PANCREATICO-BILIARY DISEASES IN THE ERA OF THE LAPAROSCOPIC CHOLECYSTECTOMY

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PANCREATICO-BILIAIRE ZIEKTEN IN HET TIJDPERK VAN DE LAPAROSCOPISCHE CHOLECYSTECTOMIE

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CONTENTS

CHAPTER 1

INTRODUCTION

The first successful choledochotomy to remove stones from the common bile duct was performed on January 21, 1890, by Courvoisier but it was not until 1940 that the bile ducts could be explored with reasonable safety for the patient (1).

Since then choledochotomy has become an accepted therapy for choledocholithiasis. However, it is accompanied by considerable morbidity and mortality, especially in elderly patients at increased operative risk and after acute surgery (2-6).

There has always been much discussion whether to use intraoperative cholangiography routinely for the detection of common bile duct stones. Many pleas for its routine use can be found in the literature from about 1965 to 1975 (7-11). Since then, preference has moved towards the selective use of intraoperative cholangiography (12-15).

From 1972, endoscopic incision of the papilla of Vater and subsequent removal of stones in the common bile duct became the therapy of choice in patients older than 50-60 years (16-22). This age limit was originally chosen because at this age mortality from papillotomy and common bile duct exploration were about the same. The 10% of patients in whom endoscopy failed remained a problem (18,23-25). In these patients, extracorporeal shock wave lithotripsy (ESWL) seemed an attractive option before contemplating surgery (26-32). This alternative was evaluated in a series of 90 elderly patients treated by ESWL for difficult common bile duct stones. The results are described in chapter 2 of this thesis.

In 1990, the first series of laparoscopic cholecystectomy was reported (33). Never was a new surgical technique introduced so rapidly and in such an uncontrolled fashion as this operation. Because of its apparent advantages, laparoscopic cholecystectomy has become the treatment of choice for symptomatic gallbladder stones in almost all Western hospitals within a few years (34-37). However, the increased incidence of lesions of the bile ducts during this operation compared to open cholecystectomy, gives rise to concern (36,38-41). Patient selection and initial reports from centers with expert biliary surgeons have led to a very optimistic view on this operation (42). The increased incidence of choledochal repairs parallel to the introduction of the laparoscopic cholecystectomy provides evidence that the incidence of iatrogenic bile duct lesions is higher than reported.

In chapter 3 we have tried to explore the advantages of the laparoscopic cholecystectomy in terms of quality of life. However, the only way to find out the real value of the laparoscopic cholecystectomy -a prospective, randomised controlled trial comparing laparoscopic

cholecystectomy with the open technique- has become practically impossible (43). This problem, which is partly consumer driven, led us to match the first 100 patients, who were operated laparoscopically in our hospital, with 100 conventionally cholecystectomized patients. This study is described in chapter 4.

Since the introduction of the laparoscopic cholecystectomy, routine common bile duct exploration is no longer available, unless a conversion to open operation is undertaken. Laparoscopic exploration of the common bile duct is not yet generally feasible (44,45), so the important issue is to detect common bile duct stones in the preoperative phase and to treat them endoscopically. This strategy has been advocated recently and also patients younger than 50 years might be submitted to it (46-49).

The discussion about the role of intraoperative cholangiography, now during laparoscopic cholecystectomy, has been revived (46-53). Its routine use could potentially protect patients from possible bile duct damage and preoperatively unsuspected stones in the common bile duct could be detected. However, to date it has not been possible to show that routine intraoperative cholangiography during laparoscopic cholecystectomy in fact prevents bile duct injury. In addition, the natural course of unsuspected -usually small- stones in the common bile duct probably is that about 90% of these stones will pass spontaneously, thus making it difficult to prove that detection of common bile duct stones will reduce complications (54,55).

Chapter 5 is a review of the literature and deals with the management of stones in the common bile duct in the era of the laparoscopic cholecystectomy. Our results of extracorporeal shock wave lithotripsy (ESWL) of common bile duct stones, as an adjuvant to laparoscopic and endoscopic techniques, are incorporated in this chapter.

Obstruction of the pancreatic duct by stones is encountered less frequently than that of the common bile duct. Pancreatic duct obstruction by stones is almost exclusively the result of chronic pancreatitis, a disease which is largely due to chronic alcohol abuse (56,57). Stones causing increased intraductal pressure are probably a major cause of the severe invalidating abdominal pain in these patients. Surgical drainage procedures fail in the long term alleviation of pain in 20-40% of the patients (56,58-61). Taking into account the morbidity and mortality of pancreatic drainage procedures, ESWL of these intraductal stones provides an alternative with minimal morbidity and to date no mortality (62-66).

Chapter 6 describes the immediate and long term results of our first 17 patients with chronic calcifying pancreatitis treated by ESWL. Also a case with an unusual indication for ESWL of pancreatic stones is described.

As with almost all therapies, initial enthusiasm is tempered by subsequent disappointing results and enthusiasm is replaced by reservation and scepsis. Finally, often after many years of evaluation, the therapy gets the credit it deserves. We have tried to assess the role of ESWL in hepato-biliary-pancreatic surgery. Instead of very optimistic or pessimistic views, patients benefit most from well-established treatment schedules in which the different modalities all have their own, sometimes limited, role. In chapter 7 this role is described using our own patient series and those of other institutions.

Finally, chapter 8 deals with malignant obstruction of the proximal bile ducts. Obstructive symptoms are almost always the presenting features of this tumor (67), that is called cholangiocarcinoma or 'Klatskin'-tumor (68). Although a slow growing tumor, more than 90% of untreated patients die within 5 years after the diagnosis has been made, mostly due to recurrent cholangitis or hepatic failure (69). Since the development and improvement of various imaging techniques tumor staging can be done more accurately. For this reason a subpopulation of patients with cholangiocarcinoma, suitable for intentionally curative operations, can be more easily defined. Radical resection of the tumor seems to give the most hopefull results (70,71). We describe our multidisciplinary approach towards 66 patients with proximal cholangiocarcinoma and discuss the role of the various treatments and the importance of tumorfree resection margins after surgery.

Chapter 9 discusses the various results and adds some closing remarks.

Aims of this study:

What is the effectiveness of ESWL as a treatment for difficult bile duct stones in patients at increased operative risk? (chapter 2).

Does laparoscopic cholecystectomy improve quality of life and biliary and gastrointestinal symptoms better than conventional cholecystectomy? (chapter 3).

Is laparoscopic cholecystectomy superior to conventional cholecystectomy with regard to complications of both techniques? (chapter 4).

Which diagnostic and treatment schedule can be followed when common bile duct stones are suspected in a patient who will undergo laparoscopic cholecystectomy? (chapter 5).

Is ESWL a better option than operation to treat intractable pain in patients with chronic calcifying pancreatitis? (chapter 6).

To what extend does ESWL play a role in todays' pancreatico-biliary surgery? (chapter 7).

How can diagnosis and treatment of proximal cholangiocarcinoma be optimized? (chapter 8).

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CHAPTER 2

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY OF STONES IN THE COMMON BILE DUCT IN PATIENTS AT INCREASED OPERATIVE RISK.

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ABSTRACT

Objective: Assessment of efficacy of extracorporeal shock wave lithotripsy (ESWL) of stones in the common bile duct.

Design: Prospective clinical study.

Setting: Department of Surgery, University Hospital Rotterdam, Rotterdam, The Netherlands.

Subjects: 90 patients with stones in the common bile duct and at increased operative risk (median age 73 years, range 27-95).

Interventions: After failure of endoscopic measures, the first 13 patients were treated under general anaesthesia with a first generation lithotriptor. Of the next 77 patients, treated with a second generation lithotriptor, only one required general anaesthesia and 68 intravenous analgesia and sedation. Eight patients needed no analgesia at all.

Main outcome measures: fragmentation, clearance, and recurrence of stones.

Results: Fragmentation of stones was achieved in all the first 13 patients and 63 of the remaining 77. The stones were completely cleared in 62 of the 90 patients (69%). There were minor complications (macroscopic haematuria and subcapsular haematoma of right kidney) in 13 and serious complications (bacteraemia) in two. At follow-up (median 28 months), two patients had recurrent stones.

Conclusion: ESWL of stones in the common bile duct is safe and effective and should be considered in high risk patients.

INTRODUCTION

The first clinical use of extracorporeal shock wave lithotripsy (ESWL) was in the treatment of kidney stones (1), and since then it has been the treatment of choice. Other applications of ESWL were studied, and in 1986 Sauerbruch et al. reported successful fragmentation of stones in the gallbladder and in the common bile duct (17). In 1988 and 1989 the first series of patients were published in whom stones in the gallbladder and the common bile duct had been treated by ESWL (16,18). Promising results of ESWL of pancreatic stones have recently been published (3).

Stones in the common bile duct can present as the first sign of gallstone disease or after

cholecystectomy wether or not the common bile duct was explored. About 9%-16% of patients with stones in the gallbladder also have choledocholithiasis (13). In the case of stones in the common bile duct, exploration is an accepted treatment but carries a considerable mortality, which reaches 8% in elderly or high risk patients (5,12,19). For this group nowadays the treatment of choice is endoscopic sphincterotomy (2,9,20). If the gallbladder is present, it is justified to leave it there after sphincterotomy, clearance of the common bile duct, and relief of symptoms (7,14). In about 10% of cases, however, it is not possible to remove the stones from the common bile duct (2,10,18), usually because of a discrepancy between the diameter of the stone and that of the bile duct, the presence of a (large) duodenal diverticulum, or signs of a previous upper abdominal operation, particularly a Roux-en-Y reconstruction. In these cases ESWL offers an attractive alternative to exploration of the common bile duct.

We present our results of ESWL in 90 consecutive patients who had stones that could not be removed endoscopically from the common bile duct.

PATIENTS AND METHODS

The entry criteria for treatment with ESWL are shown in table I.

Table I
Criteria for treatment of stones in the common bile duct by ESWL

Symptomatic common bile duct stones (jaundice, abdominal pain, fever)
Endoscopic extraction impossible
Visualisation of stones by fluoroscopy after injection of contrast and successful positioning of the patient on the lithotriptor
No lung tissue, cysts, or aneurysms in the path of the shock waves
No bleeding disorders
No pregnancy

Ninety patients were treated between April 1986 and July 1992, the first 13 with a first generation lithotriptor, the Dornier HM3[r] (with water bath). The remaining 77 were treated with a second generation lithotriptor, the Siemens Lithostar[r] (without water bath). The principles of generation of the shock waves for these two lithotriptors are different (6). The characteristics of the patients are shown in table II.

Table II
Characteristics of 90 patients with stones in the common bile duct before treatment by ESWL. Figures are number (%) of patients unless otherwise stated.

Sex:	
Male	33 (37)
Female	57 (63)
Median (range) age (years):	73 (27-95)
Symptoms:	
Upper abdominal pain	48 (53)
Jaundice	44 (49)
Cholangitis	18 (20)
Sphincterotomy	79 (88)
Drainage:	
Naso-biliary drain	68 (76)
Percutaneous transhepatic drain	11 (12)
T-tube	11 (12)
Gallbladder in situ:	42 (47)
No of stones:	
Solitary	38 (42)
Two	21 (23)
Three or more	31 (34)
Intrahepatic stones	8 (9)
Mean (range) diameter of largest stone (mm)	25 (10-50)

The first 13 patients (treated with the Dornier lithotriptor) were given general anaesthesia. Of the next 77 patients, only one patient was given a general anaesthetic at his own request, 68 were given only intravenous analgesia and sedation with fentanyl and midazolam, and eight needed no analgesia at all.

The stones were visualised by injection of contrast medium (Telebrix 38[r], Guerbet, Gorinchem, The Netherlands) into the bile ducts (through an endoscopically placed nasobiliary drain, [n=68], or a percutaneous transhepatic drain [n=11], or a T-tube left in after cholecystectomy [n=11]). The shock waves could then be focussed on the stones under fluoroscopic guidance. All patients were given antibiotic prophylaxis (1000/200 mg amoxycillin/clavulanate intravenously half an hour before ESWL, and 8 and 16 hours afterwards). The day after ESWL the amount of fragmentation was evaluated by a new cholangiogram. If there was no obvious reduction in the diameter of the largest stone the patient underwent up to four ESWL sessions. If the diameter of the stone had been reduced, or if there were other signs of fragmentation (lines of contrast medium visible within the stone or quick disappearance of the contrast medium from the biliary tree), the bile ducts were lavaged with four liters of sterile water/24 hours through the biliary drain (saline was not used, to prevent overload of sodium). After two days of lavage, a control cholangiogram was done and, in the case of the remaining fragments, further attempt was made to remove them endoscopically or percutaneously. If this was not successfull or if there was no fragmentation of stones, the patient had either an elective exploration of the bile duct or had an endoprosthesis inserted. The latter procedure was done if the patient had an unacceptably high operative risk.

RESULTS

Fragmentation and clearance of stones

The mean (SEM) number of sessions of ESWL/patient was 1,8 (0,1) with 4360 (106) shock waves/session. The results are summarised in Figure I.

Fragmentation and subsequent clearance of stones was achieved in 62 patients (69%). In 15 cases biliary lavage alone was sufficient to clear the bile ducts, though in 47 patients additional treatment was necessary. In 14 patients (16%) the stones were fragmented but we were unable to clear them. Six underwent successful endoscopic placement of an endoprosthesis past the fragmented stones.

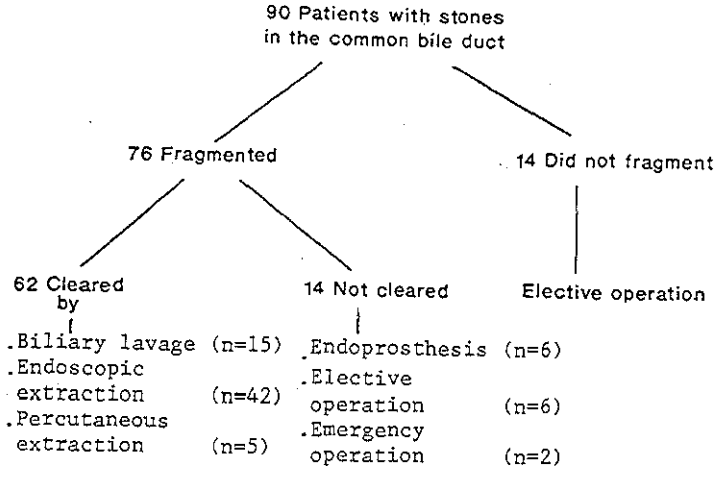

Figure 1
Results of ESWL of 90 patients with common bile duct stones.

Six underwent elective exploration of the common bile duct and two required emergency operations because of complications that developed during endoscopic attempts to clear the common bile duct (1 perforation of the common bile duct with a Dormia basket, 1 arterial bleeding after extension of a sphincterotomy). These two recovered uneventfully.
All patients in whom fragmentation by ESWL failed (n=14, 16%), underwent elective exploration of the common bile duct without complications.

Complications of ESWL

Eleven patients (12%) had transient macroscopic haematuria after ESWL, two patients (2%) developed subcapsular haematoma of the right kidney shown on ultrasonography and one of these also had macroscopic haematuria. The haematomas resolved without clinical consequences.

Despite antibiotic prophylaxis, two patients (2%) developed bacteraemia with positive blood cultures (Pseudomonas aeruginosa and Escherichia coli); both were treated sucessfully with antibiotics (piperacillin and gentamicin).

Follow-up

The median duration of follow-up (range) was 28 months (1-60). During this period six patients died of non-biliary causes and two others were lost to follow-up one and four months after ESWL, respectively.

In two patients stones recurred in the common bile duct. One patient, aged 84 also had a gallbladder full of stones, and he was treated successfully with ESWL for the stones in the common bile duct. He was seen 27 months later with recurrent jaundice and abdominal pain and at endoscopic retrograde cholangiography (ERC) a stone 15 mm in diameter was removed from the common bile duct with a Dormia basket.

The other high risk patient was 76 years old. He had had a cholecystectomy and then successful ESWL for stones in the common bile duct. He presented again 31 months later, with fever and abdominal pain and this time had an ERC at which four stones were seen in the common bile duct. He left hospital without complaints after repeated sessions of ESWL. To date, none of the other 80 patients have had any biliary symptoms or signs since their last treatment.

DISCUSSION

Since the introduction of endoscopic sphincterotomy, surgical exploration of the common bile duct has ceased to be the preferred treatment for stones in the common bile duct. Particularly in elderly or high risk patients, morbidity and mortality after cholecystectomy increase considerably if the common bile duct is explored at the same time (5,12,19), so endoscopic removal of stones from the bile duct is attempted as a primary procedure in these patients.

Nowadays most cholecystectomies are done laparoscopically. To preserve the minimally invasive character of laparoscopic cholecystectomy in the case of stones in the common bile duct, it is likely that the rate of endoscopic interventions before or after laparoscopic cholecystectomy will increase. As a result the number of patients in whom endoscopic removal of the stones fails will also increase. We can therefore expect a growing population of patients from whom the gallbladder has been removed laparoscopically but who have retained stones in the common bile duct, even after endoscopic sphincterotomy. Among this group there will be a considerable number of elderly patients (8) at increased operative risk and they are potential candidates for ESWL. This profile of the patient who is suitable for ESWL of stones in the common bile duct can be seen clearly in our own group of patients; more than half had already had the gallbladder removed and their mean age was high (Table II).

Finally, we achieved complete clearance of the stones in the common bile duct in 69% of our patients after ESWL together with endoscopic or percutaneous procedures. The alternative for these patients would have been an exploration of the common bile duct.

An important point is that the first 13 patients were treated with a first generation lithotriptor, the Dornier HM3^{r} (with water bath). We achieved a better fragmentation rate with this lithotriptor than with the second generation machine that we used thereafter (the Siemens Lithostar^{r} without water bath). The shock waves for the two lithotriptors are generated in different ways (6), which accounts for the fragmentation rate of 100% with the first lithotriptor compared with 82% for the second one, as there was no significant difference in the number of stones between the two groups.

The patients treated with the first generation lithotriptor were all given general anaesthesia because we thought that the treatment would be too painful, but Lindström et al. (11) have recently reported good results using the Dornier HM3^{r} lithotriptor without general anaesthesia. With the second generation lithotriptors, there is no need for general anaesthesia (one of our patients was given general anaesthesia at his own request). We saw macroscopic haematuria only in the patients treated with the first machine. One haematoma of the kidney occurred after treatment with each machine.

We have achieved a fragmentation rate of 82% and a clearance rate of 64% with our present lithotriptor, which is similar to the results obtained by Nicholson et al. with the same lithotriptor (15). They achieved fragmentation in 44 of their 54 patients (81%) with stones

in the common bile duct, and complete clearance of the duct in 38 (70%). Dobrilla et al. (4) recently reported their results with a similar second generation lithotriptor. They achieved fragmentation in 46 out of 49 patients (94%) and complete clearance of the bile duct in 43 (88%). They had a particularly aggressive protocol in their study and used a mean total of 12 474 shock waves/patient (compared with 7848 shock waves/patient in our study). In addition, 67% of their patients had a single stone (compared with 42% in our study). To avoid the still considerable number of explorations of the duct after failure of ESWL, it could be argued that more aggressive ESWL should be undertaken, but this would be at the expense of more associated complications (in the study by Dobrilla et al. 8% of the patients had blood in the bile). The patients in our series whose stones did not fragment after ESWL had uneventful explorations of their bile ducts, which indicates that only a controlled study can exactly define the advantages and disadvantages of ESWL compared with exploration of the duct.

Our rate of clearance tended to be better in patients who had single stones with smaller diameters, but this was not significant. Patients with a 'relative' distal stenosis of the common bile duct on ERC, however, seem to have less favourable clearance rates (unpublished observation) and this condition should be investigated further as a possible negative prognostic factor in ESWL of stones in the common bile duct.

The complication rate after ESWL is low. The two patients with bacteraemia after ESWL had already had cholangitis with periods of infection before the treatment. Nevertheless, serious morbidity and eventual mortality after endoscopic sphincterotomy or a percutaneous intervention must be borne in mind, because these procedures are essential adjuvants to ESWL treatment of stones in the common bile duct.

We conclude that ESWL of stones in the common bile duct is a rapid, non-invasive, and effective treatment with minimal discomfort for the patient. In case endoscopic removal of the stones proves impossible, it should be tried before operation is undertaken, particularly in elderly or high hisk patients.

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ADDENDUM:

at the time of writing this thesis, the median follow-up of 100 patients treated by ESWL for their bile duct stones, had considerably augmented: four patients were lost to follow-up. Twenty patients died with a median follow-up of 20 months (range: 2-62). In 18 cases this was not related to biliary causes. One patient died of acute cholangitis 2 months after unsuccessful ESWL. Another patient had recurrent stones in the common bile duct 29 months after ESWL and he died of complications of a surgical bile duct exploration performed elsewhere. Of the remaining 76 patients the median follow-up is now 3 years (range: 2-83 months). As already mentioned, two of these patients developed recurrent stones at 27 and 31 months follow-up, respectively. Both of them were again treated successfully by ESWL and endoscopic extraction. At last follow-up, none of the other 74 patients experienced recurrent biliary symptoms after their final treatment.

Another interesting feature of ESWL is that it can be used for the management of impacted Dormia baskets: Among our patients there were 6 with an impacted Dormia basket as a complication of the initial endoscopic treatment. Four of them were successfully treated by ESWL; the stone in the basket was fragmented and subsequently, the basket could be removed. The fifth patient developed a common bile duct lesion after an attempt to retract the basket. At the subsequent operation a fragmented stone was found in the basket. In the sixth patient the stone could not be fragmented and she underwent a choledochotomy for removal of stone and basket.

CHAPTER 3

QUALITY OF LIFE AND THE COURSE OF BILIARY AND GASTROINTESTINAL SYMPTOMS AFTER LAPAROSCOPIC AND CONVENTIONAL CHOLECYSTECTOMY.

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ABSTRACT

A prospective study was set up to compare the quality of life and the course of biliary and gastrointestinal symptoms after laparoscopic cholecystectomy (LC) and conventional cholecystectomy (CC).

Fourteen patients underwent LC and 17 patients CC. Quality of life questionnaires and symptom profiles were taken before and at 3, 6, 12, 18 and 24 months after operation. Pain diaries covered the periods 0-3, 3-6, 6-12 and 12-18 months. Median follow-up was 12 and 24 months for LC and CC, respectively.

Quality of life significantly improved after 6 months in the LC-group and to a similar degree after 12 months in the CC-group. Bloating, fat intolerance and nausea improved significantly at 3, 6 and 6 months after LC and at 6, 18 and 24 months after CC, respectively. Vomiting and belching had a tendency to improve slightly, while pyrosis, constipation and diarrhoea did not improve in either group. Biliary pain was relieved in 81% of the patients (25/31) directly after cholecystectomy and was no longer reported in any patient 6 months after operation.

Cholecystectomy improves quality of life and cures nausea, fat intolerance, bloating and biliary pain. LC improves quality of life and symptomatology to the same degree but at an earlier stage than CC. Therefore, from the point of view of quality of life and early relief of abdominal symptoms, LC is preferable to CC for the treatment of uncomplicated symptomatic gallstones.

INTRODUCTION

Any form of elective surgery is directed primarily to improvement of quality of life, i.e. the relief of disability, discomfort and disfigurement [1,2]. Especially in the treatment of symptomatic gallstones, improving the patient's quality of life should be the most important aim of the intervention [3]. We studied the effects of cholecystectomy on the quality of life. We also studied its effects on biliary and gastrointestinal symptoms. Finally, we studied differences between the effects of laparoscopic cholecystectomy as compared to conventional cholecystectomy, the gold standard [4,5].

PATIENTS AND METHODS

Thirty one patients with uncomplicated, symptomatic biliary stone disease were recruited from a surgical outpatient biliary clinic, in the period January 1990 - January 1993. Patients were diagnosed as 'symptomatic' according to the Roma Working Team-definition [6]. With this definition, symptomatic stone disease is characterized by acute biliary pain involving one or more episodes of abdominal pain (usually epigastric or right upper quadrant) lasting more than 15 minutes but less than five hours. Biliary complications were excluded by physical examination, a white blood cell count, liver function tests and ultrasonography of the abdomen. Since all patients opted for laparoscopic operation, the kind of operation was performed according to availability of laparoscopic sets, thus avoiding patient selection.

Laparoscopic cholecystectomy (LC): Fourteen patients, 1 male and 13 female, underwent laparoscopic cholecystectomy. Their mean age was 45 years (range 30-68). Median Quetelet-index was 24.8 kg/m^2 (range 20.5-38.1). LC was performed via four abdominal incisions after insufflation of carbon dioxide. LC was performed under general anesthesia, as an inpatient procedure. Intra-operative cholangiography was not performed.

Conventional cholecystectomy (CC): Seventeen patients, 3 male and 14 female, underwent conventional cholecystectomy. Mean age was 49 years (range 30-67). Median Quetelet-index was 24.5 kg/m^2 (range 19.5-38.1). CC was performed by laparotomy, via an oblique subcostal incision. It was performed under general anesthesia, as an inpatient procedure. Intra-operative cholangiography was not performed.

Follow-up: Follow-up consisted of self-administered health questionnaires, symptom profiles and pain diaries. A Dutch translation of the Nottingham Health Profile was used for the quality of life assessment [7]. This health profile questionnaire consists of 6 so-called domains, which are explored in 38 questions requiring a 'yes' or 'no' answer (dichotomous). The more questions answered with 'yes' and the higher the patient scores, the lower is the quality of life. 'Health gain' can be defined as the decrease in median score (the median decrease in the number of positively answered questions). On the symptom profiles, the patients had to score whether they suffered from the following gastrointestinal complaints: nausea, fat intolerance, vomiting, bloating, pyrosis, belching, constipation and diarrhoea. Scoring was performed on a semi-quantative scale (absent, mild, moderate or severe). On the self-administered 'pain diaries', patients had to fill in the date, the duration and severity

(mild, moderate or severe) of pain, when experiencing pain. Patients experiencing pain had to indicate specifically whether this pain was similar or different from the pain they experienced before cholecystectomy. Health questionnaires and symptom profiles were taken before therapy (t=0) and at 3, 6, 12, 18 and 24 months after therapy. Pain diaries covered only the post-operative phase, i.e. 0-3, 3-6, 6-12 and 12-18 months. Health questionnaires, symptom profiles and pain diaries were sent by mail and double-checked by telephone 1 month after receipt.

Statistics: Statistical analysis was done with the Kruskal-Wallis test, Wilcoxon rank test and a standard test for comparing proportions assuming binomial distributions. A p-value of <0.05 was considered statistically significant.

RESULTS

Laparoscopic cholecystectomy: Mean and median hospitalization time, including the days of admission and discharge, were 5 days (range: 4-9). No laparoscopic cholecystectomy was converted into conventional cholecystectomy. Postoperatively, no complications occurred and there was no mortality. Mean follow-up was 13.1 months (median : 12; range : 3-24). No patient was lost to follow-up.

Conventional cholecystectomy: Mean and median hospitalization time, including the days of admission and discharge, were 9 days (range: 6-12). Postoperatively, one patient had to be observed for 6 hours at an intensive care unit for an epileptic insult. One patient suffered from wound dehiscence, treated conservatively. Two patients complained of persistent scar pain. There was no mortality. Mean follow-up was 23.6 months (median : 24; range : 18-24). No patient was lost to follow-up.

Quality of life: NHP-questionnaires were returned and filled in correctly in 96.5% (165/171) of the cases. It was found that the median overall percentage of items answered positively, decreased to the same degree in both treatment groups after operation (Figure 1). This decrease, however, became significant 6 months after LC and only 12 months after CC. Health status remained significantly better thereafter in both groups (not shown). There was no significant difference at baseline between the two treatment groups.

Symptom profiles: The reported frequencies of nausea, fat intolerance and bloating in the course of 1 year, are depicted in Table 1. Both fat intolerance and nausea improved significantly and consistently after 6 months in the LC-group but not in the CC-group. Here, a significant improvement in fat intolerance and nausea occurred only after 18 and 24 months, respectively (not shown). Bloating improved significantly after 3 and 6 months in the LC and CC-group, respectively. Vomiting and belching improved only slightly in both treatment groups, but improvements were statistically insignificant. Reported frequencies of pyrosis, constipation and diarrhoea did not change after therapy. There were no significant differences in reported symptoms between the two treatment arms at baseline.

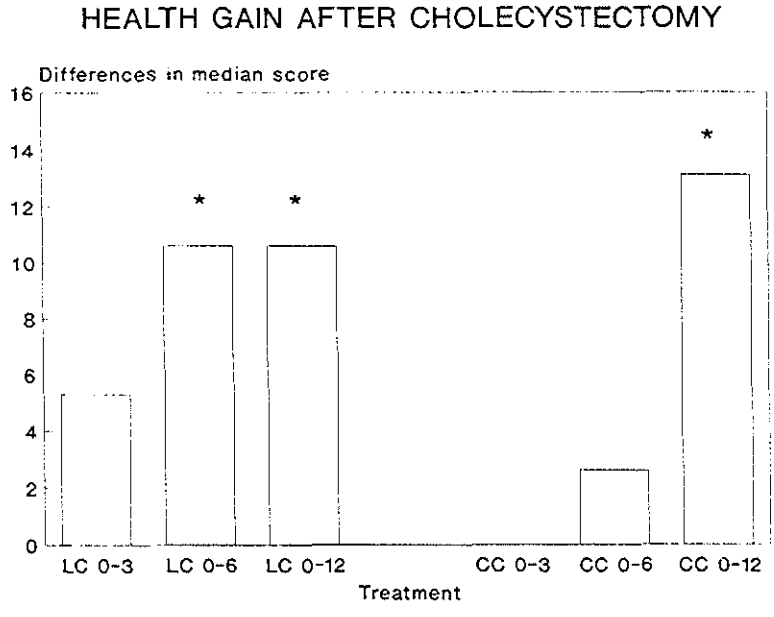

Figure 1
Median total scores (in %) on Nottingham Health Profiles after cholecystectomy.
*) $p < 0.05$; compared with $t=0$
LC: laparoscopic cholecystectomy; CC: conventional cholecystectomy; on the abscissa: months

Pain diaries: Post-cholecystectomy biliary pain was found in 5 patients in the CC-group (29%) and 1 patient (7%) in the LC-group. This difference is not statistically significant (p=0.12) In the CC-group, 4 patients complained of 2-4 and 1 patient of 11 pain episodes, respectively. The LC-patient reported only 1 episode. Pain episodes were considered mild, moderate or severe in 29, 48 and 24%, respectively. No biliary pain was reported in either group 6 months after cholecystectomy.

Table 1
Reported frequencies (in %), graded moderate or severe, of fat intolerance, nausea and bloating after laparoscopic (n=14) and conventional cholecystectomy (n=17).

Time (mths)	Fat intolerance		Nausea		Bloating	
	LC	CC	LC	CC	LC	CC
0	47	37	47	37	33	47
3	33	21	8[a]	16	0[b]	32
6	0[b]	33	0[b]	17	10	11[a]
12	0[b]	16	0[b]	26	0[b]	11[b]

LC: laparoscopic cholecystectomy; CC: conventional cholecystectomy

a) $p < 0.05$; compared with t=0
b) $p < 0.02$; compared with t=0

DISCUSSION

Laparoscopic cholecystectomy has revolutionized surgical practice to a great extent and it has been claimed that it is the new gold standard for the treatment of symptomatic gallstone disease [8]. However, well-controlled studies are unavailable [5] and there is little or no prospect of a randomized study ever being performed [9].

The few available controlled studies all have some drawbacks. Firstly, they have all used historic controls [10-12]. Secondly, they focussed on complications and mortality [11,12]. Since both laparoscopic and conventional cholecystectomy were accompanied by relatively low morbidity and mortality rates, these rates were insensitive and, therefore, inappropriate for detecting differences between the two treatment arms in small series of patients [1,13,14]. Thirdly, they also focussed on operation time, length of hospital stay and use of analgetics [10], factors which were of only partial interest to the patient.

We studied laparoscopic cholecystectomy prospectively in comparison to conventional cholecystectomy, which has been the standard operation for gallstone disease for more than a century [4]. We focussed on quality of life, because this would be of major interest to the patient. Moreover, minimally invasive surgery is an area particularly well suited for quality-of-life research [14] and in fact, improving quality of life should always be the most important aim in the elective treatment of symptomatic gallstones [3]. No other reports on quality of life after laparoscopic cholecystectomy are available.

We chose the Nottingham Health Profile, since it is well validated and one of the most widely used general measures of quality of life [13]. Moreover, it can be easily administered by mail and makes relatively small demands on patient time and effort [13-15]. Because there was a significant difference in the length of follow up between the two treatment groups ($p=0.027$), we only analyzed the data of the first year in the LC-group.

We found that both operations were safe, relieving biliary colics and improving both quality of life and three gastrointestinal complaints, i.e. fat intolerance, nausea and bloating. We also found that other dyspeptic symptoms may persist after cholecystectomy, which is in agreement with the literature [16-19]. Because of the specific design of the pain diaries and symptom questionnaires, we were able to confirm that the reported symptoms were usually mild and of short duration [16-19]. We, therefore, confirmed that cholecystectomy is justified as a treatment of uncomplicated symptomatic gallstone disease.

In comparison with conventional cholecystectomy, we have demonstrated that laparoscopic cholecystectomy achieved an improved quality of life at a significantly earlier time. This was also the case with fat intolerance, nausea and bloating. The cause of the earlier disappearance of these dyspeptic symptoms after laparoscopic cholecystectomy remains unclear. Finally, we confirmed that laparoscopic cholecystectomy caused a marked reduction in the length of hospital stay.

The drawbacks of our study were that it was not randomized and that the number of patients studied was relatively small. Our study could not be designed as a randomized study, because it was initiated in a phase where we did not constantly have a laparoscopic set at our disposal. Consequently laparoscopy could not be planned and in fact it was unpredictable what treatment hospitalized patients would get. Also, we doubt whether randomization would have been possible: when laparoscopic sets were constantly available, patients simply refused random assignment of treatment and chose laparoscopic cholecystectomy. Despite of these defects, the present study was prospective, controlled and had a relatively long follow up. We have, therefore, provided more circumstantial evidence that laparoscopic cholecystectomy is superior to conventional cholecystectomy.

SUMMARY

We prospectively studied the course of quality of life and gastrointestinal and biliary complaints after laparoscopic and conventional cholecystectomy. It was found that cholecystectomy improves quality of life and cures fat intolerance, nausea, bloating and biliary pain. It was also found that laparoscopic cholecystectomy improved quality of life and symptomatology at an earlier stage than conventional cholecystectomy. More circumstantial evidence is provided that laparoscopic cholecystectomy is superior to conventional cholecystectomy.

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CHAPTER 4

LAPAROSCOPIC CHOLECYSTECTOMY IN AN UNSELECTED POPULATION: A PLEA FOR A RESERVED APPROACH.

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ABSTRACT

Objective: comparison of the results of laparoscopic and conventional cholecystectomy.

Design: matched clinical study.

Setting: department of Surgery, University Hospital Rotterdam, Rotterdam, The Netherlands.

Subjects/interventions: the first 100 -unselected- patients with a laparoscopic cholecystectomy (median age 46 years, [21-78]), operated on in the period September 1990 to October 1992 were matched with patients who had undergone open cholecystectomy (median age 45 years, [21-82]) in the period August 1988 to August 1991.

Main outcome measures: conversion, complications of both techniques.

Results: patients with acute cholecystitis or a chronically inflamed gallbladder had an increased risk of conversion (50%). Also older patients had an increased risk (23%). There was no mortality in both groups. Major, minor and late complications of laparoscopic cholecystectomy occurred in 5, 6 and 3%, respectively. For open cholecystectomy these rates were 3, 6, and 3%, respectively.

Conclusion: Both techniques are safe, but the complications of the laparoscopic cholecystectomy were more serious. Careful evaluation of this technique, preferably in the form of a randomised trial, is still necessary.

INTRODUCTION

Gallstone disease is an important clinical problem with great economical concequences (14,23,28,29). Gallstones become symptomatic in about 10-15% of the patients and only then require treatment (8,24,26,32). Since the first successful gallbladder resection in 1882 (15), cholecystectomy is considered the therapy of choice for symptomatic cholecystolithiasis (16). Cholecystectomy is considered curative and is accompanied by a morbidity of 10-30% and a mortality of 0.1-0.6% (13,16,17). The first series of laparoscopic cholecystectomies was reported in 1990 (7). Laparoscopic cholecystectomy is a variant of open cholecystectomy but major advantages of this technique are a markedly diminished need for postoperative narcotic analgesics, early discharge from the hospital and a quicker return to work (4,30,31). The cosmetic result is experienced as another advantage. Contraindications for a laparoscopic cholecystectomy are sepsis, peritonitis, distended bowels and pregnancy (10). However,

recently successful laparoscopic cholecystectomy has been described in the first 2 trimesters of pregnancy (11). Relative contraindications are previous upper abdominal surgery, acute cholecystitis and a chronically inflamed gallbladder; they form the main causes of conversion to open cholecystectomy in about 5-10% of the cases (2,12,31). The most severe complication of laparoscopic cholecystectomy is bile duct injury. This is mostly due to misidentifying the common bile duct for the cystic duct, a short cystic duct or inaccurate placement of clips. The reported higher incidence of bile duct injury compared to open cholecystectomy gives rise to concern (5,18,22,31).

A proper comparison between open and laparoscopic cholecystectomy could only be achieved in the context of a randomised controlled trial. However, after the rapid introduction of laparoscopic cholecystectomy, what is said to be partly consumer driven (3), very few controlled studies have been performed (30).

Since the advantages of laparoscopic cholecystectomy are obvious and the procedure has gained its place in routine surgical practice, a randomised trial will probably never be conducted (19). Therefore, the first 100 cases of laparoscopic cholecystectomy performed in our hospital were compared with 100 matched patients who had undergone an open cholecystectomy in the period preceding the introduction of the laparoscopic cholecystectomy.

PATIENTS AND METHODS

From September 1990 to October 1992, 100 unselected patients with symptomatic gallbladder stones underwent laparoscopic cholecystectomy. To compare the results of this operation with open cholecystectomy, the patients were matched for sex, age, ethnic group and ASA-classification (anaesthetic risk, [20]) with patients who had had an open cholecystectomy during the period August 1988 to August 1991. In the period between September 1990 and August 1991, both open and laparoscopic cholecystectomies were performed. Patients were operated laparoscopically if laparoscopic equipment was available and if not, they had an open cholecystectomy. Therefore, the nature of the operation only depended on the place on the waiting list, thus avoiding selectivity. After August 1991, all cholecystectomies were performed laparoscopically because of the continuous availability of laparoscopic sets. Patients, who underwent cholecystectomy in combination with a common bile duct exploration

were excluded from the study since this procedure is not yet performed laparoscopically in our hospital. Finally, a 15-year old patient in the laparoscopic group was excluded from the study because she could not be age-matched. This patient underwent an uncomplicated laparoscopic cholecystectomy.

Table 1 shows the characteristics of both groups.

Table 1
Characteristics of 2 groups of patients operated by either laparoscopic or open cholecystectomy.

	Laparoscopic cholecystectomy	Open cholecystectomy
# (m/f)	100 (27/73)	100 (25/75)
Median age (range)	46 (21-78)	45 (21-82)
Ethnic minority	n=29	n=29
ASA-class I-II	n=94	n=95
ASA-class III-IV	n=6	n=5

#: number of patients; m: male; f: female; ASA-class: ASA-classification (29)

One female patient treated by laparoscopic cholecystectomy underwent laparoscopic sterilization in the same session without complications.

Laparoscopically operated patients were followed prospectively, patients who had an open cholecystectomy retrospectively.

In the laparoscopic group the presence of relative contraindications for laparoscopic cholecystectomy was assessed preoperatively. Suspicion of concomitant common bile duct stones was not regarded as a relative contraindication but resolved preoperatively by endoscopic treatment. All complications, conversion to open cholecystectomy and the duration

of the operation were recorded. The total number of hospitalization days was counted, starting from the day of operation and including days of readmittance. At follow-up, patients were asked about postoperative pain, biliary symptoms and gastrointestinal complaints.

In the open cholecystectomy group, all complications, duration of the operation and the number of hospitalization days were recorded.

In comparing the complications of the laparoscopic and open cholecystectomy, a conversion from the laparoscopic to the open technique in itself was not considered a complication but, of course, could be the consequence of a complication.

Statistical analysis was performed using a standard test for comparing proportions assuming binomial distributions.

RESULTS

Duration of the operation and of the hospital stay are depicted in Table 2, comparing the open with the laparoscopic technique.

Table 2
Operation time and hospitalization.

	Open cholecystectomy	Laparoscopic cholecystectomy
Median duration operation (hours)	1.0 (0.5-2.8)	1.5 (0.8-4.3) converted: 2 (1.3-3.3) not converted: 1.5 (0.8-4.3)
Median duration hospitalization (days)	7 (4-38)	4 (1-140) converted: 7 (4-140) not converted: 4 (1-36)

Conversion

Thirteen patients had a conversion to open cholecystectomy (overall conversion rate: 13%). Of the first 25 patients, four were converted. Of the next three groups of 25 patients, five, one and three were converted, respectively. Four out of seven patients with clinical and ultrasonographic signs of acute cholecystitis were converted. In another seven patients, an inflamed gallbladder was found at preoperative ultrasound. Three of these patients were converted. Two conversions were due to adhesions, causing insufficient abdominal distension (one patient) and restricted view (one patient). Finally, four conversions followed an intraoperative complication. Thus, the conversion rate for 14 patients with relative contraindications for laparoscopic cholecystectomy was 50% (7/14) and for 86 patients without relative contraindications 7,0% (6/86, $p<0.001$; two sample proportion test).

Age was found to be a risk factor for conversion. Ten of the 44 patients aged 50 years and older (23%) had a conversion, whereas three of the 56 patients aged 49 years and younger (5.4%) had a conversion ($p= 0.01$; two sample proportion test).

There were no conversions due to the presence of common bile duct stones. In six patients concomitant common bile duct stones were suspected: in three, a preoperative endoscopic sphincterotomy and stone extraction cleared the common bile duct. In the other three patients, normalization of liver function tests before the operation led to the diagnosis of spontaneous passage of common bile duct stones. Intraoperative cholangiography, performed in one of them, did not show any abnormalities.

Complications (Table 3)

There was no mortality in both groups.

Laparoscopic cholecystectomy: Fourteen complications occurred in 12 patients. There were five major complications: one patient had a perforation of the cecum at trocar introduction, necessitating conversion. three patients had a laparotomy after signs of postoperative bile peritonitis. Two of them had bile duct lesions -1 at the confluence of the cystic duct and the other of the common bile duct- which were repaired. The third patient had a clip dislodgement, what could be managed by ligation of the cystic duct. In one patient with acute cholecystitis, a -presumably infected- stone was lost in the abdominal cavity. He developed a bacterial peritonitis and an infected hematoma, for which laparotomy was necessary. There were six minor complications: intraoperative bleeding occurred in three patients (one

mesenterial vein bleeding and two bleedings from the gallbladder bed due to minor ruptures of liver tissue) which was stopped after conversion. In two patients, wound infection occurred at the site of introduction of a trocar and in one patient, a cystic duct leak was managed by endoscopic drainage. Three patients were readmitted for repair of an incisional hernia: two after a converted laparoscopic cholecystectomy and one after a laparoscopic cholecystectomy.
Open cholecystectomy: Twelve complications occurred in 11 patients. Three patients had major complications: one had a lesion of the duodenum, needing intraoperative repair. One patient had a relaparotomy for postoperative bleeding and one patient needed prolonged drainage (29 days) for a subphrenic abcess. No bile duct lesions occurred. Six minor complications (Table 3) were managed conservatively. Three patients were readmitted, one for repair of an incisional hernia and two for unsuspected retained common bile duct stones, that could be successfully treated by an endoscopic sphincterotomy.

Follow-up

Ninety four patients in the laparoscopic group were seen 10-14 days after discharge from the hospital. Thirteen of them (14%) complained of wound pain; six of those had been converted. The other seven patients reported only moderate pain at the sites of introduction of the trocars. Eight patients (9%) had an elevated serum alkaline phosphatase level (up to twice reference values) what declined after two more weeks in five patients. In the other three patients it remained elevated without other signs of biliary ductal obstruction. This was probably related to medication taken for concomitant diseases because it was already present preoperatively. One patient reported a one day-period of fever up to 39 degrees which did not recur. Another patient twice observed pale coloured stools which did not recur.
All patients reported to have resumed daily activities. No gastrointestinal complaints of importance were reported.

Table 3
Complications in 100 laparoscopic cholecystectomies and in 100 open cholecystectomies.

Laparoscopic cholecystectomy	Open cholecystectomy
Major (n=5)	**Major (n=3)**
Cecal perforation	Duodenal laceration
Bile leak	Postoperative bleeding
Common bile duct	Subfrenic abcess
Cystic/common bile duct	
Cystic duct	
Infected stone in abdomen	
Minor (n=6)	**Minor (n=6)**
Intraoperative bleeding	Mild decrease hemoglobin level
Mesenterial (1)	Postoperative fever (2)
Gallbladder bed (2)	Wound infection (3)
Cystic duct leak	
Wound infection (2)	
Late (n=3)	**Late (n=3)**
Incisional hernia	Incisional hernia
Converted patients (2)	Retained common bile duct stones (2)
Not converted patient (1)	
Total: 14	Total: 12

n: number of patients

DISCUSSION

For more than a century, cholecystectomy by laparotomy has been the treatment of choice in case of symptomatic cholecystolithiasis for two basic reasons. In the first place cholecystectomy can be performed in almost any patient and secondly there is no possibility of stone recurrence. Laparoscopic cholecystectomy has proved to have important advantages over the open technique (4,30,31). However, critical evaluation of morbidity and mortality of this technique are necessary and especially data on the incidence of bile duct lesions are important (5,18,22,31).

Almost all studies of laparoscopic cholecystectomy are descriptive (2,4,7,10-12,22,31) and controlled studies only comprise limited numbers of patients (30). Therefore we decided to compare the first 100 laparoscopically cholecystectomized patients with 100 conventionally treated patients. The patients were only selected for the presence of symptomatic cholecystolithiasis and were adequately matched (Table 1).

In the laparoscopic group, the conversion rate was 13%. In the presence of acute cholecystitis or a chronically inflamed gallbladder, the conversion rate was 50%, whereas if these patients were excluded, this rate would have been 7.0%, a significant difference. This finding is in accordance with other studies, reporting conversion rates of 33-60% in cases of acute cholecystitis (9,12). Older patients had a significantly increased risk of conversion (23%), largely due to a high rate of acute cholecystitis and chronically inflamed gallbladders in this group. As a consequence, patients with relative contraindications should have the increased risk of conversion pointed out clearly to avoid raising expectations of minimal hospital stay and early return to daily activities.

Mortality in both groups was zero, and this confirms the relative safety of both techniques. Morbidity of the open cholecystectomy was consistent with other series (13,16,17). When comparing both groups, morbidity was more serious in the laparoscopic group (Table 3): four patients had to be reoperated for various reasons, whereas in the open cholecystectomy group, this was the case in only one patient. In the laparoscopic group, two -minor- bile duct lesions had to be repaired; bile duct lesions did not occur in the open cholecystectomy group.

We also wish to draw attention to the possibility of spilling infected bile and stones into the abdomen: when removing the gallbladder laparoscopically, it is more likely to rupture than during the open technique. This spill may cause intra-abdominal infections: a reason for being careful in performing a laparoscopic cholecystectomy in patients after acute cholecystitis which should therefore be done under antibiotic cover.

A learning curve in the laparoscopic technique could not be demonstrated in this series: in the first group of 25 patients four being converted; in the next three groups of 25 patients five, one, and three being converted respectively. Also, the number of complications did not decline as the number of laparoscopically operated patients increased. The two bile duct lesions and cecal perforation occurred in the last 25 patients. This is in accordance with the observation in open cholecystectomy, where most complications occur after the operator has performed the first 25 operations (1). Furthermore, it is likely that in a teaching hospital a

learning curve will emerge later because of the considerable number of surgical trainees specializing in biliary surgery.

Although laparoscopic cholecystectomy is now claimed to be the treatment of choice (27), our approach towards this new and rapidly introduced technique should be cautious, especially in an unselected, symptomatic population. Many reports of laparoscopic cholecystectomy are the work of expert biliary surgeons (2,4,7,10-12,21,25,27,30,31). Consequently, it can be expected, that complication rates will be higher in less expert hands. A large survey of 4,292 hospitals and 77,604 cases of laparoscopic cholecystectomy demonstrated a mean rate of bile duct injury of 0.6% and significant complications were identified in 2% (6). It was stated, that patient selection was an important factor.

We conclude, that the complications of laparoscopic cholecystectomy may still be underestimated. Despite its apparent advantages, comparison with the open technique in a randomised clinical trial is still warranted.

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CHAPTER 5

DETECTION AND MANAGEMENT OF COMMON BILE DUCT STONES IN THE ERA OF LAPAROSCOPIC CHOLECYSTECTOMY.

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ABSTRACT

Routine surgical bile duct exploration and extraction of stones is no longer available during a laparoscopic cholecystectomy, unless conversion to open operation is undertaken. The consequences of this phenomenon are therefore to manage suspected bile duct stones preoperatively and unsuspected retained stones postoperatively. Through a review of the literature combined with our experience with extracorporeal shock wave lithotripsy (ESWL) we conclude that endoscopic sphincterotomy (ES) and ESWL together can achieve stone clearance in 97-99% of all patients with choledocholithiasis. Routine intraoperative cholangiography during laparoscopic cholecystectomy can be replaced by a selective preoperative endoscopic retrograde cholangiography, followed by ES if necessary. Unsuspected retained stones can be treated with postoperative ES and ESWL.

INTRODUCTION

It is generally agreed that only patients with symptomatic cholecystolithiasis require therapy (1-3). Most patients remain asymptomatic, but 10-15% develop biliary colics (4). Stones in the common bile duct are sometimes the reason for these colics. About 9-16% of the patients with symptomatic cholecystolithiasis also have choledocholithiasis (5,6).

The management of patients with cholecystolithiasis and possible choledocholithiasis has been discussed extensively in the literature. Since the introduction of the laparoscopic cholecystectomy routine surgical bile duct exploration and extraction of stones is no longer available, unless conversion to open operation is undertaken. To develop an adequate strategy for this problem, we reviewed the literature and incorporated our results of extracorporeal shock wave lithotripsy (ESWL) of common bile duct stones.

In jaundiced patients with upper abdominal pain, fever and documented cholecystolithiasis the probability of concomitant choledocholithiasis is as high as 36-60% (7,8). Biochemical variables (elevated liver function test results) can add to this suspicion (7-9). A combination of these variables increases the probability of choledocholithiasis to more than 90% (8). Finally, various imaging techniques can be used to complete the investigations for choledocholithiasis. Ultrasonography can demonstrate common bile duct dilatation and, less frequently, the presence of stones. The probability of choledocholithiasis increases with the

diameter of the common bile duct: more than 34% if the diameter exceeds 10mm and more than 80% if it exceeds 12mm (7,8). A combination of positive clinical, biochemical and imaging indicators makes the diagnosis choledocholithiasis almost certain (8). Intravenous cholangiography (IVC) for the detection of common bile duct stones has been abandoned almost entirely. Recent reports, however, suggest there still may be a role for IVC: new contrast agents are claimed to be safer and hypo-allergic at the correct infusion rate (10). Results of routine IVC are reported to equal those of routine intraoperative cholangiography (IOC)(11-14). IOC during an open cholecystectomy is a sensitive method for detecting common bile duct stones with a positive predictive value of about 60-90% and a negative predictive value of almost 100% (15). There has been much discussion whether to use IOC routinely (16-21) or selectively (15,22-26). Detection of common bile duct stones with IOC will almost invariably lead to a choledochotomy and common bile duct exploration (CBDE) to extract the stones. Surgical CBDE is an accepted therapy but is associated with an appreciable mortality, rising to 8% in elderly or high-risk patients (27-30). This mortality rate is even higher in emergency procedures regardless of age (31). It is known that the population with cholecystolithiasis and concomitant choledocholithiasis is significantly older than the population with only cholecystolithiasis (7,8,32-34). Since the introduction of endoscopic retrograde cholangiography (ERC) combined with endoscopic sphincterotomy (ES)(35,36), this has become the treatment of choice for choledocholithiasis in elderly and high-risk patients (37-41). Morbidity from ES (pancreatitis, cholangitis, bleeding and retroperitoneal perforation) is reported to be 5-15% versus 15-30% after CBDE (27,37,41-44). Mortality from ES is about 1-2% (37,41,42,44) and does not increase with age and the presence of medical risk factors (43) in contrast to mortality after a CBDE (27-30). In selected patients with a high operative risk, the gallbladder can be left in situ after ES (43,45-48).

PROBLEMS

Nowadays, laparoscopic cholecystectomy has become the routine treatment modality for patients with symptomatic cholecystolithiasis. Here, too, there is much debate on whether to use IOC routinely (49-51) or selectively (52,53). However, the consequences of a positive IOC have changed in case of laparoscopic cholecystectomy: a conversion to laparotomy is needed for a CBDE to remove the stones. Not only will this increase morbidity and mortality, but also the advantages of a laparoscopic cholecystectomy (diminished need for narcotic analgesics, early discharge from the hospital, quicker return to work (54-56)) will be lost. False positive IOC occur in from 8% up to more than 30% of the cases (15,16,19,32,38,57-59), leading to unnecessary CBDE and, in case of laparoscopic cholecystectomy to unnecessary conversion and CBDE. In addition, bile duct injury during open cholecystectomy can be caused simply by placement of cholangiographic cannula (60,61), and there is no reason to believe that this would not occur during laparoscopic cholecystectomy.

To preserve the minimal invasive character of the laparoscopic cholecystectomy, it would be simpler to anticipate and focus on indicators of choledocholithiasis in the preoperative period. A preoperative ERC can be performed on the basis of these indicators and an ES to remove any common bile duct stones. Therefore, it is important to define a subset of clinical, biochemical, and radiological parameters which can predict choledocholithiasis with a reasonable probability.

The age limit for ES must also be defined because of its potential long-term complications, such as stenosis of the sphincterotomy or reflux of air and intestinal contents into the biliary tree and subsequent bacterial overgrowth (62). For these reasons, to date, ES has been largely confined to patients with an age-limit of about 50-60 years (63,64). However, if the above-mentioned objections should prove to be invalid, it would be unreasonable to deny a preoperative ES in combination with a laparoscopic cholecystectomy to the younger patient with choledocholithiasis in favour of a laparotomy with at least a considerably longer hospital stay and higher morbidity.

An important remaining problem is that endoscopic extraction of common bile duct stones proves impossible in about 10% of the cases (37,44,45,65). Common bile duct stones with a diameter exceeding 20 mm are increasingly difficult to remove, even with a balloon or a Dormia basket (66).

Finally, there will always be a rate of 2-8% of unsuspected choledocholithiasis (32,67-71). If the routine use of IOC were to be abandoned, these stones would be missed, which could eventually lead to symptoms after the laparoscopic cholecystectomy.

POSSIBLE SOLUTIONS

Table I summarizes the factors indicative of choledocholithiasis. All these indicators can predict choledocholithiasis with a probability of more than 34% (7-9), which should give enough reason to perform a preoperative ERC and, if necessary, ES. Combinations of these indicators increase the probability up to 100% (8).

Serum transaminases are of less importance in predicting choledocholithiasis (8,72), and, although pancreatitis has an aetiologic relationship with biliary tract stone disease, pancreatitis in itself or an elevated serum amylase is of little value as a predictor of choledocholithiasis (7-9,33,73).

Table I
indicators for common bile duct stones.

Indicators	PPV
Jaundice, light feces, dark urine	>44%
Septic fever, cholangitis	>36%
Bilirubin and alkaline phosphatase > twice elevated	>40%
Diameter of common bile duct > 10 mm on ultrasound	>34%
Stone visible in common bile duct on ultrasound	>85%
any combination of the above mentioned indicators	>90%

PPV: positive predictive value (7-9); >: more than.

In our view the age limit for ES can be less than 50 years. The long-term effects of ES are still unknown but seem to be better than expected. The rate of stenosis of the papilla after ES for choledocholithiasis is about 0-1% after 1-2 years and 2-4% after 5 years (63,74-77). Retained or recurrent stones are found in about 6% after 5 years (63,77). This will be a good end-estimate because stone recurrence most probably occurs within 3 years after ES (78). In patients treated with a surgical sphincterotomy comparable to ES, a follow-up of 20-25 years has been achieved (79). Although this study only comprised 43 patients, none of them had experienced negative side-effects at follow-up.

Recurrent biliary problems also occur after CBDE: the majority of benign biliary strictures are iatrogenic and due to previous cholecystectomy combined with CBDE and T-tube drainage in 9-32% of the cases (80-83). Retained or recurrent stones occur in about 5% of the cases after CBDE (27,38,84-86), which is comparable with ES.

In case of failure of endoscopic extraction of bile duct stones, ESWL is an attractive alternative: in 70-88% of these patients clearance of the common bile duct still can be achieved (87-92). In the period between April 1986 and July 1992 we treated 90 patients (33 men, 57 women, median age 73 years, range: 27-95) with difficult common bile duct stones (median diameter: 25 mm) with ESWL. Sixty-two patients (69%) became free of stones. Six patients (7%) had an endoprosthesis placed past fragmented stones and 22 patients (24%) finally underwent an operation (93).

Because of the low morbidity and mortality rates, we strongly argue also to treat patients younger than 50 years with ESWL. Only in case of failure of ESWL can a CBDE or bilio-intestinal anastomosis be undertaken, and in the unfit patient an endoprosthesis can be placed past the common bile duct stones to ensure biliary drainage.

Finally, it is estimated that only 10% of patients with unsuspected choledocholithiasis become symptomatic (15). So, 90% of the patients undergoing laparoscopic cholecystectomy probably will not benefit from an IOC-indicated conversion and CBDE and only have the risk of the additional morbidity and mortality. Prospective randomised trials, in both open and laparoscopic cholecystectomy, do not show advantages of routine IOC in detecting unsuspected common bile duct stones (94,95). Emphasis must be put on preoperative clinical criteria. Any unsuspected stones, causing symptoms after laparoscopic cholecystectomy, can be treated with ES (53,96), after which a reoperation seldom will be necessary (38). This will especially be the case if ESWL is added to the therapeutic regimen.

DISCUSSION

To achieve a reliable treatment strategy concerning the possibility of choledocholithiasis in patients undergoing laparoscopic cholecystectomy, we reviewed the literature and considered our results of ESWL of common bile duct stones. We shall not discuss definite emergency situations in which endoscopy has the advantage over emergency surgery, namely acute severe cholangitis and acute severe pancreatitis associated with bile duct stones.

Since laparoscopic cholecystectomy is the new standard treatment of cholecystolithiasis (97), surgical CBDE and stone extraction is no longer available, unless conversion to open operation is undertaken. Laparoscopic exploration of the bile ducts has already been described (98,99) but is not yet generally feasible.

Routine laparoscopic IOC can be replaced by selective preoperative ERC, based on clinical presentation, laboratory evaluation and ultrasonography (Table I)(53,95,96,100,101). However, in selected cases IOC retains a role as a road map for the laparoscopic surgeon.

Patients aged 40 years and older can have a preoperative ES. It remains questionable whether this would be wise in patients younger than 40 years, who only rarely harbour common bile duct stones. In case of difficult common bile duct stones, ES can be combined with ESWL as a non-invasive, effective treatment modality with very low morbidity and mortality rates. ESWL treatment can clear the common bile duct of difficult stones in up to 88% of the cases (91), which means that ES and ESWL together can achieve stone clearance in 97-99% of all patients with choledocholithiasis. In fact, this would be a better clearance rate than after a CBDE, for which it is about 95% (27,38,84-86). Morbidity from ESWL of common bile duct stones is low: transient macrohematuria occurs in 2-11% of the patients and transient hemobilia in 2-8% (87,88,91,93). Septic fever in 3-6% of the cases is often regarded as an exacerbation of already existing cholangitis (87-89,92,93). To the best of our knowledge, death from ESWL has not been reported to date. Unsuspected stones are estimated to cause symptoms in only 10% of the cases (15). In case of symptoms a postoperative ES must be attempted, when necessary in combination with ESWL.

Further development of new techniques has led to the recent use of endoscopic ultrasound of the bile ducts. This method is not only valuable for detection and staging of tumours of the common bile duct (102) but also accurate in diagnosing stones in the common bile duct (103). Another promising technique for the treatment of common bile duct stones is endoscopic or

percutaneous laser lithotripsy under direct visual control (104). Further improvements of these methods can be expected, and they probably will become a valuable supplement in the diagnosis and non-surgical treatment of common bile duct stones.

We conclude that ES and ESWL together can achieve stone clearance in 97-99% of all patients with choledocholithiasis and is therefore the preferred treatment strategy as the first step in symptomatic patients before laparoscopic cholecystectomy. Thus, conversion to laparotomy and CBDE can be avoided in almost all cases. This implies that these patients should be treated in centres where both ERC and ESWL are available. In an increasing number of these centers endoscopic ultrasound and lithotripsy will also be available.

There will always be some cases in which indicators of choledocholithiasis are doubtful or marginally present. Here, the role of IVC should be reconsidered (11-14).

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CHAPTER 6

EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY OF PANCREATIC DUCT STONES: IMMEDIATE AND LONG-TERM RESULTS.

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ABSTRACT

To study the efficacy of extracorporeal shock wave lithotripsy (ESWL) of pancreatic duct stones, seventeen patients (mean age: 42 years) with recurrent attacks of abdominal pain as a result of chronic calcifying pancreatitis, were treated with this method. In all cases, endoscopic removal of the stones proved impossible. In case of fragmentation the remaining calculi and fragments either evacuated spontaneously or attempts were made to extract them endoscopically followed by flushing. In 13 patients (76%) fragmentation of stones was achieved, 11 of which had a dramatic relief of pain directly after ESWL (65%). However, in only 7 patients (41%) complete ductal clearance of stones was achieved; at last follow-up (12-59 months after ESWL, mean: 30 months) all 7 were free of symptoms. Of the 6 patients with stone fragmentation without ductal clearance, 3 were operated on because of recurrent complaints. The only complication due of the procedure was an exacerbation of pancreatitis in 1 patient, which could be treated conservatively. If pancreatic stones cannot be removed endoscopically, ESWL seems to be preferable to surgery which may be performed in case of failure. It seems important to achieve ductal clearance and not merely stone disintegration to obtain the desired clinical long-term effects.

INTRODUCTION

Treatment of chronic calcifying pancreatitis (CCP) is a difficult clinical problem, for which extensive surgery has often to be performed (1-3). Alcohol abuse is considered to be the main cause of CCP (3,4) and up to 90% of the patients with alcoholic chronic pancreatitis develop stones in the main pancreatic duct (4). The course of this disease can eventually result in endocrine as well as exocrine insufficiency of the pancreas, leading to insulin dependent diabetes mellitus and steatorrhea and creatorrhea, respectively.

The treatment of CCP should be focussed on pain relief, management of biliary obstruction and drainage of pancreatic pseudocysts (5). If stones are present in the main pancreatic duct, the treatment of choice is nowadays sphincterotomy of the pancreatic orifice followed by endoscopic stone extraction or placement of an endoprosthesis in the main pancreatic duct (6,7). However, endoscopic stone extraction is sometimes impossible because of a discrepancy

between the diameter of the stones and the diameter of the distal pancreatic duct and due to ductal strictures as a result of fibrosis of pancreatic tissue (7). Furthermore, previous upper abdominal surgery can make endoscopic access to the pancreatic orifice impossible. After failure of endoscopic measures, these patients are usually treated surgically (side-to-side pancreato- jejunostomy, partial pancreatic resection, main pancreatic resection). Pancreatic surgery, however, is accompanied by a considerable morbidity and mortality of 20-40% and 2-5% respectively (8,9).

The first case of ESWL of pancreatic stones was described in 1987 (10). Encouraged by this and our first results of ESWL of common bile duct stones (11), we wanted to know whether this non-invasive treatment method could be an alternative to pancreatic surgery in selected cases. We present the results of our first 17 patients with pancreatic stones treated by ESWL associated with therapeutic endoscopy in our institution.

PATIENTS & METHODS

From June 1988 until February 1992 we applied ESWL to 17 patients (10 male, 7 female; mean age: 42 years, range: 19-55 years) with pancreatic stones. The characteristics of these patients are shown in Table 1.

The diagnosis 'chronic pancreatitis' was based on patients' history (chronic upper abdominal pain or recurrent attacks of upper abdominal pain), the presence of calcifications in the pancreatic region on a plain abdominal roentgenography and the radiological aspect of chronic pancreatitis on endoscopic retrograde cholangio-pancreaticography (ERCP)(12). Two patients (3 and 14) had a common bile duct stenosis that complicated the course of their disease. This could be treated successfully by placement of an endoprosthesis in the common bile duct.

ESWL was performed by a physician using a second generation lithotriptor, the Siemens Lithostar^{R}, (Siemens, Erlangen, Germany) which operates on an electromagnetical shock wave generation principle (13). In every case endoscopic pancreatic sphincterotomy and stone extraction had been attempted first, but failed because of a discrepancy between the diameter of the stone and the diameter of the distal pancreatic duct.

Table 1
Patient and treatment characteristics of 17 patients with chronic calcifying pancreatitis.

Patient	m/f	age (years)	# of stones	Diameter largest stone(mm)	Alcohol abuse	# of sessions	total shock waves	#Duration follow-up (months)
1	♀	55	1	30	yes	2	10000	59
2	♀	47	2	15	no	2	6000	54
3	♂	41	2	30	yes	1	3000	52
4	♂	44	1	12	yes	2	8000	50
5	♀	37	4	25	yes	1	1500	48
6	♀	22	2	20	no	1	8000	44
7	♂	48	1	16	yes	2	10000	44
8	♀	43	4	18	no	3	11000	34
9	♂	44	>4	20	yes	3	11000	30
10	♂	44	1	22	yes	2	8000	27
11	♀	54	1	40	?	2	8000	26
12	♂	38	1	20	yes	2	12000	19
13	♀	19	>10	14	no	4	23000	18
14	♂	45	>4	18	yes	1	6000	18
15	♂	42	3	17	yes	1	4000	14
16	♂	55	4	15	no	2	11000	14
17	♂	31	8	22	no	2	10000	12

m/f: male(♂) or female(♀); #: number.

Before ESWL the following investigations were performed: a plain abdominal roentgenography, an ERCP, a coagulation profile, white blood cell count, hemoglobin, serum levels of amylase, total bilirubin, and liver enzymes (alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase and gamma-glutamyl-transpeptidase). We made sure patients had no acute pancreatitis, acute cholecystitis, cholangitis or concomitant common bile duct stones at the time of ESWL. All patients were treated in prone position under 24-h antibiotic prophylaxis (amoxicillin/clavulate, 1000/200 mg intravenously half an hour before

the treatment and 8 and 16 hours after the treatment). In 15 patients stones could be visualized by fluoroscopy without contrast medium (Figure 1a). In 2 patients (13 and 15) the stones had such a low grade of calcification, that it was necessary to inject contrast medium via a naso-pancreatic drain that was placed before ESWL. In the presence of 2 or more stones, the shock waves were focussed on the stone thought to cause the obstruction, usually the stone situated most distally in the pancreatic duct. If the vertebral column was in the shock wave path, the patients' right hip was slightly elevated to avoid exposure of vertebrae to shock wave energy. One patient was treated under general anesthesia on his own request, 15 patients had intravenous analgo-sedation (fentanyl up to 0.1 mg and midazolam up to 5 mg intravenously) and 1 patient needed no analgesia at all. The shock waves were delivered at a mean energy level of 18,5 kV (range 16.2-19.0 kV).

The day after ESWL a plain abdominal roentgenography was made and serum total bilirubin, amylase and liver enzymes were determined. The 2 patients with non-calcified stones were evaluated with repeat pancreatogram. If no stone fragmentation was seen on the abdominal X-ray, a second or third ESWL session was performed. If stone fragmentation was seen (clear change of contour of stone [Figure 1b]), a new attempt to extract the fragments endoscopically was made, after which a naso-pancreatic drain was left in place. Via this drain the pancreatic duct was flushed with 2 liters saline per 24 hours, which was tolerated well in all patients. If no stone material was detected following ESWL, flushing of the pancreatic duct was omitted and spontaneous clearance of the duct was assumed. If stone fragmentation did not occur after repeated ESWL and endoscopic sessions, surgery was recommended to the patient. Statistical evaluation was performed by the Wilcoxon test for matched pairs.

RESULTS

Short term results

Of all 17 patients, treatment characteristics are shown in Table 1; results are shown in Table 2.

Stone fragmentation: Thirteen patients (76%) showed radiologically proven stone fragmentation. Four patients (24%) had no stone fragmentation, although in one (patient 5) treatment was ended prematurely (after 1500 shocks) because it was too painfull. Of the patients without stone fragmentation, 3 underwent a side-to-side pancreato-jejunostomy during the same admission.

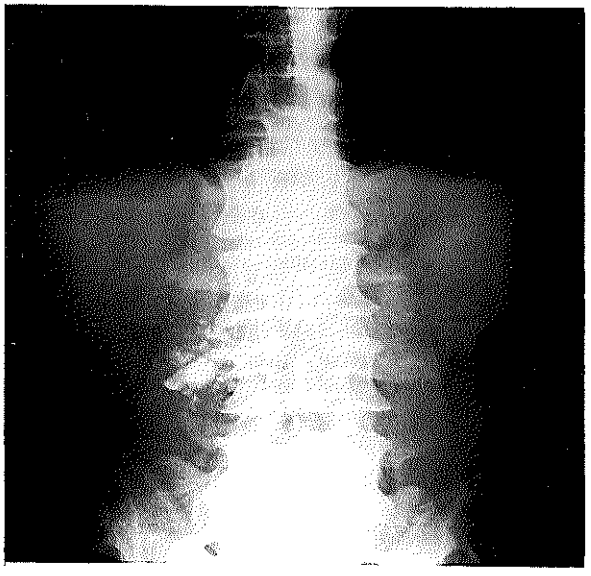

Figure 1a

Plain abdominal film showing a large calculus in the pancreatic region; confirmed by ERCP.

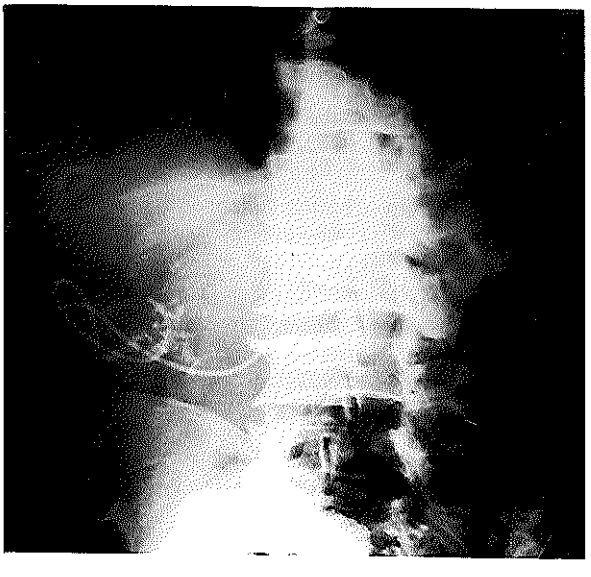

Figure 1b

Plain abdominal film showing typically fragmented stone of Figure 1a after ESWL; contour of stone has changed and is shaped to ductal pattern.

Pain relief: Only patients who reported no further pain attacks in the upper abdomen and absence of continuous pain were scored as having pain relief. Of the 13 patients with stone fragmentation, 11 (85%) had immediate pain relief after ESWL, while two (15%) had not. All 4 patients without fragmentation, had no pain relief after ESWL.

Stone clearance: Seven patients (41% of all patients) eventually had complete stone clearance. This was achieved either spontaneously (3 patients) or following endoscopic extraction and lavage with saline through a naso-pancreatic drain (4 patients; Table 3).

Table 2
Results after ESWL of pancreatic stones in 17 patients with chronic calcifying pancreatitis.

	n	Initial pain relief	Pain recurrence	Surgery
Stone fragmentation:	13			
With complete clearance	7	6/7	0/7	0/7
Without complete clearance	6	5/6	3/6	3/6
No fragmentation	4	0/4	4/4	3/4

n: number of patients

Table 3
Follow-up of 7 patients with stone clearance after ESWL of pancreatic stones.

Pat	Stone clearance	pain relief after ESWL	duration follow-up (months)	remarks
1	Endoscopic extraction and flushing	yes	59	still pain-free
3	Spontaneously	yes	52	still pain-free
7	Endoscopic extraction and flushing	yes	44	pain-free: 1 pain attack after alcohol consumption
8	Endoscopic extraction and flushing	yes	34	still pain-free
9	Endoscopic extraction and flushing	no	30	pain-free: last 25 months
13	Spontaneously	yes	18	still pain-free
15	Spontaneously	yes	14	still pain-free

pat: patient.

Long term results

The mean duration of follow-up after ESWL for all patients was 30 months (range: 12-59 months; Table 1).

Patients with ductal clearance: All 7 patients were free of pain at follow-up (Table 3): patient 9 was the only patient with persistent pain immediately after successful ESWL. However, at 15 and 30 months follow-up he reported to be free of abdominal pain.

Patients without ductal clearance: Three of the 6 patients, in whom stone fragmentation did not result in complete clearance, had recurrent pain attacks at 12, 24 and 5 months after ESWL (patients 2, 6, and 16, respectively). Plain abdominal films still showed major calcifications and they consequently underwent a side-to-side pancreato-jejunostomy. One patient (#17) never experienced pain relief since ESWL and repeated endoscopic attempts to clear the pancreatic duct or to place an endoprosthesis failed, so a surgical drainage procedure is now contemplated.

Surgery: At follow-up, 6 patients underwent surgery; 3 directly after failure of ESWL and 3 after recurrent pain attacks. Of these patients, 2 are pain free, 3 have only partial pain relief and 1 has no pain relief at all. One patient has developed an insulin dependent diabetes mellitus.

Complications

The only complication related to ESWL was an exacerbation of pancreatitis in patient 6 with an increase of her serum amylase level up to 3690 IU/l (normal: < 130 IU/l). The pancreatitis resolved rapidly with medical management in 3 days and this patient was discharged in good condition 4 days later. The mean serum amylase levels (standard error) of the other patients dropped from 304 (117) IU/l to 206 (105) IU/l after ESWL ($p < 0.01$, Wilcoxon test). Other laboratory parameters did not differ significantly before and after the ESWL treatment ($p > 0.1$ in all cases).

Case report

Of special interest is the case of patient 13, a 19 years old woman with idiopatic, recurrent pancreatitis since childhood. Eventually she developed multiple pancreatic stones. She suffered from chronic upper abdominal pain with frequent exacerbations which were difficult to control. Twenty months before ESWL treatment she underwent a left pancreatic resection and a pancreato-jejunostomy. However, she kept suffering from abdominal pain attacks, which required morphinomimetic medication. At ERCP multiple stones with a low grade of calcification were seen in the ducts of the uncinate process (Figure 2a). Resection of the head of the pancreas would almost inevitably have led to complete pancreatic insufficiency. We decided to treat her with ESWL using contrast medium via the naso-pancreatic drain to localize the stones. After 4 ESWL sessions no stone material could be demonstrated anymore (Figure 2b) and 18 months later she was still free of upper abdominal pain.

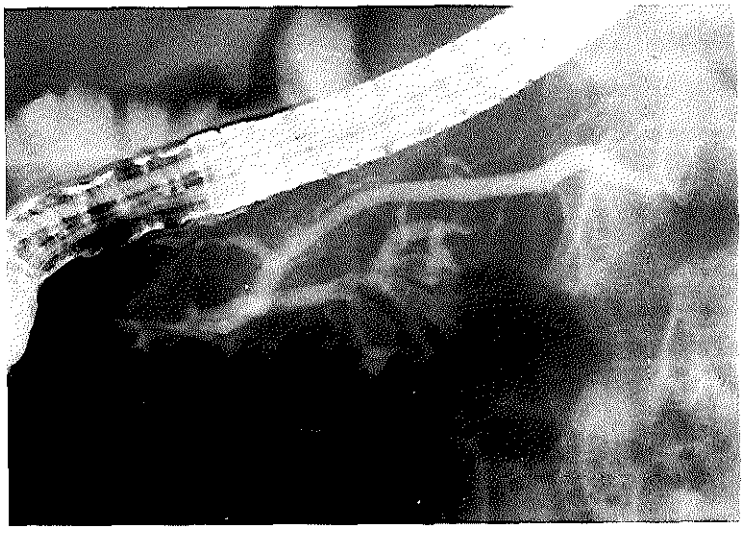

Figure 2a: ERCP of patient 13 before ESWL; multiple stones in the uncinate process of the pancreas.

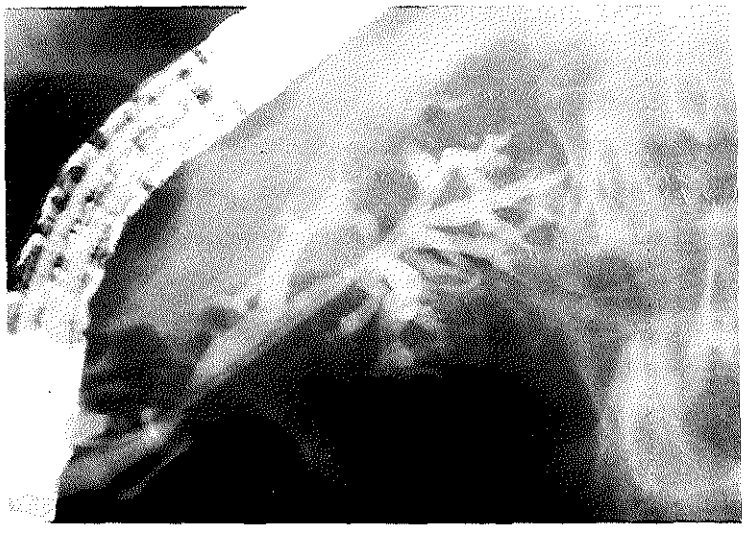

Figure 2b: ERCP of patient 13 after ESWL; clearance of the small pancreatic ducts in the uncinate process.

DISCUSSION

Seventeen patients with CCP were treated with ESWL. Eleven patients (65%) were free of abdominal pain directly after the treatment. Although it remains uncertain whether pancreatic stones are the main cause of the pain in CCP, we observed a clear relation between stone fragmentation and the relief of upper abdominal pain in our patient series (11 out of 13 patients; Table 2).

The question whether long lasting pain relief will follow stone fragmentation without complete ductal clearance remains to be answered. In our series 3 patients with stone fragmentation without complete clearance (2, 6 and 16) had an operation 12, 24 and 5 months after ESWL, respectively, because of recurrent abdominal pain. In the other 3 patients with only stone fragmentation (12, 14, and 17) the duration of follow-up is still short (Table 1) and patient 17 probably will be operated in the near future because he still reports on abdominal pain. This suggests, that fragmentation alone results in pain relief only on short term and recurrence of symptoms becomes more probable at longer follow-up. Recurrence of symptoms is not necessarily related to the presence of remaining fragments but can also very well be due to strictures in the pancreatic duct. Here, stent placement has proven to be a viable alternative to a surgical drainage procedure, especially in cases of ductal strictures in the head of the pancreas with upwards dilatation (14).

In 41% of our patients ESWL resulted in clearance of stone material. Also on long term these results seem promising: none of these patients had an operation yet, and almost all of them are free of pain after ESWL. Only one patient still had complaints directly after ESWL, which subsided in the following months (Table 3).

Advantages of ESWL compared to an operation are the following: It is minimally invasive, there is usually no need for general anesthesia and the number of complications is low (in our series 1 exacerbation of pancreatitis). The hospitalization time is short (about 3 days per ESWL session) and finally, to date there have been no reports on severe complications or mortality caused by ESWL.

Also in other institutions ESWL of pancreatic stones has been reported with fair initial results. Sauerbruch et al. (15) reported their initial experience with ESWL in 8 patients. Fragmentation was successful in 7 cases and complete clearance was achieved in 4. Three of the 8 patients had complete relief from abdominal pain attacks. Their latest results are similar

to ours with complete clearance in 42% and partial clearance in 29% (16). Soehendra et al.(17) achieved stone clearance in all of their 8 patients and 6 of them remained pain free during a follow-up period of 2 to 8 months. Neuhaus et al.(18) reported stone fragmentation in all of their 12 patients and stone clearance in 8 cases. After a median follow-up of 8 months 5 of their patients remained continuously free of pain. Recently, Delhaye et al.(19) reported on a group of 123 patients with CCP treated with ESWL and subsequent endoscopic drainage. They achieved stone fragmentation in 99% and stone clearance in 59% of their patients. In order to achieve these good results they emphasize the importance of deep endoscopic drainage in the pancreatic duct after ESWL. Furthermore, they conclude that their results in fact are equal to those achieved with an operation. Indeed, an operation for pain relief in CCP does not always lead to the expected result: in our series 4 out of 6 patients, who had an operation after ESWL, still had abdominal pain. This is probably due to patient selection but also in large series of patients operated for CCP, long lasting pain relief cannot be achieved in 20-40% of the cases (3,8,9,20,21). The benefit of an operation in CCP is thus debatable (4).

We conclude that, if endoscopic extraction of stones in the pancreatic duct turns out to be impossible, ESWL associated with endoscopic drainage should be chosen first before surgery is considered. The main indication is a calcified stone leading to main pancreatic duct obstruction but also multiple radiolucent stones in the minor ducts can be treated as shown in our series. Furthermore, we conclude that it seems important to achieve complete ductal clearance of stones and not mere stone fragmentation. Remaining strictures may require stenting. Longer duration of follow-up and a larger number of patients will have to confirm this in the future. Of course, abuse of alcohol should also be treated to maintain success of this therapy of CCP.

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CHAPTER 7

THE ROLE OF EXTRACORPOREAL SHOCK WAVE LITHOTRIPSY IN HEPATO-BILIARY-PANCREATIC SURGERY

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ABSTRACT

Since the early 1980s, extracorporeal shock wave lithotripsy (ESWL) has partially replaced major operative procedures in various fields of surgery. In the interest of the patient, it is important to determine the exact role of ESWL in surgery. Comparing our own prospectively followed patients with other patient series, we have tried to assess this role. We treated 133 patients with cholecystolithiasis, 80 patients with choledocholithiasis, and 17 patients with pancreatic stones using a second generation lithotriptor, the Siemens Lithostar® (Siemens, Erlangen, Germany).

The results suggest a limited role of ESWL for cholecystolithiasis, in which it is reserved for patients with high operative risk and patients who reject an operation. For choledocholithiasis ESWL seems to become an integral part of the treatment in the elderly patient in whom endoscopic stone removal proved impossible. Finally, ESWL could become a first option for the treatment of intractable pain in patients with chronic calcifying pancreatitis.

INTRODUCTION

Shock waves, which can be used to disintegrate stones because of their physical characteristics, can be generated by 3 methods (1-3).

Since 1980 extracorporeal shock wave lithotripsy (ESWL) has been used in the case of urolithiasis and has replaced surgical treatment almost entirely (4,5). ESWL of gallbladder stones has been applied since 1985 (6,7), and the first reports on ESWL of common bile duct stones and pancreatic stones appeared in 1989 (8,9). Despite the initial enthusiasm, restrictions for ESWL of gallbladder stones especially soon became evident. Rigid entry criteria, expensive adjuvant dissolution therapy, moderate results, and the possibility of stone recurrence after gallbladder-preserving therapies are major drawbacks (7,10-17).

ESWL of common bile duct stones is useful in patients in whom endoscopic removal proves impossible (8,18-21). ESWL of pancreatic stones in chronic calcifying pancreatitis (CCP) is still relatively unknown but seems effective (22). The morbidity and mortality associated with ESWL are minimal (7,8,11-13,18-22) and compare favorably to those with surgery. Therefore we have tried to assess the exact role of ESWL in this field with our own prospectively followed patients and other patient series.

PATIENTS AND METHODS

Using a so-called second-generation lithotriptor, the Siemens Lithostar® (Siemens, Erlangen, Germany), which operates on a electromagnetic principle, we treated patients suffering from cholecystolithiasis (n=133, group I), choledocholithiasis (n=80, group II), and pancreatic stones (n=17, group III). Characteristics of these patients are depicted in Table 1, and entry criteria for ESWL in the three groups are shown in Table 2.

Group I

All patients were treated on an outpatient basis. Directly after the first ESWL-session, adjuvant oral bile acid (OBA) therapy (urso-and chenodeoxycholate) was started. Ten days after each session an ultrasound examination (US) was done to determine the fragmentation result; If fragments remained larger than 5 mm after repeated sessions, ESWL was considered a failure, and cholecystectomy was advised. US was performed at regular intervals (3 months, 6 months, 1 year, 1.5 years, and 2 years) after the first session. If US did not demonstrate stone material at 2 consecutive occasions, clearance of the gallbladder was assumed and the OBA therapy stopped.

Group II

All patients had 1 or more of the symptoms, depicted in Table 1.

The stones were visualized by radiology and injection of contrast medium in the bile ducts via a biliary drain (Table 1). In 11 patients the biliary sphincter could not be reached at endoscopy. In those patients and in 7 others, percutaneous drains and T-tubes were used. Of the 47 patients without gallbladder, 12 had had a cholecystectomy recently and had also undergone a choledochotomy. In these patients, overlooked common bile duct stones were discovered on a postoperative T-tube cholangiogram. The possibility of spontaneous clearance of the stones after endoscopic sphincterotomy was thougt to be low because of the large size and impacted character of the stones. All treatments were performed under antibiotic coverage and continuous lavage of the bile ducts with 4 liters of sterile water per 24 hours. Shortly after ESWL the result was evaluated by cholangiography. In case of fragmentation (reduction of stone diameter, lines of contrast medium visible within the stone, or quick disappearance of the contrast medium from the biliary tree), cholangiography was repeated after 2 days of

lavage. In the case of remaining fragments, a new endoscopic or percutaneous stone extraction was attempted. If it was not successfull or in cases where stone fragmentation was never demonstrated, the patient underwent an elective bile duct exploration or had an endoprosthesis placed in the common bile duct.

Table 1
patient characteristics before ESWL treatment.

Characteristic	Group I	Group II	Group III
Patients (M/F)	133 (34/99)	80 (33/47)	17 (10/7)
Mean age (range)	49y (24-81)	73y (27-91)	42y (19-55)
Stones (no. patients)			
1	70 (53%)	34 (43%)	6 (35%)
2-5	55 (41%)	32 (40%)	7 (41%)
6-10	8 (6%)	14 (18%)	4 (24%)
Mean diameter of stone (range)	17mm (5-40)	25mm (10-50)	21mm (14-40)
Patients (no) with			
ES		69 (86%)	17 (100%)
Biliary drain			
NBD		62 (78%)	
PTD		6 (8%)	
T-tube		12 (15%)	
Symptoms			
biliary colics		39 (49%)	
jaundice		36 (45%)	
fever > 38.5 C.		16 (20%)	
Cholecystectomy		47 (59%)	
Previous pancreatic surgery			3 (18%)
History of alcohol abuse			10 (59%)

m: male; f: female; y: years; no: number; ES: endoscopic sphincterotomy; NBD: naso-biliary drain; PTD: percutaneous transhepatic drain.

Table 2
Criteria for ESWL of gallbladder, common bile duct, or pancreatic stones.

Gallbladder stones
Symptoms: biliary colics
Opacification of gallbladder at oral cholecystography
No. of stones: 1-10; diameter of largest stone > 5 mm
Calcified rim of stone < 2 mm
No cholecystitis, cholangitis, pancreatitis, or concomitant choledocholithiasis at the time of ESWL
Common bile duct stones
Symptoms: obstruction of common bile duct (jaundice, abdominal pain, fever)
Endoscopic extraction impossible
Visualization of stones with contrast medium via a biliary drain
Pancreatic stones
Symptoms: recurrent abdominal pain
Endoscopic extraction impossible
Visualization of stones without contrast medium
No acute pancreatitis, acute cholecystitis, cholangitis, or concomitant choledocholithiasis at the time of ESWL
Gallbladder, common bile duct, and pancreatic stones
No lung tissue, cysts, or aneurysms in the shock wave path
No bleeding disorders
No pregnancy

Group III

The diagnosis 'chronic pancreatitis' was based on the patient's history (chronic upper abdominal pain or recurrent attacks of upper abdominal pain), the presence of calcifications in the pancreatic region on plain abdominal roentgenography, and the radiologic aspect of chronic pancreatitis on endoscopic retrograde cholangiopancreatography (23). All patients were treated under antibiotic coverage. In 15 patients the stones could be visualized as

calcifications by radiology alone. Shock waves were focussed on these calcifications. In 2 patients additional injection of contrast medium via a naso-pancreatic drain was necessary for visualization of the stones because of a low calcification grade. After the ESWL treatment a plain abdominal roentgenogram was obtained. If stone fragmentation was observed (clear change of contour of stone), another endoscopic stone extraction was attempted, after which a nasopancreatic drain was left in place for lavage (2 liters sterile water per 24 hours). If no stone material was observed, spontaneous clearance of the duct was assumed. If ESWL repeatedly failed in fragmenting the stones, an operation was contemplated.
Statistics were performed using the test for comparing proportions with binominal distributions and the Wilcoxon test for matched pairs.

RESULTS

Table 3 summarizes the characteristics of the ESWL sessions for all three groups of patients. Table 4 depicts the fragmentation and clearance rates for all three groups. For group I the median follow-up (range) is 14 months (1-45 months), in group II 23 months (1-50months) and in group III 20 months (3-41 months).

Group I

Stone fragmentation (decrease of diameter of the largest stone >25%) could be achieved in most patients (89%); but after adjuvant OBA therapy stone clearance could be achieved in only 32% of the patients to date. In the remainder of the patients, OBA therapy continues or a cholecystectomy has been undertaken because of persistent biliary complaints or insufficient stone fragmentation. Patients with a solitary stone had a significantly better chance to become stone-free than patients with multiple stones: 26 of 52 (50%) versus 5 of 60 (8,3%), respectively, after 1 year of follow-up ($p < 0.001$: two sample proportion test).
Fourteen percent of patients with stone clearance (6/43) had stone recurrence: four of the six were not symptomatic, one underwent a cholecystectomy and in one OBA therapy was restarted.
A total of 57 patients (43%) had biliary colic shortly after the ESWL treatment. Other complications were obstruction of the common bile duct in nine patients (7%), five of whom

became jaundiced and in four of whom pancreatitis developed. Two patients (1.5%) had transient hematuria, one had acute cholecystitis after ESWL. OBA therapy resulted in diarhea in 15 patients (11%), which resolved in all cases after lowering the dose of OBA for 2 weeks. No mortality was observed.

Group II

Stone clearance was achieved in 52 patients (65%); in 14 cases biliary lavage was sufficient to clear the bile ducts; in 34 cases the remaining fragments were extracted endoscopically and in 4 cases percutaneously. In case of failure of the additional endoscopic or percutaneous attempts (n=14, 18%), the final treatment -taking into account the patient's physical status- consisted in placing an endoprosthesis past the fragmented stones (n=6) or undertaking an elective bile duct exploration (n=6). In two cases emergency surgery was necessary after complications of an endoscopic procedure (one perforation of the common bile duct with a Dormia basket, one arterial bleeding after extension of a sphincterotomy). These two patients had an uneventful recovery.

Two patients (3%), one with and one without a gallbladder, had stone recurrence at 27 and 30 months after ESWL, respectively. The first patient could be treated with a renewed endoscopic extraction, and the other had a successful repeated ESWL treatment.

One patient had a subcapsular hematoma of the right kidney, as demonstrated on US. The hematoma resolved without clinical consequences. Notwithstanding antibiotic prophylaxis one patient developed sepsis with a positive blood culture (E. coli). This patient received adequate medical treatment. There was no mortality after ESWL and adjuvant treatments.

Group III

Thirteen patients had stone fragmentation (76%), of whom 11 (65%) had immediate pain relief after ESWL. The other two patients, with fragmentation but without clearance of stones, had recurrent pain attacks and consequently underwent a side-to-side pancreatojejunostomy 12 and 24 months after ESWL, respectively (Table 4). Seven patients (41%) had complete stone clearance (in three the pancreatic duct cleared spontaneously after ESWL, and in four the duct was cleared after 2 days of lavage with sterilized water). To date, none has had recurrent abdominal pain except one patient who had a pain attack after a large alcohol intake. The median follow-up of these seven patients was 22 months (6-41 months). Of the four

patients without stone fragmentation, three had a side-to-side pancreaticojejunostomy. However, all 3 of them still report abdominal pain at 38, 31, and 14 months after the operation, respectively. One has developed insulin-dependent diabetes mellitus.

The only complication directly after ESWL was an exacerbation of pancreatitis in one patient that could be treated medically. Again, there was no mortality after ESWL.

Table 3
Characteristics of ESWL sessions in 3 groups of patients.

Characteristic	Group I (n=133)	Group II (n=80)	Group III (n=17)
Sessions/patient (range)	2.2 (1-7)	1.9 (1-4)	1.9 (1-4)
SW/session	2817	4703	4660
range:	75-4000	1200-6000	1000-8000
Duration/session	62 min	64 min	73 min
range:	35-210	30-150	20-105
Patients (no)			
GA	0	1	1
AS	133	71	15
No GA/AS	0	8	1

SW: shock waves; min: minutes; no: number; GA: general anaesthesia; AS: analgo-sedation.

Table 4: results of ESWL of gallbladder, common bile duct and pancreatic stones.

Group	no fragmentation	fragmentation →	stone clearance
I (n=133)	15 (11%) 8 expectant 7 operated	118 (89%) → 52 still OBA 23 operated	43 (32%) 6 recurrence 4 expectant 1 operated 1 OBA
II (n=80)	14 (18%) all operated electively	66 (83%) → 6 endoprosth 6 operated electively 2 operated emergently	52 (65%) 14 lavage 34 endoscopic extraction 4 percutaneous extraction
III (n=17)	4 (24%) 1 expectant 3 operated	13 (76%) → 4 pain relief 2 operated	7 (41%) all pain relief

OBA: oral bile acid therapy; endoprosth: endoprosthesis.

DISCUSSION

The role of ESWL in surgery is becoming clarified. With the results achieved in our patients and in other patient series, more reasoned statements can be made now. Instead of optimistic or pessimistic views, patients benefit most from a well established treatment scheme in which the different modalities have their own, though sometimes limited, role.

Gallbladder stones

(Laparoscopic) cholecystectomy remains the gold standard as the treatment for symptomatic cholecystolithiasis (24,25). Cholecystectomy carries morbidity and mortality rates of about 10 to 30% and 0.1 to 0.3%, respectively, and these rates increase with age (25). With laparoscopic cholecystectomy these figures may be lower, but the higher incidence of bile duct injuries gives reason for concern (26). There is no reported mortality associated with ESWL of gallbladder stones, and the rate of major complications is low (7,11). In our series, nine

patients (7%) had common bile duct obstruction, and one patient had an acute cholecystitis after ESWL.

After optimistic initial reports in which finally more than 90% of the selected patients became stone- free (7), less favorable results gave rise to pessimistic comments (27). However, most patient series have reported overall stone-free rates at 12 months of 30 to 84%, depending largely on stone characteristics (10-14, 28-31). This point is in accordance with our own findings, that ESWL therapy is found to be more effective for solitary than multiple stones, for radiolucent than slightly calcified stones, and for smaller than for larger stones. In view of the above, we think that only patients with a high operative risk (ASA classification III-IV, (32)) or patients who reject an operation should undergo ESWL, provided they comply with strict criteria to achieve the highest possible stone clearance rate. We estimate this rate to be about 50% after 1 year.

Common bile duct stones

In the case of choledocholithiasis, surgical common bile duct exploration is an accepted therapy but carries a considerable mortality rate, which may be as high as 8% in the elderly or in high-risk patients (33-35). Among this population, the treatment of choice is endoscopic sphincterotomy (ES) (36-38). However, in about 10% of the cases it proves impossible to clear the bile ducts with endoscopy alone (8,36,39). The natural history of common bile duct stones, with or without ES, still is not well known (37). However, all our patients were symptomatic and needed therapy for the short term. In these patients ESWL is an attractive alternative to surgery: stone clearance was achieved in 65% of our patients and in up to 88% in other studies (8,18-21,40,41).

The failure rate can be due to the possibility of false positivity during radiologic targeting via a biliary drain. The morbidity rate of ESWL of common bile duct stones is low: macrohematuria (in 2-11% of the patients) and hemobilia (2-8%), are reported to resolve within a few days (8,18,20). Septic fever in 3 to 6% of the cases is often regarded as an exacerbation of already existing cholangitis (8,18,19). There has not been any ESWL-related mortality, but mortality associated with the adjuvant endoscopic or percutaneous procedures, which is about 1% (36,39), must be borne in mind. At least for the patient with an increased operative risk, ESWL should be considered before surgery after failure of endoscopic measures.

Pancreatic stones

Although it remains uncertain whether pancreatic stones are the main cause of the pain in chronic calcifying pancreatitis (CCP), 11 of 13 patients with stone fragmentation were free of abdominal pain directly after the ESWL treatment (Table 4). Whether fragmentation without stone clearance can lead to long lasting pain relief is doubtful. In our series two of six patients with stone fragmentation but no stone clearance had recurrent abdominal pain and an operation after ESWL. The other four patients have reported pain relief only at limited follow-up (median 7 months, range 5-10 months]). ESWL resulted in clearance of stone material in 41% of our patients, and all of them have pain relief to date.

Stone clearance in 59% of 123 patients with CCP, treated with ESWL and subsequent endoscopic drainage, has been reported recently (22). The authors emphasized the importance of deep endoscopic drainage in the pancreatic duct after ESWL.

The ESWL technique compares favorably with an operation for pain relief in CCP: it is noninvasive, there is no need for general anesthesia, no mortality has been reported, and the number of complications is low (in our series one exacerbation of pancreatitis). It is unlikely that pancreatic insufficiency will be induced by ESWL. Furthermore, the hospitalization time is short (about 3 days per ESWL session). Pancreatic surgery is accompanied by considerable morbidity and mortality (rates of 20-40% and 2-5%, respectively) (42,43). In large surgical series, long-lasting pain relief cannot be achieved in 20% to 40% of the cases (42-46). In view of the above, a randomized trial comparing ESWL with surgery or the natural history of this disease is warranted.

In conclusion, if a decision must be made about whether to operate on a patient with CCP or treat him or her with ESWL followed by endoscopic drainage, we think that ESWL is the better alternative. It seems important to achieve stone clearance and not mere stone fragmentation. Of course abuse of alcohol must be treated as a condition that may interfere with the success of this therapy of CCP.

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CHAPTER 8

PROXIMAL CHOLANGIOCARCINOMA: A MULTIDISCIPLINARY APPROACH.

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ABSTRACT

Objective: To evaluate our diagnosis and treatment of proximal cholangiocarcinoma.

Design: Retrospective clinical study.

Setting: Department of Surgery, University Hospital.

Subjects: 66 patients with proximal cholangiocarcinoma [median age (range): 64 years (28-87)].

Interventions: Ultrasonography (n=65), computed tomography (n=55), endoscopic retrograde cholangio-pancreaticography [ERCP] (n=54), percutaneous transhepatic cholangiography [PTC] (n=32), angiography (n=19) and cytology (n=13) were used in diagnosis. Treatment consisted of: insertion of a stent (n=37), resection of the tumour (n=16), and biliary-enteric anastomosis (n=9). Twenty eight patients received radiotherapy, three patients received no active treatment.

Main outcome measures: Usefulness of diagnostic methods, survival.

Results: Ultrasonography, ERCP and PTC were helpful whereas computed tomography, angiography, and cytology added little additional information. Mean (SEM) survival after resection was 35.8 months (7.4) and after consevative treatment 10.4 months (1.5) ($p < 0.001$).

Conclusion: A multidisciplinary approach is necessary and the tumour should be resected if possible.

INTRODUCTION

Nearly all tumours of the biliary tree are sclerosing, nodular or papillary adenocarcinomas (21). They spread perineurally, through local lymph nodes and the subepithelial plane of the bile ducts and often produce an extensive local fibrotic reaction (21). In a later stage of the disease they spread to distant nodes. Obstructive jaundice caused by obstruction of the bile ducts is almost invariably the first sign of the disease (1). Cholangiocarcinomas carry a poor prognosis, most patients dying within a year of diagnosis and an overall survival rate of about 8% at five years (20). There has been an obvious tendency to move from palliative to radical treatment since the introduction of improved and advanced pre-operative imaging techniques like ultrasonography (US), computed tomography (CT), percutaneous transhepatic

cholangiography (PTC), endoscopic retrograde cholangio-pancreaticography (ERCP) and angiography.

At present resection is the treatment of choice (3,16); this includes resection of most of the extrahepatic bile duct, often with removal of the left and right hepatic ducts. To obtain resection margins that are free of tumour, resection of segment I (or segment IV or both) is often necessary. The survival for patients with clear resection margins is better than that for patients in whom they contain tumour (2,5). Biliary-enteric continuity should be re-established with a Roux-en-Y hepaticojejunostomy. About 20% of proximal cholangiocarcinomas are suitable for radical resection (7). The rest of the patients have lymph node involvement or liver metastases diagnosed preoperatively. Ingrowth into the portal vein or hepatic artery (main trunk or both branches), and extension of the tumour past secondary bifurcations of the biliary tree in both the left and the right lobes of the liver are almost always signs of unresectability (6). Finally, a number of patients are not fit enough to be able to survive such an operation. In these cases palliative treatment will be necessary to secure flow of bile into the duodenum. Treatment options are percutaneous (for proximal strictures: left or right hepatic ducts) or endoscopic (for distal strictures: common hepatic duct, common bile duct) insertion of stents through the obstructed bile ducts (19). A biliary-enteric anastomosis can also bypass the obstruction. Both external and internal (for example intraluminal placement of ^{192}-iridium wire) radiotherapy are useful after both palliation and resection.

We describe here 66 consecutive patients who attended our hospital for treatment of proximal cholangiocarcinoma over a period of 10 years.

PATIENTS AND METHODS

We evaluated the medical records of 66 patients who were diagnosed in our hospital with a proximal or mid-ductal cholangiocarcinoma from 1980 to 1990, and their details are shown in Table I.

Diagnostic procedures (Table II)

The most commonly used diagnostic tool was US, and most patients had CT and ERCP. In only 13 patients could material for cytological examination be obtained: in nine by ultrasound guided puncture and in four by endoscopic brushing.

Table I
Details of the 66 patients with proximal cholangiocarcinoma.
Figures are number (%) of patients unless otherwise stated.

Sex:	
Male	28 (42)
Female	38 (58)
Median age (years):	64
Range	28-87
Diagnosis:	
Histologically confirmed	46 (70)
Clinical alone	20 (30)
Presenting symptoms:	
Obstructive jaundice	62 (94)
Prominent abdominal pain	3 (4)
Haemobilia	1 (2)
Non-specific symptoms:	
Loss of weight	35 (53)
Vague abdominal pain	32 (48)
Fatigue	20 (30)

Table II
Diagnostic procedures in 66 patients with proximal cholangiocarcinoma.

Procedure	No (%) of patients
Ultrasonography	65 (98)
Computed tomography	55 (83)
ERCP	54 (82)
PTC	32 (48)
Angiography	19 (29)
Cytology	13 (20)

Treatment (Table III)

Resectability of the tumour was assessed from the results of the investigations and patients were assigned to the appropriate treatment. Table III summarises the different initial treatments. Thirty seven patients were given a permanent stent as palliation. In 12 patients it was possible to bypass the obstruction with an endoprosthesis; in seven cases this was done endoscopically and in five percutaneously. In five patients, only external, percutaneous drainage was possible and 20 required a combination of both internal and percutaneous drainage to relief the obstruction to the biliary tree. Sixteen of these 37 patients received radiotherapy; three patients received only external beam radiation (dose: 40 Gy in 16 fractions of 250 cGy), two patients received only intraluminal radiation through a stent (insertion of ^{192}-iridium wire, dose: 25 Gy at 1 cm) and 11 patients were given a combination (40 Gy externally, 25 Gy by iridium wire). The criterion for radiotherapy after resection was microscopic evidence of residual tumour in the proximal resection plane without hepatic or lymph node metastases. Of the 16 patients treated by a resection, six met this criterion; two were given 40 Gy externally and four 40 Gy externally and 25 Gy at 1 cm through a postoperative drain. Of the nine patients treated by biliary-enteric anastomosis five received radiotherapy (two were given 40 Gy externally and three 40 Gy externally and 25 Gy at 1 cm through a postoperative drain).

Table III
Treatment of 66 patients with proximal cholangiocarcinoma.

Treatment	Total No of patients	No who received radiotherapy
Insertion of stent	37	16
Resection	16	6
Biliary-enteric anastomosis	9	5
Radiotherapyalone	1	1
No treatment	3	0

In four of the 16 patients treated by radical resection and in six of the nine treated by biliary-enteric anastomosis, a stent was inserted beyond the tumour to achieve preoperative relief of the jaundice.

Fifty patients were unsuitable for radical resection: in 25 the tumour was too extensive or metastases were diagnosed before operation could be contemplated; 11 were too old or not fit for a major operation; and in nine the tumour was inoperable at laparotomy. One patient refused blood transfusion on religious grounds, and in four the reason was not known.

The significance of differences between groups was assessed by the Mann-Whitney and the Wilcoxon tests. Survival analysis was by the logrank test.

RESULTS

Diagnostic procedures

US showed dilated bile ducts in 85% of patients with obstructive jaundice (Table IV). A hilar mass was seen in only about a third of cases, but the percentage increased if CT was also done. Both ERCP and PTC suggested malignancy in almost all cases. In one case ERCP failed and in another suggested sclerosing cholangitis rather than malignant stenosis. Cytological aspiration yielded malignant cells in only a few cases. Angiography was done in 19 cases; on two occasions it showed involvement of the hepatic artery and in one involvement of the portal vein. The latter was also diagnosed by US.

The sites and classification of the tumours are given in Table V.

Table IV
Number (%) of diagnostic procedures which suggested proximal cholangiocarcinoma in 66 patients.

Procedure	Total No	No (%) that suggested malignancy	
Ultrasonography	65	Dilated bile ducts	55 (85)
		Hilar mass	20 (31)
Computed tomography	55	Hilar mass	24 (44)
ERCP	54	Presence of tumour	52 (95)
PTC	32	Presence of tumour	31 (97)
Cytology	13	Malignant cells	3 (23)

Table V
Sites and classification of the 66 cholangiocarcinomas. Figures are number (%) of patients.

Site of tumour:	
Junction of right and left hepatic duct	47 (71)
Common hepatic duct	14 (21)
Proximal common bile duct	5 (8)
Classification (5):	
Type I (at junction of right and left hepatic duct, not obstructed)	2 (3)
Type II (at junction of right and left hepatic duct with obstruction)	14 (21)
Type III (extension past secondary bifurcations in right or left hepatic duct, or both)	37 (57)
Unknown	13 (20)

Treatment of patients (Figures I&II)

Figure I shows the survival of the 37 patients treated by insertion of a stent divided into those treated by stent insertion alone (n=21) and those treated by stent insertion and adjuvant radiotherapy (n=16). Median survival for the whole group was 5.3 months (range 0.7-44.0) (Table VI).

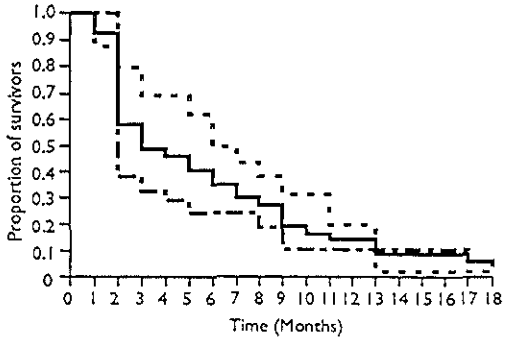

Figure 1: Survival after insertion of stent. The dashed line indicates those who were treated with radiotherapy (n=16), the dotted lines those who were not (n=21), and the solid line shows the cumulative survival (n=37).

Of the 37 patients treated by insertion of a stent, mean total bilirubin concentration before, and 1, 3, 6, and 12 months after insertion were 268 μmol/l (n=37), 91 μmol/l (n=23), 94μmol/l (n=14), 73 μmol/l (n=13), and 27 μmol/l (n=10), respectively.

Twenty three patients required renewal of their stents (mean: 3.0 new stents/patient). Among the 21 patients treated by stent insertion alone, the frequency of stent replacement was 1/115 days, whereas in the group of 16 who had adjuvant radiotherapy it was 1/149 days.

Complications in the 62 patients who were treated by some form of intervention are shown in Table VI, and figure 2 shows survival curves for those who had resections (n=16) compared with all other forms of treatment (n=47).

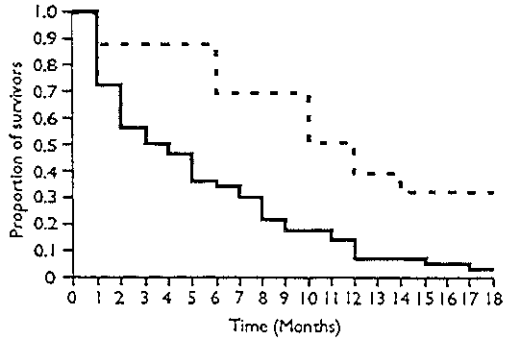

Figure 2: Survival after resection (dashed line, n=16), and all other treatments (solid line, n=47).

Table VI
Results of treatment in 62 patients who had some form of intervention.

	Insertion of stent (n=37)			Resection of tumour (n=16)			Biliary-enteric anastomosis (n=9)		
	With RT (n=16)	Without RT (n=21)	Total	With RT (n=6)	Without RT (n=10)	Total	With RT (n=5)	Without RT (n=4)	Total
Median survival (months)	13.8	3.0	5.3	20.4	29.4	23.4	9.9	8.3	9.9
Range	1.8-40.2	0.5-44.0	0.5-44.0	10.8-71.6	0.6-105.6	0.6-105.6	6.4-14.9	0.7-20.	90.7-20.9
No of operative deaths		Not applicable				2			1
Complications									
Blockage of stent			16		Not applicable			not applicable	
Cholangitis			23			2			2
Wound infection			0			4			4
Haemorrhage			0			2			0
Anastomotic leak			0			1			0

RT: Radiotherapy

DISCUSSION

It is obvious that early detection of cholangiocarcinoma is of major importance: in patients who present with obstructive jaundice in the absence of biliary stones, malignancy in the area of the biliary tree should always be excluded, particularly if the patient has recently lost weight, or has vague abdominal symptoms, or both. In these patients US should be the first imaging procedure used (18). This was done in all but one of our patients and showed dilated bile ducts in 85% of cases (Table III). A hilar mass was detected by US in 31%, but CT was more sensitive (44% of cases). Although CT is sensitive in defining liver atrophy in the case of hilar cholangiocarcinoma (8), the additional value of CT over US can be questioned, particularly if (in cases suspected of malignancy) US is done by an expert. Angiography did not improve on US in our group of patients.

Both PTC and ERCP were highly sensitive in diagnosing malignancy (Table III), and in addition they can also be used for therapeutic interventions, for example, insertion of a stent. Whether to use PTC or ERCP depends on the skill and experience available in different centres. Another important factor is the level of obstruction: proximal obstructions (at the hepatic hilar confluence) can more easily be bypassed by PTC (19). This stresses the growing importance of the role of the interventional radiologist in diagnosis and treatment of hilar cholangiocarcinoma. Distal obstructions in the common bile duct demand the expertise of an experienced endoscopist.

Cytology was done in only 20% of patients and with poor results: in only three out of 13 patients were malignant cells found, so we did not find that cytology was helpful in confirming the diagnosis.

The best treatment for cholangiocarcinoma is, in suitable patients, resection of the tumour: median survival in the 16 patients with a resection was 23.4 months, with five patients still alive at 24.3, 34.4, 48.2, 76.9, and 105.6 months after their operation, respectively. In the 47 patients with non-resective therapy this was 6.4 months, with three patients still alive at 17.2, 25.2, and 40.2 months after their intervention ($p < 0.001$).

Figure 2 shows the survival curves of the 16 patients treated by resection compared with the 47 patients treated with stent placement, a biliary-enteric anastomosis or radiotherapy. The three year survival was 30% for patients treated by a resection, even if the resection margins were not free of tumour and adjuvant radiotherapy was given. The patients treated by

resection had a significantly better survival rate than the rest of the patients ($p < 0.05$). If resection margins were free, survival was even better, five of the 10 patients being still alive after their operation. At longer follow-up this radical treatment could turn out to have been curative. Obviously a strict selection of patients was responsible for these figures: only patients who were physically fit, with moderate regional extension of tumour (mostly classes I and II) and without metastases underwent a radical resection. In our series 16 patients fulfilled these conditions (resectability rate: 24%). In other studies, comparable resectability rates were achieved. Blumgart et al. (7) found resectable lesions in 18 of 94 patients (19%). Langer et al. (15) treated 90 patients of whom 69 were diagnosed as having proximal or mid-ductal adenocarcinoma of the bile ducts. Eighteen of these 69 patients (26%) had resections. Lai et al (12) reported a resectability rate of 30% (29 of 97 patients with proximal bile duct cancer). Bismuth et al (5) did resections for 23 of 122 patients (19%) with hilar cholangiocarcinoma.

One of our goals should be to detect these tumours at the earliest stage possible to increase the percentage of patients who are eligible for a resection.

Because of the advanced stage of the disease most patients were eligible only for palliative treatment. Survival after insertion of a stent or a biliary-enteric anastomosis did not differ significantly (median survival: 5.3 months and 9.9 months, respectively), but the quality of life should be taken into account because of the duration of hospital stay and the serious morbidity after biliary-enteric anastomosis.

Despite frequent episodes of cholangitis caused by blocking of the stent, insertion of a stent (either percutaneously or endoscopically) was adequate palliative treatment, giving a significant fall in serum total bilirubin concentration within a month ($p < 0.001$). The recent introduction of self-expanding metal stents seems promising in spite of the considerable increases in cost. Better patency rates and lower replacement rates have been reported (13,17), as well as ease of insertion and reduced damage during insertion (11,14).

Positive results have been described for the use of radiotherapy in addition to other treatments (9,10). Looking at the median survival and the survival curve (figure 1) it could be claimed that radiotherapy did prolong life expectancy, though not significantly. Patient selection influences these figures here as well, because only patients in good condition were eligible for radiotherapy. Another possible advantage of radiotherapy could be to decrease the need for replacement of stents; it is conceivable that it inhibits tumour growth at the proximal and

distal ends of the stent. Patients who did not have radiotherapy (n=21) had their stents replaced about every 115 days, whereas those who had radiotherapy (n=16) required one stent every 149 days. Randomized studies will be necessary to establish the possible value of adjuvant radiotherapy in the treatment of proximal cholangiocarcinoma.

We conclude that in hilar cholangiocarcinoma the limits of therapeutic potential, both in cure and in palliation, have still not been reached. Interdisciplinary cooperation is necessary for optimal treatment.

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CHAPTER 9

GENERAL DISCUSSION AND CONCLUSIONS

This thesis was written at a time where the therapeutic options for gallstones are rapidly changing. As most medical literature is a reflection of practice at the time of writing, this thesis also is: it offers solutions for current problems in a rapidly changing field. But it also is aimed at preventing too rapid change, as occurred in the introduction of laparoscopic cholecystectomy. Impressed by the short term results, both the medical world and patients left no choice but to adopt this technique as quick as possible. However, since almost all initial series of laparoscopic cholecystectomy have been reported by experts in the field, it is possible that the real results of laparoscopic cholecystectomy, especially with regard to complications such as intraoperative damage to the bile ducts, could turn out worse than those published recently in important medical literature. Furthermore, patient selection is still an important factor in the case of laparoscopic cholecystectomy, leading to more optimistic results as well.

Randomised controlled trials should be performed in order to evaluate newly introduced techniques. Laparoscopic exploration of the common bile duct will be the next exciting development but introducing it in an uncontrolled fashion as well could lead to disastrous consequences with regard to iatrogenic bile duct lesions. Therefore in future it would certainly be wise to compare this technique with endoscopic stone extraction and ESWL.

ESWL has proven to be a safe and integral part of the management of common bile duct stones: further research is warranted in increasing the success rate of ESWL of common bile duct stones: it is important to identify those factors found at endoscopy which influence the success rate of ESWL in a negative sense. Stone diameter and composition play a role but of greater importance are the diameter of the distal common bile duct and the papilla of Vater, the presence of a papillary stenosis and the length of this stenosis (unpublished observations). Prior knowledge of these factors may change the treatment strategy: then the first option will be either an operation or endoscopic insertion of a permanent stent in the common bile duct, depending on the physical status of the patient.

The introduction of laparoscopic cholecystectomy has revived the discussion about the management of suspected common bile duct stones. Routine use of intraoperative cholangiography can be replaced by selective preoperative endoscopic cholangiography, based on clinical indicators. The role of intraoperative cholangiography as a road map for the surgeon who performs a laparoscopic cholecystectomy can be discussed; a considerable part of iatrogenic lesions of the common bile duct allready will occur before the common bile duct

is canulated.

ESWL for the treatment of the invalidating pain in chronic calcifying pancreatitis seems to be an underestimated technique; in view of the mortalility and morbidity of pancreatic operations and their success rate of about 60-80%, a treatment algorithm with ESWL as the first step will be fully justified. Allthough the main indication for ESWL is a calcified stone leading to obstruction of the main pancreatic duct, also other stones can be treated.

Malignant obstruction of the bile ducts is a slow but almost always fatal disease. If cholangiocarcinoma can be diagnosed at the earliest possible stage, the resectability rate will be higher and also, the physical condition of the patient at operation will be better. This will lead to a higher percentage of curative operations. However, since the presenting symptom of this disease is almost always jaundice, tumor extension often allready is beyond the possibility of resection before the patient is diagnosed as having cholangiocarcinoma. To achieve the highest possible resectibility rate a combined effort of various specialists is absolutely necessary.

CONCLUSIONS OF THIS THESIS:

1. ESWL of stones in the common bile duct is a rapid, non-invasive, and effective treatment with minimal discomfort for the patient. Both short and long term results are good. In case endoscopic removal of the stones proves impossible, ESWL should be undertaken, particularly in elderly or high risk patients, but also in younger patients.

2. Laparoscopic cholecystectomy improves quality of life and symptomatology to the same degree but at an earlier stage than conventional cholecystectomy. From this point of view laparoscopic cholecystectomy is preferable to conventional cholecystectomy.

3. From the point of view of complications laparoscopic cholecystectomy still has not proven to be superior to conventional cholecystectomy. Only a randomised controlled trial can adequately compare both techniques but it seems not very probable that it ever will be conducted.

4. Endoscopic papillotomy and ESWL together can achieve stone clearance in 97-99% of all patients with choledocholithiasis. If stones in the common bile duct are suspected in patients who will undergo laparoscopic cholecystectomy, then these stones should be managed in the preoperative period.

5. If endoscopic extraction of stones in the pancreatic duct turns out to be impossible, ESWL associated with endoscopic drainage should be chosen first before surgery is considered. It is important to achieve complete ductal clearance and not mere stone fragmentation.

6. ESWL for cholecystolithiasis should be reserved for patients with high operative risk and patients who reject an operation, provided they comply with strict criteria. For choledocholithiasis ESWL becomes an integral part of the treatment in the elderly patient in whom endoscopic extraction proves impossible. ESWL could become a first option for the treatment of pain in patients with chronic calcifying pancreatitis.

7. Only a combined effort of surgeon, gastroenterologist, radiologist, and radiotherapist can achieve optimal treatment for cholangiocarcinoma, both in cure and in palliation. Early detection of cholangiocarcinoma is essential to augment the rate of patients who can be treated with a potentially curative resection.

SUMMARY

Gallstones are a major health problem: about 10% of the Western population has cholecystolithiasis and about 10% of these patients has choledocholithiasis.

Chapter 2 of this thesis describes the problems of large, difficult common bile duct stones: surgery carries its risks, especially in elderly patients. If endoscopic extraction has been attempted but has failed, both surgeon and gastroenterologist are in an awkward position. Treatment with ESWL will offer the solution in about 70% of these patients and should be undertaken before the decision to operate has been made.

Chapter 3 describes the quality of life after laparoscopic or conventional cholecystectomy. Patients have a quicker improvement of quality of life after a laparoscopic cholecystectomy.

Chapter 4 tries to temper the euphoria about the laparoscopic cholecystectomy. A good randomised trial comparing the laparoscopic with the conventional technique is still not published because of this euphoria. Therefore, a group of laparoscopically operated patients is matched with historical controls who recently underwent conventional cholecystectomy. Although the wellknown advantages of the laparoscopic technique (less pain, quicker discharge from the hospital and quicker return to work) are obvious in this study as well, its complications are more serious than those of the conventional technique.

Through a review of the literature, chapter 5 offers a solution of the problem how to cope with eventual stones in the common bile duct when laparoscopic cholecystectomy will be undertaken. If on the basis of clinical indicators common bile duct stones are selectively removed by means of an endoscope and ESWL, the chance of an unsuspected common bile duct stone is small and the chance of it becoming symptomatic even smaller. Following this strategy, the number of complications is not higher than that of a surgical exploration of the bile ducts.

Chapter 6 describes another application of ESWL: the treatment of stones in the pancreatic duct in chronic pancreatitis. On short term as well as on long term, the invalidating abdominal pain can be successfully treated with ESWL in about 60% of the patients. In this way, an operation can be avoided.

In chapter 7 the role of ESWL in todays pancreatico-biliary surgery is evaluated. Our own results and those of other investigators are incorporated.

Finally, in chapter 8 the treatment of a group of patients with malignant obstruction of the bile ducts -cholangiocarcinoma- is evaluated in a retrospective study. A radical operation is, if possible, the best treatment with regard to length of survival and possible curation. Only by means of close cooperation between surgeon, gastroenterologist, radiologist and radiotherapist this tumor can be classified and treated as quick as possible.

SAMENVATTING

Galstenen vormen een omvangrijk gezondheidsprobleem: ongeveer 10 % van de westerse bevolking heeft stenen in de galblaas en ongeveer 10% dáárvan heeft stenen in de galwegen.

Hoofdstuk 2 van dit proefschrift beschrijft de problematiek rond grote, vastzittende stenen in de ductus choledochus: de geëigende operatie hiervoor is risicovol, met name bij een oudere patiëntenpopulatie. Wanneer dan wordt overgegaan naar een poging tot endoscopische extractie en deze blijkt te mislukken, zit zowel chirurg als gastro-enteroloog met de handen in het haar. Een ESWL-behandeling biedt dan bij ongeveer 70% van deze patiënten uitkomst, en zou dus altijd eerst uitgevoerd moeten worden voordat tóch besloten wordt om te opereren.

Hoofdstuk 3 beschrijft de kwaliteit van leven, die patiënten ervaren na ofwel een laparoscopische, of een conventionele cholecystectomie. Patiënten blijken een snellere verbetering van kwaliteit van leven te ervaren na de laparoscopische cholecystectomie.

Hoofdstuk 4 tracht wat tegengas te geven bij de euforie rond de laparoscopische cholecystectomie. Een degelijk, goed gerandomiseerd vergelijkend onderzoek tussen de laparoscopische en conventionele techniek is nog niet gepubliceerd vanwege dezelfde euforie. Daarom is een groep laparoscopisch geopereerde patiënten gekoppeld aan een historische controlegroep, welke recent een conventionele cholecystectomie ondergingen. Hoewel de overbekende voordelen van de laparoscopische techniek (minder pijn, sneller ontslag uit ziekenhuis en snellere hervatting van werk) ook in dít onderzoek duidelijk zijn, blijken de complicaties ernstiger dan die van de conventionele techniek.

Ondersteund door literatuuronderzoek biedt hoofdstuk 5 een oplossing voor het vraagstuk hoe men om moet gaan met eventuele stenen in de ductus choledochus wanneer men een laparoscopische cholecystectomie wil verrichten. Indien op basis van klinische aanwijzingen choledochusstenen selectief verwijderd worden met behulp van de endoscoop en ESWL, is de kans op een gemiste steen klein en de kans op symptomen door deze steen nog kleiner. Bij deze strategie ligt het aantal complicaties niet duidelijk hoger dan bij een operatie aan de galwegen.

Hoofdstuk 6 beschrijft een andere toepassing van ESWL: de behandeling van stenen in de ductus pancreaticus bij chronische pancreatitis. Zowel op korte als op lange termijn blijkt de invaliderende buikpijn bij ongeveer 60% van deze patiënten weg te blijven na ESWL-behandeling. Een operatie kan op deze manier worden voorkomen.

In hoofdstuk 7 volgt een evaluatie van de rol die ESWL in de hedendaagse pancreatico-biliaire chirurgie speelt. Daarbij worden de eigen resultaten en die van andere onderzoekers meegenomen.

Tenslotte wordt in hoofdstuk 8 de behandeling van een groep patiënten met maligne obstructie van de galwegen -het cholangiocarcinoom- geëvalueerd in een retrospectief onderzoek. Een radicale operatie is, indien mogelijk, de beste behandeling met de langste overleving en misschien zelfs genezing. Slechts door een goede samenwerking tussen chirurg, gastro-enteroloog, radioloog en radiotherapeut kan deze tumor zo snel mogelijk in kaart gebracht en behandeld worden.

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CURRICULUM VITAE

René van der Hul werd geboren op 17 april 1966 te Schiedam. Hij volgde het middelbare onderwijs aan Scholengemeenschap Spieringshoek Schiedam, alwaar hij in mei 1984 het eindexamen Atheneum B behaalde.

In september 1984 werd begonnen met de studie geneeskunde aan de Erasmus Universiteit Rotterdam. Na het behalen van het doctoraalexamen in juli 1988 begon hij onder begeleiding van Prof.Dr. T.J. Visser en Prof.Dr. G. Hennemann met wetenschappelijk onderzoek naar transport van schildklierhormonen op het laboratorium Inwendige Geneeskunde III van het Academisch Ziekenhuis Rotterdam. Hij behaalde zijn artsexamen op 19 april 1991.

Van mei 1991 tot juni 1993 werd het klinisch-wetenschappelijk onderzoek verricht, dat de basis vormt voor dit proefschrift. Dit gebeurde onder begeleiding van eerst Prof.Dr. O.T. Terpstra en later Prof.Dr. H.A. Bruining op het Rotterdamse ROGAL-project van de afdeling Heelkunde van het Academisch Ziekenhuis Rotterdam (Hoofd: Prof.Dr. J. Jeekel).

Vanaf juli 1993 is hij arts-assistent op de afdeling Chirurgie van het Ziekenhuis Leyenburg, Den Haag (Hoofd: Dr. W.M. Oosterwijk).