22          | 0.07–0.69 |

Test for goodness of fit:  $p = 1.000$  (Brown)  $\alpha = 0.01$ .



**Figure 1.** Odds for postoperative morbidity according to age after radical surgery of carcinoma of the pancreas and the papilla of Vater. Footnote: OR = 1 with age 60 years.



**Figure 2.** Odds for postoperative mortality according to preoperative Karnofsky's index after radical and palliative surgery of carcinoma of the pancreas and the papilla of Vater. Footnote: OR = 1 with Karnofsky's index 70.

rate of 11% in the present study. After palliative surgery in the same period, both morbidity and mortality declined,<sup>51</sup> but most authors<sup>22,53,58-61</sup> still report a morbidity rate between 20–30%, and a mortality rate between 15–26%, consistent with a morbidity rate of 23% and a mortality rate of 14% in the present study. A higher morbidity rate but a comparable or even lower mortality rate<sup>51,54,57,59,60</sup> after radical surgery compared with a palliative operation is consistent with the results of the present study. This conclusion was substantiated by the results of the multivariate analyses.

### Total Pancreatectomy Versus Whipple's Procedure

Total pancreatectomy is reported<sup>53</sup> to have lower morbidity rate than a Whipple's procedure, while others<sup>16,56,62</sup> report the contrary. A lower mortality rate after total pancreatectomy versus a Whipple's procedure is also reported,<sup>8,62</sup> but most authors<sup>16,20,56,60</sup> report the highest mortality rates after total pancreatectomy. This study revealed comparable risks for postoperative morbidity and mortality between the two radical surgical

procedures, a conclusion further substantiated by the results of the multivariate analyses. Difficulties with diabetic management after total pancreatectomy is reported in 18% of the patients;<sup>56</sup> uncontrolled diabetes is reported to be the direct cause of death in 4–5% of these patients.<sup>63,64</sup> Because better long-term survival after total pancreatectomy compared with a Whipple's procedure is based on theoretical grounds and not on a proven survival benefit,<sup>56</sup> the present study discerned no benefit from total pancreatectomy compared with a Whipple's procedure.

### Splenectomy

Splenectomy performed in a radical procedure doubled the postoperative morbidity rate. In particular, it increased the rate of infectious complications and was revealed by the multivariate analysis as a true independent significant risk factor. Metastases to the lymph nodes along the spleen and the pancreatic tail from tumors of the pancreatic head and the papilla of Vater is not reported.<sup>65</sup> Consequently the results of this study suggest preserving the spleen if possible in radical operations of tumors of the pancreatic head and the papilla of Vater.

### Type of Complications

The “general” complications (cardial, pulmonary, and thromboembolic) were frequent after radical surgery. This result is consistent with that of Gilsdorf and Spanos<sup>9</sup> while others<sup>11,19,52,56,64,66</sup> report general complications as infrequent causes of death. Differences in selection of patients for radical surgery may partly explain this inconsistency. Anastomotic leaks, hemorrhage and intraabdominal infections in these reports,<sup>11,19,52,56,64,66</sup> are responsible for 50–70% of the postoperative deaths. These results are not contradicted by the present study because there is a multifactorial cause of postoperative

**Table 12. SUMMARY OF LOGISTIC REGRESSION ANALYSIS OF RISK FACTORS FOR POSTOPERATIVE MORTALITY AFTER RADICAL RESECTIONS IN PATIENTS WITH CARCINOMA OF THE PANCREAS OR PAPILLA OF VATER (N = 85)**

| Variable                           | Coef-ficient | SE    | p Value | Category | Odds Ratio | 95% CI    |
|------------------------------------|--------------|-------|---------|----------|------------|-----------|
| Karnofsky's index before operation | -0.092       | 0.035 | 0.005   | x        | 1          |           |
|                                    |              |       |         | x + 10   | 0.40       | 0.20-0.79 |
|                                    |              |       |         | x + 20   | 0.16       | 0.04-0.63 |
|                                    |              |       |         | x + 30   | 0.06       | 0.01-0.50 |

Test for goodness of fit: p = 0.25 (Hosmer); p = 0.39 (Brown) alpha = 0.01.



Table 13. SUMMARY OF LOGISTIC REGRESSION ANALYSIS OF RISK FACTORS FOR POSTOPERATIVE MORBIDITY AFTER PALLIATIVE OPERATIONS IN PATIENTS WITH CARCINOMA OF THE PANCREAS OF PAPANICOLAOU (N = 243)

| Variable                  | Coefficient | SE    | p Value | Category | Odds Ratio | 95% CI    |
|---------------------------|-------------|-------|---------|----------|------------|-----------|
| Diabetes before operation | -0.969      | 0.442 | 0.034   | yes      | 1          |           |
|                           |             |       |         | no       | 0.38       | 0.16-0.90 |

Test for goodness of fit:  $p = 1.000$  (Brown)  $\alpha = 0.01$ .

complications and death. Anastomotic leaks are reported<sup>9,11,17,19,20,52,53,56,63,66,68</sup> in 13-37% and pancreatic fistula in 4-24% of radical resected patients,<sup>9-11,16,17,19,52,53,56,66,67</sup> and as a major factor for postoperative death in 7-75% of patients consistent with the results of the present study. Infectious complications with the exception of intra-abdominal sepsis, is reported in 10-35% of radical operated patients,<sup>9,11,16,19,52,66</sup> which is consistent with a corresponding rate of 15% in this study. Contrary to what is reported,<sup>26</sup> the present study revealed no positive effect from antibiotic prophylaxis on postoperative complications by taking other risk factors into account simultaneously in the multivariate analysis. This result must be interpreted with care as antibiotic and thrombose prophylaxis were the sole data retrospectively accrued in this trial.

After palliative operations, a morbidity rate between 13-46% and a mortality rate between 1-41% is reported,<sup>6,23,24,56,69</sup> in consistency with a morbidity rate of 23% and a mortality rate of 14% in this study.

### Biliary Versus Biliary and Duodenal Bypass

After biliary bypass, a risk of secondary duodenal obstruction is reported in 6-50% of the patients,<sup>22,23,56,59,61,69-72</sup> while concomitant duodenal bypass compared

with bile diversion alone is reported to increase the morbidity rate<sup>23,51,69</sup> and the mortality rate.<sup>60</sup> Contrary results are reported from Glantz and Ozeran,<sup>70</sup> who did not find any increased morbidity or mortality rate after a double-bypass, compared with bile diversion alone. Comparable, or even lower morbidity and mortality rates after double bypass are also reported from others.<sup>23,51,59,61,69,72</sup> This study revealed comparable postoperative complication and mortality rates after the two palliative bypass procedures. This conclusion was further substantiated by the results of the multivariate analyses.

### Hospital Groups and Complications

Centralization of radical pancreatic surgery to specialized centers to lower postoperative morbidity and mortality is suggested by several authors,<sup>9,26,57,63</sup> while others<sup>52,54</sup> suggest a strict patient selection, rather than the experience of the surgeon, to be the most important issue in reducing postoperative complications and death. The hospital group was not found as an influential factor on the postoperative mortality rates, whereas hospital group might have some influence on the complication rates after radical surgery, with lowest risks at the university hospitals.

Table 14. SUMMARY OF LOGISTIC REGRESSION ANALYSIS OF RISK FACTORS FOR POSTOPERATIVE MORTALITY AFTER PALLIATIVE OPERATIONS IN PATIENTS WITH CARCINOMA OF THE PANCREAS OR PAPANICOLAOU (N = 180)

| Variable                           | Coefficient | SE    | p Value | Category | Odds Ratio | 95% CI    |
|------------------------------------|-------------|-------|---------|----------|------------|-----------|
| Karnofsky's index before operation | -0.057      | 0.014 | 0.0000  | x        | 1          |           |
|                                    |             |       |         | x + 10   | 0.57       | 0.43-0.74 |
|                                    |             |       |         | x + 20   | 0.32       | 0.18-0.55 |
|                                    |             |       |         | x + 30   | 0.18       | 0.08-0.41 |
| Liver metastasis                   | -1.603      | 0.500 | 0.0008  | yes      | 1          |           |
|                                    |             |       |         | no       | 0.20       | 0.08-0.52 |
| Diabetes before operation          | -1.606      | 0.595 | 0.0088  | yes      | 1          |           |
|                                    |             |       |         | no       | 0.20       | 0.06-0.64 |

Test for goodness of fit:  $p = 0.22$  (Hosmer);  $p = 0.21$  (Brown)  $\alpha = 0.01$ .

**Table 15. SUMMARY OF LOGISTIC REGRESSION ANALYSIS OF RISK FACTORS FOR POSTOPERATIVE MORBIDITY AND MORTALITY IN PATIENTS WITH CARCINOMA OF THE PANCREAS OR PAPANICOLAOU OF VATER WITH RADICAL VERSUS PALLIATIVE SURGERY INCLUDED IN THE MODEL (N = 251)**

| Variable                           | Coefficient | SE    | p Value | Category   | Odds Ratio | 95% CI    |
|------------------------------------|-------------|-------|---------|------------|------------|-----------|
| Morbidity                          |             |       |         |            |            |           |
| Surgical procedure                 | -0.993      | 0.291 | 0.0006  | Radical    | 1          |           |
|                                    |             |       |         | Palliative | 0.37       | 0.21-0.66 |
| Mortality                          |             |       |         |            |            |           |
| Karnofsky's index before operation | -0.052      | 0.012 | 0.0000  | x          | 1          |           |
|                                    |             |       |         | x + 10     | 0.59       | 0.47-0.75 |
|                                    |             |       |         | x + 20     | 0.35       | 0.22-0.56 |
|                                    |             |       |         | x + 30     | 0.21       | 0.10-0.43 |
| Liver metastasis                   | -1.145      | 0.395 | 0.0043  | yes        | 1          |           |
|                                    |             |       |         | no         | 0.32       | 0.15-0.69 |

Test for goodness of fit (morbidity):  $p = 1.000$  (Brown);  $\alpha = 0.01$ .

Test for goodness of fit (mortality):  $p = 0.82$  (Hosmer);  $p = 0.68$  (Brown).

## Preoperative Biliary Drainage and Complications

Preoperative biliary drainage (PBD), by the percutaneous transhepatic approach (PTBD),<sup>73</sup> or by retrograde endoscopic transpapillary inserted drains (EBD),<sup>33</sup> has replaced the previous initial operative bile diversion. Complications and deaths after PTBD, is reported in 5–72%<sup>27,29–32,35,37,74–76</sup> and in 0–6%,<sup>29,30</sup> respectively. After EBD, a complication rate of 19% was reported<sup>76</sup> and 6% of patients died within 30 days after this procedure. Many retrospective studies report a beneficial effect from PBD or a deleterious effect from high bilirubin levels on postoperative morbidity and mortality<sup>9,11,20,26,28,32,67,77,78</sup> while others<sup>29,57</sup> report no effect. Two prospective nonrandomized studies reported contrary results.<sup>31,79</sup> In two randomized studies, no beneficial effect from PBD was discovered,<sup>27,30</sup> whereas Lygidakis et al.<sup>80</sup> reported a significant reduced complication rate after PBD but a comparable mortality rate in the two groups. In a retrospective study of risk factors analyzed multivariately, Dixon et al.<sup>81</sup> reported a high bilirubin level as a risk factor for postoperative mortality but not for complications. The present study was not randomized, because it was not feasible. Reliable results may be obtained by applying multivariate models as in the present study, which did not reveal any beneficial effect from PBD on postoperative complications and deaths.

## Risk Factors

A high age of the patient increases both the morbidity and mortality rate after radical surgery.<sup>26,56,67,77</sup> This study revealed a marginally increased risk for postoperative complications independently due to an increasing

age in patients radically operated on, but age had no significant independent effect on the postoperative mortality rate. This result is in agreement with other reports.<sup>9,55</sup> Other reported risk factors for complications and deaths after radical surgery are: weight loss, diabetes, presenting pain, high s-bilirubin, stage, tumor invasion of duodenum, antibiotic prophylaxis, and the experience of the surgeon.<sup>9,26,77</sup> Of these reported risk factors, the present study revealed only stage as a marginal independent factor of risk for complications. This study did not confirm any of these risk factors to independently influence the mortality after radical surgery. The clinical performance of the patient as judged by the Karnofsky's index was revealed as the only true risk factor for death.

In palliative pancreatic surgery, the risk factors for complications and death are sparingly mentioned in the literature. Technical expertise, weight loss, age, and a high bilirubin level, are reported as risk factors.<sup>51,77,81</sup> None of these reported risk factors were confirmed as true factors of risk in this study.

## CONCLUSIONS

To reduce the risks of postoperative morbidity and mortality in pancreatic cancer surgery, a pancreatoduodenal resection, i.e., a Whipple's operation without splenectomy should be preferred as the radical procedure in tumors of the papilla and the pancreatic head. Preoperative biliary drainage may be omitted before radical surgery. High age should be considered as a relative contraindication for radical surgery; a low Karnofsky's index should prohibit almost any attempt of radical surgery.

Biliary and duodenal bypass simultaneously should be the preferred palliative bypass procedure. In patients

Table 16. COMPARISON OF SUMMARY OF LOGISTIC REGRESSION ANALYSES OF RISK FACTORS FOR POSTOPERATIVE MORBIDITY AND MORTALITY ACCORDING TO ALPHA = 0.05 WITH BONFERRONI'S ADJUSTMENTS AND ALPHA = 0.01 AS AN END POINT FOR THE COMPARISONS IN THE ANALYSES

| Dependent Variable                         | Variable  | p Value (0.05) | p Value (Bonferroni's Adjustment) | p Value (0.01) |
|--|---|----------------|-----------------------------------|----------------|
| Postoperative morbidity<br>Radical surgery | Age   | 0.008          | Significant                       | *              |
|  | Antibiotic prophylaxis                            | 0.032          | NS                                | *              |
|  | Splenectomy                                       | 0.0004         | Significant                       | 0.0059         |
|  | TNM stage   | 0.002          | Significant                       | *              |
|  | Invasion of duodenum & Hospital group             | 0.002          | Significant 0.044**               | *              |
| Palliative surgery                         | Diabetes at admission                             | 0.028          | Marginal                          | 0.034          |
|  | Tumour site & tumour extension into large vessels | 0.020          | Significant 0.048**               | *              |
| Radical and palliative surgery             | Age   | 0.028          | Marginal                          | *              |
|  | Surgical procedure                                | 0.0002         | Significant 0.0282**              | 0.0006         |
| Postoperative mortality<br>Radical surgery | Karnofsky's index before operation                | 0.005          | Significant                       | 0.005          |
|  | Diabetes at admission                             | 0.009          | Significant                       | 0.0088         |
|  | Karnofsky's index before operation                | 0.0000         | Significant                       | 0.0000         |
|  | s-bilirubin before operation                      | 0.043          | NS                                | *              |
|  | Liver metastases                                  | 0.0003         | Significant 0.0523**              | 0.0008         |
| Radical and palliative surgery             | Karnofsky's index before operation                | 0.0000         | Significant                       | 0.0000         |
|  | s-Bilirubin before operation                      | 0.038          | NS                                | *              |
|  | Liver metastases                                  | 0.002          | Significant 0.040**               | 0.0043         |

\* Variables not included in the model with alpha = 0.01 for the comparisons.

\*\* Overall alpha level of the model with Bonferroni's adjustment.

with obvious unresectable tumors, nonsurgical palliation of jaundice should be considered according to the presence of independent risk factors, i.e., diabetes, low Karnofsky's index, and liver metastases.

### Other Participants in the Trial

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Viste, Jon A. Søreide, Olav Dahl, Arild Horn, Arne Skarstein, Tor Torkelsen, Gunnar Tronstad, Ijaz Abbasi, Arne Reisæter, Stein Haram, Egil Lien, Arve Sæbø, Inge H. Nygaard, Ove J. Lange, Ludvig Hope, Ronald Mårvik, Knut Skreden, Knut Johannesen, Tormod Bjerkeset, Erik Ellekjær, Renato Capoferro, Steinar Danielsen, Dag Johansen, Arthur Revhaug, Glen Thorsen, Rune Vilkenen.

### Participating Norwegian Hospitals

Østfold Central Hospital, Fredrikstad; Askim Hospital, Askim; Moss Hospital, Moss; Bærum Hospital, Bærum; Akershus Central Hospital, Lørenskog; Rikshospitalet, Oslo; Ullevål Hospital, Oslo; Aker Hospital, Oslo; Lovisenberg Hospital, Oslo; Hedmark Central Hospital, Elverum; Tynset Hospital, Tynset; Lillehammer Hospital, Lillehammer; Gjøvik Hospital, Gjøvik; Buskerud Central Hospital, Drammen; Vestfold Central

Hospital, Tønsberg; Telemark Central Hospital, Skien; Aust-Agder Central Hospital, Arendal; Vest-Agder Central Hospital, Kristiansand; Rogaland Central Hospital, Stavanger; Haugesund Hospital, Haugesund; Haukeland University Hospital, Bergen; Haraldsplass Hospital, Bergen; Stord Hospital, Lervik; Odda Hospital, Odda; Voss Hospital, Voss; Sogn og Fjordane Central Hospital, Førde; Ålesund Hospital, Ålesund; Volda Hospital, Volda; Molde Hospital, Molde; Kristiansund Hospital, Kristiansund; Trondheim University Hospital, Trondheim; Orkdal Hospital, Orkdal; Innherred Hospital, Levanger; Nordland Central Hospital, Bodø; Rana Hospital, Mo i Rana; Tromsø University Hospital, Tromsø; Harstad Hospital, Harstad; Hammerfest Hospital, Hammerfest.

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