Preoperative Biliary Drainage for Cancer of the Head of the Pancreas

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ABSTRACT

BACKGROUND
The benefits of preoperative biliary drainage, which was introduced to improve the postoperative outcome in patients with obstructive jaundice caused by a tumor of the pancreatic head, are unclear.

METHODS
In this multicenter, randomized trial, we compared preoperative biliary drainage with surgery alone for patients with cancer of the pancreatic head. Patients with obstructive jaundice and a bilirubin level of 40 to 250 µmol per liter (2.3 to 14.6 mg per deciliter) were randomly assigned to undergo either preoperative biliary drainage for 4 to 6 weeks, followed by surgery, or surgery alone within 1 week after diagnosis. Preoperative biliary drainage was attempted primarily with the placement of an endoprosthesis by means of endoscopic retrograde cholangiopancreatography. The primary outcome was the rate of serious complications within 120 days after randomization.

RESULTS
We enrolled 202 patients; 96 were assigned to undergo early surgery and 106 to undergo preoperative biliary drainage; 6 patients were excluded from the analysis. The rates of serious complications were 39% (37 patients) in the early-surgery group and 74% (75 patients) in the biliary-drainage group (relative risk in the early-surgery group, 0.54; 95% confidence interval [CI], 0.41 to 0.71; P<0.001). Preoperative biliary drainage was successful in 96 patients (94%) after one or more attempts, with complications in 47 patients (46%). Surgery-related complications occurred in 35 patients (37%) in the early-surgery group and in 48 patients (47%) in the biliary-drainage group (relative risk, 0.79; 95% CI, 0.57 to 1.11; P=0.14). Mortality and the length of hospital stay did not differ significantly between the two groups.

CONCLUSIONS
Routine preoperative biliary drainage in patients undergoing surgery for cancer of the pancreatic head increases the rate of complications. (Current Controlled Trials number, ISRCTN31939699.)
Obstructive jaundice is the most common symptom in patients with periampullary cancer (located near the ampulla of Vater) or cancer of the pancreatic head. For patients with a resectable tumor who have no radiologic evidence of metastasis, surgical resection is the only option for cure.\textsuperscript{1-3} Since surgery in patients with jaundice is thought to increase the risk of postoperative complications, preoperative biliary drainage was introduced to improve the postoperative outcome.\textsuperscript{4} In several experimental studies and retrospective case series, preoperative biliary drainage reduced morbidity and mortality after surgery.\textsuperscript{4-7} However, two meta-analyses of randomized trials and a systematic review of descriptive series showed that the overall complication rate in patients undergoing preoperative biliary drainage was higher than that in patients who proceeded directly to surgery.\textsuperscript{8,9} This difference was partially explained by complications associated with the preoperative biliary drainage procedure itself. Nevertheless, preoperative biliary drainage has been incorporated into the surgical treatment of cancer of the pancreatic head in many centers.\textsuperscript{10-12} To assess the rates of serious complications and death and the length of hospital stay associated with preoperative biliary drainage, we conducted a multicenter, randomized trial comparing the preoperative procedure, followed by surgery, with surgery alone.

METHODS

STUDY DESIGN
We recruited patients 18 to 85 years of age who had a serum total bilirubin level of 40 to 250 µmol per liter (2.3 to 14.6 mg per deciliter) and no evidence on computed tomography (CT) of distant metastasis or local vascular involvement (which was defined as tumor surrounding portal or mesenteric vessels for more than 180 degrees of their circumference or an irregular vessel margin). The interval between CT and randomization was set to be less than 4 days. Endoscopic ultrasonography was selectively performed if the CT findings were inconclusive.

Patients with a serious coexisting illness (Karnofsky performance score, \(<50\) [on a scale of 0 to 100, with higher scores indicating better performance]), another contraindication for major surgery, ongoing cholangitis, or previous preoperative biliary drainage with stenting by means of endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) were excluded. Other exclusion criteria were the current receipt of neoadjuvant chemotherapy or the presence of a serious gastric-outlet obstruction (tumor-related duodenal stenosis, which was defined by vomiting and an oral intake of \(<1\) liter per day). All patients provided written informed consent.

Patients were randomly assigned to undergo either endoscopic preoperative biliary drainage for 4 to 6 weeks, followed by surgery, or surgery alone within 1 week after diagnosis. Randomization, which was stratified according to study center, was performed with a computer program at the coordinating trial center. The medical ethics committee at each study center approved the protocol, which has been described previously.\textsuperscript{13}

STUDY OVERSIGHT
The study coordinator collected data at each study site. The trial was sponsored by the Netherlands Organization for Health Research and Development, which did not have access to outcome data during the trial and did not participate in data analyses or the preparation of the manuscript. The study coordinator, the clinical epidemiologist, and the lead academic author analyzed the data and vouch for the completeness and accuracy of the analyses. No endoscopic equipment or stents were donated by the manufacturer.

ENDOSCOPIC PREOPERATIVE BILIARY DRAINAGE
An attending gastroenterologist who was experienced in endoscopic preoperative biliary drainage performed the procedure using ERCP with plastic stent placement, with or without antibiotic prophylaxis, according to local policy. If the procedure was unsuccessful, the patient was referred to a tertiary center for a second attempt. PTC with stent placement to achieve preoperative biliary drainage was considered a rescue option in case of failed ERCP. Biliary drainage was defined as successful if the serum bilirubin level decreased by 50% or more within 2 weeks after the procedure. A new stent was placed if signs of inadequate bile drainage, with or without cholangitis, developed. After 4 to 6 weeks of drainage, patients underwent surgery.

SURGERY
Five academic and eight regional hospitals agreed to provide operating-room capacity to ensure that early surgery could be performed as required by
the protocol. Each of the participating hospitals performed at least 10 resections of cancer of the pancreatic head per year.

All patients received perioperative antibiotics. As prophylaxis only if indicated, patients received vitamin K for coagulation disorders and octreotide or its analogues for the treatment of a pancreas with a soft texture or a nondilated pancreatic duct. The standard surgical procedure for resectable tumors was the pylorus-preserving pancreateoduodenectomy, including removal of all lymph nodes on the right side of the portal vein and mesenteric artery.\textsuperscript{14}

If metastasis into the proximal duodenum or pylorus was suspected, a classic Whipple procedure was performed, with resection of the distal stomach. If limited metastasis into the portal or superior mesenteric vein was found, a wedge resection of these vessels was included in the procedure.\textsuperscript{14,15} No specific modifications of surgical technique were expected for patients with jaundice, particularly with respect to creating the hepaticojejunostomy. The extrahepatic bile duct becomes dilated after distal obstruction, with concomitant induction of fibrosis in the duct wall, and usually remains dilated after preoperative biliary drainage because of decreased compliance of the duct. If resection was deferred because of metastasis or local spread, biopsy samples were obtained for histologic analysis. Palliative treatment generally consisted of the creation of a hepaticojejunostomy with or without gastroenterostomy and celiac plexus neurolysis.\textsuperscript{14,16,17} If a hepaticojejunostomy was not feasible, an expandable metal stent was inserted postoperatively by means of ERCP.

EVALUATION OF OUTCOMES

The primary outcome was the rate of serious complications up to 120 days after randomization, including any complication related to the drainage procedure or the surgical treatment that prompted an additional medical, endoscopic, or surgical intervention resulting in an extension of the hospital stay, readmission to the hospital, or death. The definitions and management of complications have been used in previous studies evaluating the management of complications on the basis of generally accepted criteria.\textsuperscript{18-25} (Definitions of all complications are listed in Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Secondary outcomes were mortality and the length of hospital stay. Symptoms or signs of progressive or recurrent tumor within the study period were not considered as treatment-related events.

Outpatient visits were scheduled at 2, 6, and 12 weeks after discharge. A standardized evaluation of symptoms and, if indicated, laboratory tests and radiologic studies were performed at each visit. In addition, data regarding hospital admissions and all performed procedures were collected, with special attention to any complication, including all additional endoscopic and surgical procedures. When necessary, the patient’s physician was consulted for additional information.

To exclude bias in evaluating potential complications, an adjudication committee reviewed all events in a blinded fashion and classified them as serious complications or not serious, according to the definitions in the study protocol.\textsuperscript{13}

STATISTICAL ANALYSIS

The principal analysis consisted of an intention-to-treat comparison of the proportion of patients with serious complications in the two treatment groups. The goal was to test for noninferiority of early surgery, as compared with preoperative biliary drainage, with respect to the primary outcome, and superiority with respect to secondary outcomes. Our previous meta-analysis was used to calculate the required sample size.\textsuperscript{9}

Assuming that there would be a complication rate of 38% in the early-surgery group and 48% in the biliary-drainage group, we would consider early surgery to be noninferior if the associated percentage of serious complications was less than 10 percentage points above the percentage of serious complications in the biliary-drainage group. We used a two-group large-sample normal approximation test of proportions, with a one-sided significance level of 0.05, to test the null hypothesis that early surgery would lead to an increase of at least 10 percentage points in the rate of complications, as compared with preoperative biliary drainage, followed by surgery. To attain a power of 80% to show noninferiority of early surgery, 94 patients were needed in each group. We also performed a logistic-regression analysis of the complication rate with adjustment for potential prognostic factors of age, sex, body-mass index, tumor site (pancreatic vs. periampullary), and degree of jaundice. We calculated two-sided 95% confidence intervals for all outcome measures.

After the enrollment of 50% of the patients, a safety committee (consisting of a gastroenterologist, a surgeon, and a clinical epidemiologist)
performed a planned, blinded interim analysis of the primary outcome, for which the nominal significance level was lowered to a more restrictive two-sided $P$ value of less than 0.01. The committee recommended the continuation of enrollment up to the calculated sample size.

**RESULTS**

**PATIENTS AND STUDY INTERVENTIONS**

Between November 2003 and June 2008, a total of 202 patients underwent randomization (Fig. 1). After randomization, two patients withdrew consent, and four patients were found to be ineligible because the serum total bilirubin level had not been in accordance with the protocol before randomization. These six patients were not included in the analyses. The demographic and clinical characteristics of the two study groups were similar at baseline, with the exception of sex and body-mass index (Table 1).

Five patients who were assigned to the early-surgery group underwent preoperative biliary drainage for the following reasons: the surgical facility was not available in time for early surgery (in the case of three patients), intercurrent cholangitis developed after earlier ERC without preoperative biliary drainage (in one patient), and hyperglycemia (serum glucose level, 77 mmol per liter) developed (in one patient).

Of the 102 patients in the biliary-drainage group 56 (55%) underwent a first attempt at preoperative biliary drainage in a community hospital, and 46 (45%) underwent a first attempt in an academic hospital. Adequate drainage was achieved in 77 patients (75%) on the first attempt. The rates of successful initial stent placement in academic centers and community hospitals did not differ significantly (83% and 69%, respectively; $P=0.13$).
Symptoms that were associated with obstructive jaundice resolved within 10 days after successful drainage. Reasons for initial failure of stent placement were an inability to cannulate the common bile duct in 12 patients with normal-appearing papilla, extensive tumor growth at the site of the papilla in 8 patients, and failure to reach the papilla in 1 patient with a Billroth type II gastric resection. After a second attempt, ERCP or PTC resulted in adequate drainage in 96 patients (94%). Three patients did not undergo drainage because of misdiagnosed choledocholithiasis (in two patients) and endoscopic removal of an adenomatous polyp (in one patient). There were technical failures in another three patients: failure of both ERCP and PTC (in one patient), ERCP-associated bile-duct perforation for which an emergency laparotomy with resection was performed (in one patient), and sphincterotomy-associated hemorrhage, which stopped the procedure (in one patient). The patient with hemorrhage died 18 days later as a consequence of cholangiosepsis with hemodynamic instability and preexisting cardiac failure.

The mean time to surgery was 1.2 weeks (95% confidence interval [CI], 0.9 to 1.4) for the early-surgery group and 5.2 weeks (95% CI, 4.8 to 5.5) for the biliary-drainage group. Surgical exploration was canceled in two patients in the early-surgery group because of choledocholithiasis in one patient and pulmonary metastases of a previous breast carcinoma identified during the work-up in the other. Seven patients in the biliary-drainage group did not undergo surgery because of choledocholithiasis in one patient and pulmonary metastases of a previous breast carcinoma identified during the work-up in the other. The body-mass index was the weight in kilograms divided by the square of the height in meters.

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The rates of serious complications were 39% (37 patients) in the early-surgery group and 74% (75 patients) in the biliary-drainage group; the relative risk of serious complications with early surgery was 0.54 (95% CI, 0.41 to 0.71) (Table 3). We rejected the null hypothesis of an increase in complications in the early-surgery group (P<0.001 by a one-sided normal-approximation test). An additional test of superiority showed that early surgery led to fewer complications than preoperative biliary drainage (P<0.001). The difference was also significant in the logistic-regression analysis (P<0.001).

Patients in the biliary-drainage group, as compared with those in the early-surgery group, had significantly more readmissions for complications.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Early Surgery (N=94)</th>
<th>Preoperative Biliary Drainage (N=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related to preoperative biliary drainage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>2 (2)</td>
<td>47 (46)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Cholangitis†</td>
<td>2 (2)</td>
<td>27 (26)</td>
</tr>
<tr>
<td>Perforation</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hemorrhage after ERCP‡</td>
<td>0</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Related to stent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>1 (1)</td>
<td>15 (15)</td>
</tr>
<tr>
<td>Need for exchange</td>
<td>2 (2)</td>
<td>31 (30)</td>
</tr>
<tr>
<td>Related to surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>35 (37)</td>
<td>48 (47)</td>
</tr>
<tr>
<td>Pancreaticojejunostomy leakage§</td>
<td>11 (12)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Grade A</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Grade B</td>
<td>4 (4)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Grade C</td>
<td>6 (6)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hemorrhage after pancreatectomy‡</td>
<td>4 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>9 (10)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Biliary leakage</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Gastrojejunostomy or duodenoojejunostomy leakage</td>
<td>2 (2)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Intraabdominal abscess</td>
<td>3 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Wound infection</td>
<td>7 (7)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Portal-vein thrombosis</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (5)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>3 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Need for repeated laparotomy¶</td>
<td>13 (14)</td>
<td>12 (12)</td>
</tr>
</tbody>
</table>

* The numbers refer to patients who had one or more complications. ERCP denotes endoscopic retrograde cholangio-pancreatography.
† In two patients, cholecystitis occurred in connection with cholangitis, prompting antibiotic treatment, without the need for cholecystectomy.
‡ Hemorrhage was defined as bleeding that required the transfusion of at least 4 units of packed red cells during a 24-hour period or bleeding that led to repeat laparotomy or another intervention.
§ Grade A refers to transient biochemical leakage that does not require treatment, grade B refers to leakage that is managed with prolonged or percutaneous drainage, and grade C refers to leakage requiring repeat laparotomy.
¶ This category refers to complications of either preoperative biliary drainage or another surgical procedure.

Table 2. Serious Complications within 120 Days after Randomization.*
and stayed on average 2 days longer in the hospital. There was no significant difference in mortality between the groups. Among patients who underwent a palliative bypass procedure, surgical complications developed in 18 of 33 patients (55%) in the biliary-drainage group, as compared with 5 of 28 patients (18%) in the early-surgery group (P=0.003).

**DISCUSSION**

In this multicenter, randomized trial, we examined whether preoperative biliary drainage should be performed routinely in patients with obstructive jaundice caused by cancer of the pancreatic head before resection. We found that endoscopic preoperative biliary drainage with placement of a plastic stent did not have a beneficial effect on the surgical outcome. Early surgery without preoperative biliary drainage did not increase the risk of complications, as compared with preoperative biliary drainage, followed by surgery.

The postoperative complication rate did not differ significantly between the two groups, as has been reported previously. With respect to complications related to endoscopic preoperative biliary drainage, the incidence of pancreatitis, perforation, or hemorrhage in our study was in accordance with the incidence reported by others. The rate of cholangitis associated with preoperative biliary drainage was high and an important reason for readmission. This high incidence of cholangitis was reported within the same range by all participating centers.

In contrast with earlier randomized studies, our study showed that preoperative biliary drainage did not necessarily prolong the length of the hospital stay. The previously observed extended hospital stay can be attributed to the use of PTC drainage, whereas endoscopic drainage, as used in our study, is often performed on an outpatient basis. The use of preoperative biliary drainage did not influence postoperative mortality. Pancreatic surgery that is performed in high-volume centers is associated with death rates that are well below 5%, an important argument for centralization of such complex surgical procedures.

In our study, the overall rate of death was 7% (which included one patient who died after the biliary-drainage procedure) and did not differ significantly between the two treatment strategies.

The optimal duration of biliary drainage before surgery has not been established. Experimental and clinical studies have suggested that a period of at least 4 to 6 weeks is needed for the restoration of normal major synthetic and clearance functions of the liver, as well as mucosal intestinal barrier functions. A short period of drainage may not lead to full recovery of the metabolic abnormalities associated with obstructive jaundice. In four randomized studies that did not show a benefit of preoperative biliary drainage, the mean duration of drainage was 7 to 18 days. Our trial called for 4 to 6 weeks of drainage. An even longer period would be unlikely to yield better results, would increase the risk of stent occlusion and inflammation of the bile-duct wall, and would result in a prolonged postponement of surgery that would be unjustifiable for a potentially resectable tumor.

Beneficial effects of preoperative biliary drainage were found in early, nonrandomized studies that involved a small number of patients and an imperfect methodologic design. In four of five randomized trials, preoperative biliary drainage by means of PTC was the standard mode of drainage, whereas ERCP, a less invasive procedure, is currently preferred. The consequences of percutaneous and endoscopic drainage differ largely in terms of restoration of the enterohepatic cycle.
Table 3. Major Outcomes. *

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early Surgery (N = 94)</th>
<th>Preoperative Biliary Drainage (N = 102)</th>
<th>Relative Risk (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall protocol-specified complications — no. (%)</td>
<td>37 (39)</td>
<td>75 (74)</td>
<td>0.54 (0.41–0.71)</td>
</tr>
<tr>
<td>Preoperative biliary drainage</td>
<td>2 (2)</td>
<td>47 (46)</td>
<td>NA</td>
</tr>
<tr>
<td>Surgery</td>
<td>35 (37)</td>
<td>48 (47)</td>
<td>0.79 (0.57–1.11)</td>
</tr>
<tr>
<td>Other complications (not included in protocol) — no. (%)‡</td>
<td>30 (32)</td>
<td>25 (25)</td>
<td>1.30 (0.83–2.04)</td>
</tr>
<tr>
<td>Death — no. (%)</td>
<td>12 (13)</td>
<td>15 (15)</td>
<td>0.85 (0.42–1.72)</td>
</tr>
<tr>
<td>From protocol-specified complication</td>
<td>4 (4)</td>
<td>9 (9)</td>
<td>0.48 (0.15–1.51)</td>
</tr>
<tr>
<td>From any cause</td>
<td>11 (12)</td>
<td>34 (33)</td>
<td>0.35 (0.19–0.65)</td>
</tr>
<tr>
<td>Hospital readmission — no. (%)</td>
<td>18 (19)</td>
<td>40 (39)</td>
<td>0.49 (0.30–0.79)</td>
</tr>
<tr>
<td>Hospital stay — days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For protocol-specified treatment§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>13</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>10–20</td>
<td>11–22</td>
<td></td>
</tr>
<tr>
<td>For any reason</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>10–21</td>
<td>11–22</td>
<td></td>
</tr>
</tbody>
</table>

* The outcome numbers refer to patients who had one or more complications. NA denotes not applicable.
† The relative risks are for early surgery versus preoperative biliary drainage.
‡ Other complications included urinary tract infection, chylous ascites, delirium, rectum prolapse, clostridium infection, pulmonary embolism, cardiac arrhythmia, hypoglycemic coma, bladder hemorrhage, catheter-related sepsis, and incisional hernia.
§ Hospital stays for protocol-specified treatment included admission for preoperative biliary drainage (after randomization and performed on an inpatient basis), surgery, and necessary readmission for any protocol-specified complication.

and bacterial colonization and inflammation of the biliary tract. 4-7 The percutaneous route is reserved for failed endoscopic attempts. In these studies, tumors causing proximal and distal bile-duct obstruction were included, but such tumors are now considered to be different diseases and to require different forms of treatment.

With the advent of neoadjuvant chemotherapy used to downstage potentially unresectable tumors in the hope of improving the outcome, the issue of preoperative biliary drainage is clinically relevant. 34-36 In light of our poor results with plastic stents, preoperative biliary drainage during the period of neoadjuvant treatment might be best achieved with metal stents, which have a higher patency rate than plastic stents and do not affect the outcome of surgery. 37-39

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APPENDIX

In addition to the authors, the following investigators participated in this study (all institutions are in the Netherlands): Academic Medical Center, Amsterdam — P.R. de Reeuw; Erasmus Medical Center, Rotterdam — M.J. Morak, C. Pek, J. van der Zee; Maasstad Hospital, Rotterdam — P.P. Coene; Medisch Spectrum Twente, Enschede — J. Klaasse, M. Russell; Academic Hospital, Maastricht — R. van Dam, J.P. Rutten, C.H. Dejong; Onze Lieve Vrouwe Gasthuis, Amsterdam — L.T. de Wit, A.E. Geraedts; Catharina Hospital, Eindhoven — S. Nienhuis; Rijnstate Hospital, Arnhem — M. Spanier; Antonius Hospital, Nieuwegein — D. Boerma, B. van Ramshorst, R. Timmer; University Hospital, Utrecht — M.G. Besselink, H.J. van Santvoort, H.G. Gooszen, P.D. Siersema; Elisabeth Hospital, Tilburg — J. Heisterkamp, C.J. van Laarhoven; Ghent Hospitals, Aalst — E.J. Hesselink; Atrium Medical Center, Heerlen — M. Sosef, P. van der Schaaf; Leiden University Medical Center — B. Bonsing, P. Doornebosch. Protocol Committee — C.H.J. van Eijck, M.J. Bruno, E.A. Rauws, S.M.M. de Castro, O.R. Busch, T.M. van Gulik, P.M.M. Copyright © 2010 Massachusetts Medical Society. All rights reserved.
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