RADIOLOGICAL ASPECTS OF NONSURGICAL THERAPY OF GALLBLADDER STONES

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Radiologische aspecten van de niet chirurgische behandeling van galblaasstenen

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CHAPTER 1

INTRODUCTION

1.1 General Introduction

In the western world gallstones are a common finding in adults. Epidemiologic studies in Italy [1-3] reported the prevalence of gallstones to be between 8.3% [1] and 13.9% [3]. The prevalence increases with age and is higher for females. Over the age of 50 years the prevalence is 10-15% for males and 20-25% for females [4]. Although 80% of the subjects with gallstones are free of symptoms [3], gallstone disease is a major health problem. It is reported to be one of the most common causes of hospitalization for surgical procedures [5]. In the United States 500,000 - 600,000 cholecystectomies are performed annually with an estimated cost of over 1 billion dollars [5].

Cholecystectomy has a hospital stay of approximately 5 days and a subsequent significant disability of 3-6 weeks. It is a safe and effective procedure and has been the standard therapy for more than 100 years. McSherry [6] recently reviewed records of more than 14,000 cases over half a century of surgically treated patients with gallstones. The total mortality rate was 1.7% with age being the most important risk factor. The mortality rate was 0.4% in patients under 50 years, 1.5% in patients between 50 and 65 years and 4.5% in patients 65 years and older. When elective cholecystectomy was performed the mortality rate was 0.09% for patients under 50 years and 0.8% for patients over 50 years.

For medico-economic reasons and due to the relative increase in the number of older patients, increasing efforts are made to treat gallstone disease without the distress of surgery. Initial experiments in this field were made with oral bile acids for dissolution of cholesterol stones. Chenodeoxycholic acid (CDCA) was introduced in the early 1970's [7]. Its mechanism is based on suppressing an enzyme of the liver for the synthesis of cholesterol, resulting in desaturation the bile of cholesterol and ultimate dissolution of gallstones [8]. The results however, proved disappointing.

In a multicenter prospective double-masked study of the National Cooperative Gallstone Study Group [9] complete dissolution of stones after 2 years administration of CDCA was achieved in only 13.5% of the patients. Reported dose-related side effects were diarrhea in up to 50%, hepatotoxicity in 3% and a 10% or more elevation of serum cholesterol level in 85% of the patients. CDCA is now largely replaced by, or combined with, another litholytic bile acid, ursodeoxycholic acid (UDCA) which is

better tolerated, has fewer side effects [8], and is more effective than CDCA [8].

In a double-blind randomized study, Erlinger et al [10] reported an efficacy rate of 28.9% after one year administration of UDCA. Adequate results of oral bile acid therapy are, however, only expected in highly selected groups of patients with success rates of about 60% for patients with a small number of stones measuring less than 1 cm and in 80-90% of the patients with floating stones, as assessed by oral cholecystography [11].

A major stimulant for non-invasive gallstone treatment was the introduction of extra corporeal shockwave lithotripsy (ESWL) [12,13]. This method to fragment stones uses shockwaves that are generated with different techniques such as electrostatic spark discharge, electromagnetic shockwaves and pulsed piezoelectric shock generation. The shockwaves are generated under water and transmitted to the stones through a water bath or, recently, a water-filled cushion and through body soft tissue. ESWL is non-invasive, only i.v. analgesia is needed, and the procedure can be performed on outpatient basis. The first machines were developed for the treatment of kidney stones and soon unleashed a revolution in the management of urolithiasis [14-16].

With the first reported results of the use of ESWL for gallbladder stones from a group in Munich (FRG), it became evident that ESWL also plays a part in the management of gallstone disease [17,18]. These researchers formulated strict criteria for the selection of patients with symptomatic gallstone disease. The most important are: (1) A solitary radiolucent gallbladder stone measuring up to 30 mm in diameter, or no more than three stones with a similar total stone mass. (2) The gallbladder has to be visualized on oral cholecystography. By these criteria, only 28% of the patients they screened were eligible for ESWL. All their patients received adjuvant oral bile acids (a combination of CDCA and UDCA), which started 2 weeks before ESWL and continued for 3 months after complete clearance of stone fragments. ESWL combined with oral bile acids appeared effective, especially for patients with solitary stones up to 20 mm, 95% was stone free after 12-18 months. Patients with 2 or 3 stones were stone free after 12-18 months in 67% of cases. Side effects of ESWL were reported as minimal and can be related to the shockwave therapy itself i.e., energy trauma. They are usually mild and limited to transient microscopic hematuria (3%) and cutaneous petechiae at the entry site of the shockwaves (14%) [18]. On the other hand, the migration of stone fragments may also lead to complications. Episodes of biliary pain occurring before the disappearance of stone fragments was reported by 35% of the patients. Mild pancreatitis was observed in two patients (1%), one of which required endoscopic sphincterotomy to

extract the fragments from the common bile duct [18].

The group from Munich, in summarizing their results, concluded that ESWL is safe and effective in selected patients. Unfortunately their favorable results have not yet been duplicated by other investigators [19-24]. The less favorable outcomes of others may be caused by several factors: Burhenne and coworkers [19,20] did not use adjuvant oral bile acids and also include calcified gallstones. They used a more vigorous ESWL regime, retreating patients with stone fragments larger than 3 mm. (the Munich protocol only retreats stone fragments larger than 5 mm). Sixty-one percent of their cases was stone free after 1 year. Patients with a solitary stone were stone free in 70% of the cases. Den Toom et al [21] and Zeman et al [22] strictly followed the Munich treatment protocol, but, expanded the inclusion criteria concerning the number and size of the stones. Only 30% of their patients was stone free after 1 year. However, even when the results of the group of patients with solitary stones are considered, the clearance rate is still lower (54%) compared to the Munich study.

The Dornier National Biliary Lithotripsy study [23,24] was designed to determine the value of adjuvant oral bile acids. The selection criteria proclaimed by the Munich study were employed, but, the number of delivered shockwaves was decreased. After 6 months only 21% of their patients treated with ESWL combined with oral bile acids were free of stones (Munich study: 63%) and 35% of the patients with solitary stones (Munich study: 78%).

It is unclear to what extent the use of different equipment with different shockwave generating techniques contributed to the differences in outcome of therapy [25]. Although many questions concerning the outcome of therapy have to be answered, it is evident that patient selection is crucial [26]. The best results are obtained in patients with a solitary radiolucent stone less than 20 mm in diameter (70-95% stone free after 1-2 years).

Local contact dissolution, another way to treat gallstones by dissolving gallstones with pharmaceutical agents, gained attention during the experiments with ESWL.

Experiments with local contact dissolution were initially developed for retained bile duct stones [27]. The first clinical application of a safe and effective cholesterol solvent mono-octanion was published by Thistle and co-workers in 1980 [28]. The method has not gained wide spread application because of the slow dissolution rate of mono-octanion (1-20 days) and due to the introduction of endoscopic retrograde cholangiography with sphincterotomy, which largely replaced other treatments for (retained) bile duct stones. A promising new option for local contact dissolution was

introduced by Allen and coworkers from the Mayo Clinic [29], who reported rapid dissolution of gallbladder stones by methyl tert-butyl ether (MTBE).

Diethyl ether, an anesthetic, was known to dissolve gallstones rapidly but its volatilization was an insurmountable problem for clinical application. A derivate MTBE boils at 55°C, remains liquid at body temperature and is therefore more stable than diethyl ether. The solvent is introduced through a percutaneous transhepatic gallbladder catheter. Both the agent and the percutaneous approach make this procedure a more invasive and hazardous one compared to oral bile acids and ESWL.

A group of investigators from the Mayo Clinic, recently reported favorable results in 75 patients with cholesterol stones [31]. They did not limit the number and size of gallstones. The average time of treatment was 5 hours per day for 1 to 3 days. Complete or more than 95% dissolution was achieved in 72 of 75 patients (96%) and side effects or complications were few. Most patients required i.v. analgesics during the first hours of therapy, one third of the patients complained of transient nausea with or without emesis. In one patient serious overflow of MTBE from the gallbladder to the bile ducts and systematic absorption of MTBE was observed with clinical signs of ulcerative duodenitis and hemolysis. Sixteen percent of the patients had abdominal pain after removal of the catheter, probably due to slight transient leakage of bile. One patient suffered hypotension and bradycardia at the time the gallbladder was punctured, and responded well to anticholinergic medication. It was concluded by the Mayo Clinic group that percutaneous MTBE contact dissolution is a useful alternative to surgery in selected patients with symptomatic cholesterol stones of the gallbladder.

In addition to the above mentioned forms of treatment, there is a range of more invasive therapeutic possibilities, consisting of several percutaneous techniques to remove gallstones from the gallbladder and/or bile ducts [32-37]. The indications for these techniques are usually limited to patients at high risk for general anesthesia and the morbidly obese. A new and relatively less invasive technique for percutaneous stone removal is rotatory gallstone cholecystolithotripsy [37]. A small impeller is introduced into the gallbladder to pulverize the indwelling gallstones. First reported results in a limited number of patients are promising with minor complications [37].

All nonsurgical treatments of gallstone disease have the preservation of the gallbladder in common. Although many patients (and fewer physicians) consider this an advantage, potential risks remain.

First, by staying intact, the gallbladder may form recurrent gallstones. Although

long-term follow-up is not yet available, a recurrence rate of about 30% within 3 years after oral bile acid therapy [38,39] and after local contact dissolution with MTBE is reported [40]. The Munich group [41] reported a lower recurrence rate after ESWL (11% after 18 months), probably because they treated a highly selected population with up to 80% patients with solitary stones [39,42].

Another risk associated with gallbladder preserving treatments for gallstone disease is the possible development of carcinoma of the gallbladder [43]. Gallbladder carcinoma has been reported to occur in 0.5-1.5% of patients who underwent cholecystectomy [43]. Large gallstones [44] and calcified or "porcelain" gallbladders [45] are associated with an increased risk for gallbladder carcinoma therefore, in these cases, cholecystectomy is recommended.

At present nonsurgical treatments of gallstone disease do not only have to compete with standard open cholecystectomy but also with laparoscopic cholecystectomy [46,47]. This technique, first performed in 1987 by Mouret in France [48], uses endoscopic equipment which was initially developed for gynecologic purposes. After small incisions four sheaths are introduced at different sites of the abdomen. One sheath in the umbilical region is used to allow introduction of a gas insufflator to create a pneumoperitoneum and followed by a video-laparoscope. Two sheaths are placed in the right upper quadrant to allow introduction of surgical instrumentation. A sheath in the epigastrium is used to dissect the cystic duct and cystic artery from the surrounding tissue and to remove the gallbladder from the hepatic fossa. The gallbladder is finally extracted through the umbilical incision.

The advantages of laparoscopic cholecystectomy, compared to standard open cholecystectomy, were stated by Soper [49]: less postoperative pain; diminished hospitalization (mean hospital stay 1-2 days) [47] and interval of disability; improved cosmetics. The disadvantages are: three-dimensional depth perception is limited by the monocular vision of the video laparoscope; most general surgeons are unfamiliar with laparoscopic techniques; poor visualization of the common bile duct and inability to deal adequately with common bile duct stones which are discovered during the procedure. The Southern surgeons club [47], in a prospective study of 1518 patients who underwent laparoscopic cholecystectomy, reported seven injuries (0.5%) to the common bile duct or the hepatic duct during the procedure. In standard open cholecystectomy the frequency of bile duct injuries is estimated at 0.1-0.2% [49]. Another possible disadvantage is the difficulty to control hemorrhages.

The Southern surgeons club [47] reported a complication rate of 5.1% which

compares favorably with the complication rates reported for standard open cholecystectomy. Laparoscopic cholecystectomy is considered a major surgical procedure, carrying with it risks similar to those of conventional cholecystectomy. According to Soper [50], the absolute contraindications for laparoscopic cholecystectomy are patients unable to tolerate general anesthesia and patients with cholangitis, peritonitis and coagulopathy. The relative contraindications include severe obstructive pulmonary disease, acute cholecystitis, common bile duct stones, previous upper abdominal surgery, advanced liver disease, known abdominal malignancy, large gallstones (> 4 cm), morbid obesity and pregnancy.

It is expected that laparoscopic cholecystectomy will become the preferred surgical therapy for gallstone disease. Thus, nonsurgical treatments of gallstone disease should be compared to the new standard: laparoscopic cholecystectomy [48]. Further investigations are needed to establish the definite position for the different nonsurgical treatment modalities [51,52].

Nevertheless, nonsurgical gallstone therapy has fundamentally changed the role of radiology in the management of gallstone disease, both diagnostically and interventionally. Aspects of this new role are described in this thesis.

1.2 Diagnostic Imaging of Patients with Gallstone Disease

Before the advent of nonsurgical treatment of gallstones, most patients with symptomatic gallstones were treated surgically by cholecystectomy. This procedure was indicated when gallstones were established either by ultrasonography or by oral cholecystography. Information concerning the nature of the stones, their size and number was not really necessary. Today, when nonsurgical treatment is considered, this specific information is mandatory. Moreover, diagnostic imaging plays a role during ESWL treatment and after nonsurgical treatment, to assess the efficacy and safety of the procedure.

1.2.1 Diagnostic imaging before nonsurgical therapy

In patients with gallstones, the selection of those suitable for treatment with nonsurgical therapy is crucial to obtain favorable results. Diagnostic imaging plays an important role in the selection of treatment for patients with symptomatic gallstone disease. It is necessary to be informed about the number, size and chemical composition of the gallstones as well as about the functional state of the gallbladder itself [53].

Table 1.1 gives an outline of the selection criteria for the currently available treatments of gallstone disease and indicates the possible radiologic examinations to assess these criteria.

The aim of this part of the thesis was to design an imaging strategy for patients with symptomatic gallstone disease. A comparative study of the various radiologic examinations that may be used to assess the selection criteria are presented in chapters 2, 3 and 4.

1.2.2 Diagnostic imaging during ESWL

The first generation of lithotriptors was specifically designed to treat kidney stones. Because kidney stones are usually radiopaque, targeting of the stones was done under fluoroscopic control. The current multipurpose machines are equipped with both fluoroscopy and ultrasound (US) for targeting.

In lithotripsy of gallbladder stones only US is used for targeting. Precise targeting is very important and is considered the most difficult element in lithotripsy of gallbladder stones [52,54-56]. It includes initial localization of the stone(s), choice of a safe and effective shockwave path, constant monitoring of the stone(s) and frequent retargeting [56,57,58]. Ultrasonography during ESWL can be hampered by shockwave related artifacts, such as cavitation bubbles which can mimic fragmentation of stones [59,60]. Effective fragmentation of gallbladder stones by ESWL is therefore highly dependent on the US experience and knowledge of cross-sectional anatomy of the treating physician [51].

Table 1.1 Treatments of symptomatic gallbladder stones: selection criteria and radiologic assessment

Selection criteria	Oral bile acids	ESWL	Contact dissolution MTBE
gallstones present/absent	present	present	present
stone size	< 10 mm	5 - 30 mm	unlimited
number of stones	small number	1 - 3	unlimited
stone composition cholesterol/pigment	cholesterol	cholesterol	cholesterol
stone calcification	no	small rim accepted	no
patent cystic duct	yes	yes	yes
concentration capability of the gallbladder	yes	yes	indifferent
contractility of the gallbladder	not mandatory	not mandatory	not mandatory
anatomy of the gallbladder	indifferent	safe shock-wave path	safe access route

US = ultrasonography
OCG = oral cholecystography
CT = computed tomography

Percutaneous stone removal	Laparoscopic cholecystectomy	Open cholecystectomy	radiological examination
present	present	present	US, (OCG)
unlimited	< 4 cm	unlimited	OCG, US
unlimited	unlimited	unlimited	OCG, US
indifferent	indifferent	indifferent	plain abdominal film, OCG, CT
indifferent	indifferent	indifferent	plain abdominal film, OCG, CT
yes	indifferent	indifferent	OCG, cholescintigraphy,US
indifferent	indifferent	indifferent	OCG
indifferent	indifferent	indifferent	US, cholescintigraphy, (OCG)
safe access route	no adhesions no variants	indifferent	US, CT

1.2.3 Diagnostic imaging after nonsurgical therapy

All nonsurgical treatments of gallstone disease have the preservation of the gallbladder in common. Follow-up of patients treated in this way is necessary. Firstly, to assess the efficacy of the specific therapy, which can be determined by the rate of fragmentation or the rate the stones are cleared from the gallbladder, and later, to detect possible recurrence of stones. Secondly, to assess complications of the treatment, which could be related to the treatment itself (e.g. energy trauma in case of ESWL) or to the migration of stone fragments from the gallbladder to the duodenum. Ultrasonography is considered the diagnostic modality of choice in the follow-up of patients after treatment.

Evaluation of US findings in the follow-up of patients treated with ESWL, with focus on its reliability in the assessment of efficacy, is discussed in chapter 6.

1.3 Interventional Radiology in Patients with Gallstone Disease

Radiological interventional techniques play a major role in nonsurgical therapy of gallbladder stones. A short review of radiological interventional techniques for cholecystostomy is presented in chapter 7 and several techniques for percutaneous fragmentation and removal or direct contact dissolution of gallstones are described.

A major drawback of nonsurgical treatments of gallstones, with subsequent preservation of the gallbladder, is the potential for recurrent gallstones [38-42]. These can be prevented by chemical ablation of the gallbladder by percutaneous administration of sclerosing agents [63-65]. Combining percutaneous treatment of stones with subsequent sclerotherapy of the gallbladder can offer a possible alternative for surgical treatment of gallstone disease.

Chapter 8 describes a one-step procedure, in which stone treatment and sclerotherapy of the gallbladder can be combined.

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CHAPTER 2

THE VALUE OF ULTRASOUND IN PREDICTING NON-VISUALIZATION OF THE GALLBLADDER ON OCG: Implications for Imaging Strategies in Patient Selection for Nonsurgical Therapy of Gallstones

2.1 Abstract

Gallbladder visualization on Oral Cholecystography (OCG) is required for most nonsurgical therapies of gallstones. In this study we attempted to establish sonographic criteria which will predict non-visualization of the gallbladder on OCG. For this purpose we compared the results of ultrasound (US) and OCG in 171 patients with gallstones, being assessed for nonsurgical therapy. Sonographic criteria for non-visualization were a contracted gallbladder and stone impaction in the gallbladder neck or cystic duct. In detecting findings which predict non visualization on OCG, US had a sensitivity of 78.3% and a specificity of 97.6%. The predictive values were: positive findings 92.3% and negative findings 92.4%. The overall accuracy was 92.4%

We conclude that US can be used as a first step in selecting patients for nonsurgical therapy and if US indicates a contracted gallbladder, 11% of the patients can be excluded from further diagnostic imaging.

2.2 Introduction

During the past 10 years, patients suspected of having gallstone disease have been predominantly evaluated by Ultrasound (US), which has become the most reliable method for detecting gallstones and has bypassed the use of oral cholecystography (OCG) [1]. With the concept of nonsurgical treatment, such as extracorporeal shockwave lithotripsy (ESWL), oral dissolution and local dissolution of stones, the role of diagnostic imaging modalities has become more demanding in selecting symptomatic patients [2]. Additional information about number, size and chemical composition of gallstones is needed.

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Moreover, visualization of the gallbladder on OCG is required because this ensures cystic duct patency and concentration capability of the gallbladder. This last issue is mostly responsible for a revival of oral cholecystography (OCG).

In this study we attempted to establish sonographic criteria which will predict non-visualization of the gallbladder on OCG. For this purpose we compared OCG and US findings in the assessment of patients with symptomatic gallstone disease for nonsurgical therapy in a blinded prospective way.

2.3 Materials and Methods

From April 1988 to June 1989, 171 consecutive patients (36 male, 135 female, mean age 51, ± 15 SD; range 22-85) with symptomatic gallstones underwent US and OCG as part of their selection for nonsurgical treatment of gallstones. Ultrasound and OCG were performed in the fasting state on the same day by different radiologists. The data were recorded on standardized forms by the performing radiologists, without knowledge of the results of previous examinations. OCG was performed after oral intake of 4g iocetamic acid (Cholebrine®, Dagra Pharma, Diemen, The Netherlands), the evening before the examination. The radiologist had to assess the gallbladder visualization and categorize it as absent or present.

Toshiba, Aloka or Philips real time US equipment were used for sonography with 3.5 MHz or 5 MHz curved array and sector transducers. Sections of the gallbladder were obtained in different planes and in supine, left posterior oblique and erect positions of the patient.

Within the scope of this study the following US findings were recorded:

1 The size and the shape of the gallbladder, i.e. normal, contracted or hydropic. A gallbladder was considered contracted when the gallbladder lumen only contained calculi without normal surrounding bile. Hydrops was assumed when the transverse diameter of the gallbladder measured more than 4.5cm [3].

2 The stones could be located in the cystic duct, the gallbladder neck, in the body or in the fundus. Impaction could be present or absent. Impaction was considered present when stones did not move with change in patient position, especially in the erect position.

3 Additional findings such as:
(I) Generally thickened gallbladder wall (> 3mm). Possible features were also recorded in order to explain the thickening of the gallbladder wall, such as chronic cholecystitis, adenomyomatosis, cholesterolosis or additional pathology associated with the thickened gallbladder wall [4]. In the case of contracted gallbladders no thickness was measured.
(II) Sludge (a layer of low echoes within the gallbladder, changing its position very slowly with gravity [5].
Non-visualization of the gallbladder on OCG was predicted by the following US findings:(1) A contracted gallbladder (Fig.1), (2) Impacted gallstone(s) in the cystic duct or the gallbladder neck (Fig.2).

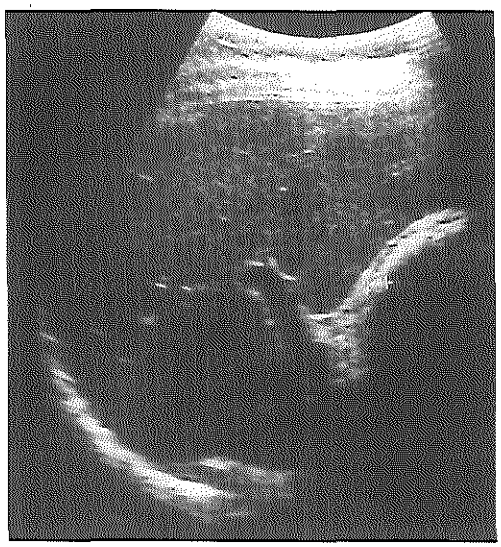

Figure 2.1 Typical example of WES triad (wall, echo,shadow) which is the most specific sign of a contracted stone-filled gallbladder [1].

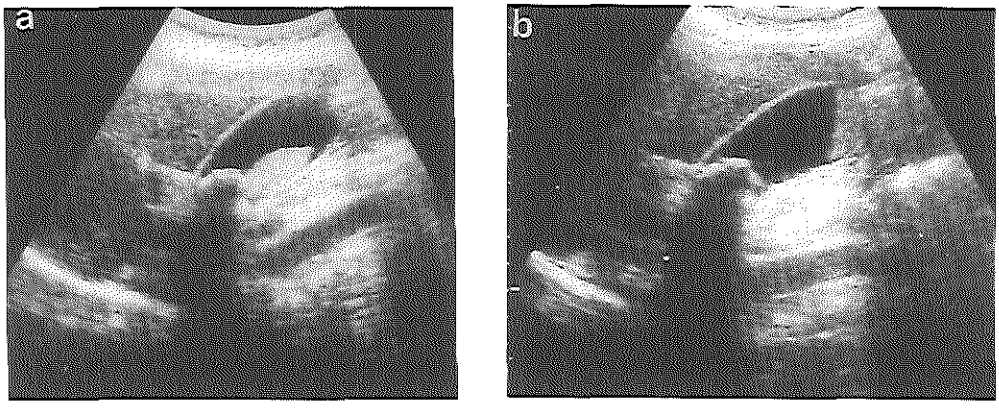

Figure 2.2 (a) Gallstone in gallbladder neck and sludge ball. (b) Same patient in erect position: the gallstone is impacted in the gallbladder neck and the sludge is lying on the bottom of the gallbladder.

Table 2.1 US findings compared with gallbladder visualization on OCG

US findings	Gallbladder visualization on OCG	Number of patients	additional US findings
Contracted gallbladder *	Absent	19	Sludge (n=2)
	Present	-	-
Stone impaction *	Absent	19	Sludge (n=5) Hydrops (n=2) General thickened gallbladderwall (n=1)
	Present	3	-
Negative findings	Absent	10	-
	Present	122	Sludge (n=3) Adenomyomatosis (n=1)
		173 *	

* Two patients had both contracted gallbladder and stone impaction (173 findings in 171 patients).

2.4 Results

The US and OCG findings are recorded in Table 1. In three cases impacted stones were observed sonographically, but these stones probably did not obstruct the duct completely, allowing the gallbladder to be visualized on OCG. In 10 other cases, although no specific sonographic findings were noted, the gallbladder was not visualized on OCG. One of these patients was diagnosed on US as having a polyp (diameter 5mm) in the gallbladder neck (lying on dependent wall with no acoustic shadow and no movement with changing the patient's position). However, computed tomography showed a dense calculus in the gallbladder neck (the diagnosis was confirmed by cholecystectomy). Within the group of patients with stone impaction and non-visualization on OCG (N=19), eight had additional US findings, such as sludge (N=5), hydrops (N=2) and one patient a generalized thickened gallbladder wall. Sludge was also found in two patients with contracted gallbladders and in three patients with visualization of the gallbladder and no other US findings. One patient had a generally thickened gallbladder wall on US, which was suspected as due to adenomyomatosis. This diagnosis was supported by OCG findings.

Table 2.2 Comparison of ultrasound with oral cholecystography

	Ultrasound positive findings	Ultrasound negative findings	Total
OCG visualization absent	36 (True positive)	10 (False negative)	46
OCG visualization present	3 (False positive)	122 (True negative)	125
Total	39	132	171

Table 2 shows the comparison of US with OCG. In detecting findings which will predict non visualization on OCG, US had a sensitivity of 78.3% and a specificity of 97.6%. The predictive values were: positive findings 92.3% and negative findings 92.4%. The overall accuracy was 92.4%.

2.5 Discussion

Non-visualization of the gallbladder on OCG is an exclusion criterion for extracorporeal shockwave lithotripsy (ESWL) and oral dissolution of gallstones. Only in the case of local contact dissolution therapy gallbladder visualization is not mandatory [6]. This study shows that ultrasound (US) can provide important information about this selection criterion.

We realize that non-visualization of the gallbladder on OCG is a troublesome finding since many non-biliary causes may be responsible [7]. Due to logistical reasons we were not able to provide repeat doses in cases of non-visualization. However, in most of the patients in whom a repeat dose resulted in normal visualization, the initial dose had given a faint visualization of the gallbladder [8]. Therefore, we categorized patients with faint visualization as visualization being present.

In our material 26.8% of the gallbladders with gallstones were not visualized on OCG. This is in accordance with the literature [9] suggesting that our data concerning OCG are reliable.

We did not use a fatty meal, either with OCG or with US because the response of the gallbladder to a fatty meal is too variable to permit valid conclusions regarding the ability of the gallbladder to empty normally [10]. Nevertheless Bellamy et al [11] reported a positive correlation between gallbladder visualization on OCG and contraction of the gallbladder on US after a fatty meal.

All gallbladders that appeared contracted on US were not visualized on OCG. From the 22 patients in whom an impacted stone was diagnosed sonographically, three gallbladders were nevertheless visualized on OCG, probably due to incomplete obstruction of the cystic duct. There were 10 false-negative cases, in which the gallbladder was not visualized on OCG and in which the gallbladder did not show abnormalities (except gallstones) on US.

Based on previous reports [1,4,5], sonographic signs, such as hydrops, thickening of the gallbladder wall and sludge, were considered as non-specific findings. Nevertheless sludge and hydrops respectively were found relatively more in patients with either a contracted gallbladder or stone impaction and non-visualization of the gallbladder on OCG (nine out of 36 patients) than in patients without a contracted gallbladder or stone impaction and present visualisation of the gallbladder on OCG (three out of 122 patients). In our opinion these additional findings increase the positive predictive value of the more specific US findings.

When sonographic findings such as a contracted gallbladder are used as a criterion for chronic cholecystitis (lack of concentration capability) and stone impaction in the gallbladder neck or cystic duct as a criterion for non-patency of the cystic duct, US has a high specificity (97.7%) and a high positive predictive value (92.3%) in predicting non-visualization of the gallbladder on OCG. Moreover, in contrast with OCG, it indicates the cause of non-visualization. This may influence the imaging strategy when patients are being selected for nonsurgical therapy of gallstones.

In the case of a contracted gallbladder no further diagnostic imaging is needed (no false-positive findings) and nonsurgical therapy is not indicated.

In the case of stone impaction the strategy is more complicated. First there are a few patients with partial obstruction of the cystic duct, who have normal gallbladder visualization on OCG (false-positive findings). Moreover, even with complete obstruction and a non-visualized gallbladder on OCG there could be a role for ESWL, since such therapy may re-establish cystic duct patency. When US findings do not indicate suspicion that a non-visualized gallbladder will exist on OCG, one should proceed with OCG, in order to avoid false-negative results.

We conclude that US, being the first diagnostic modality for detecting gallstones, can also be used as a first step in selecting patients for nonsurgical therapy of gallstones and if US indicates a contracted gallbladder, 11% of the patients can be excluded from further diagnostic imaging.

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CHAPTER 3

ACCURACY OF ULTRASOUND AND ORAL CHOLECYSTOGRAPHY IN ASSESSING THE NUMBER AND SIZE OF GALLSTONES: Implications for nonsurgical therapy

3.1 Abstract

Prior to nonsurgical therapy of gallstones it is important to assess the number and size of gallstones. In order to evaluate the accuracy of ultrasound (US) and oral cholecystography (OCG) to count and measure gallstones a prospective blind study was conducted to compare the results of US (N = 99) and OCG (N = 36), either alone or in combination (N = 34), with the number and size of gallstones retrieved after cholecystectomy. The number of gallstones was accurately estimated by US and OCG in 74% and 69% of the cases, respectively. In assessing the presence of up to 3, 5 or 10 gallstones both US and OCG proved reliable. In measuring the size of gallstones, there was 19% accuracy with US compared to only 3% with OCG. With an accepted measurement error of 3 mm these values increased to 80% for US and 44% for OCG.

US proved more reliable than OCG in discriminating gallstones smaller or larger than 10 mm and smaller or larger than 20 mm, but with US detection of gallstones larger than 30 mm was problematic. With both US and OCG there was underestimation of gallstone size. The combination of both techniques did not significantly improve the assessment of either number or size of gallstones compared to the results obtained with US or OCG alone. It is concluded that 1) both US and OCG have some limitations in assessing the number and size of gallstones, 2) the combination of both examinations does not improve the results, 3) patient selection for nonsurgical therapy of gallstones can be started with US alone.

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3.2 Introduction

With the introduction of nonsurgical therapy of gallstones, the demands for diagnostic imaging of gallstone disease have changed. It is no longer sufficient to establish only the presence of gallstones. In order to select the proper nonsurgical treatment, information is also needed about the number, size and chemical composition of gallstones and about the functional status of the gallbladder [1].

The primary imaging modalities for gallstone disease are ultrasound (US) [2] and oral cholecystography (OCG) [3,4]. US has certain limitations in assessing the number and size of gallstones [1,5-8], whereas OCG is reported to be more appropriate in this respect [4]. The aim of this investigation was to evaluate the accuracy of US and OCG, in combination or alone, in assessing the number and size of gallstones. For this purpose we compared, in a prospective blind study, the results of US and OCG with the number and size of gallstones retrieved after cholecystectomy.

3.3 Materials and Methods

From April 1988 till May 1990, 99 patients (22 male, 77 female, mean age 52 years, range 20-83) with symptomatic gallstone disease underwent ultrasound (US) and oral cholecystography (OCG) as part of their diagnostic workup for selection for nonsurgical treatment of gallstones. The patients underwent cholecystectomy either because they were randomized to operation in our on-going trial lithotripsy vs cholecystectomy [9] or because they did not meet the criteria for lithotripsy [9]. US and OCG were performed in the fasting state on the same day by different radiologists and data were recorded on standardized forms, without knowledge of the results of the other examination. Ultrasonography was performed with real-time equipment (Toshiba, Aloka) with 3.5 MHz or 5.0 Mhz curved array and sector transducers. Sections of the gallbladder were obtained in different planes with patients in supine, left posterior oblique and erect positions. OCG was performed after oral intake of 4 g iocetamic acid (Cholebrine®, Dagra Pharma B.V., Diemen, The Netherlands) the evening before the examination. OCG examinations included supine, prone oblique and erect spot films of the gallbladder, made during fluoroscopy on a bucky table. Only examinations with diagnostically sufficient opacification of the gallbladder (N = 36) were included. When both US and OCG examinations were available for the same patient (N = 34), the largest diameter and largest number of gallstones recorded, were considered as the outcome of the combined examinations. After cholecystectomy, the gallbladder content was collected for analysis.

Only stones with a diameter of ≥ 3 mm were counted. The numbers of gallstones were categorized as 1, 2, 3, 4, 5, 6-10 or more than 10 stones. Only the largest gallstone was measured. In case of non-spherical stones the largest diameter was recorded. Measurements of stone size by OCG was corrected for an empirically determined magnification factor of 1.3.

Data analysis

The percentage correct was defined as 100 times the proportion of US or OCG which agreed with the post-operative results, divided by the total number of examinations. This proportion is referred to as the positive predictive value. Percentages correct were compared using a standard test to compare two proportions assuming a binomial distribution [10]. Receiver-operating characteristic (ROC) graphs [11] were used to compare the efficacy of US and OCG to predict gallstone sizes at various cutoff points.

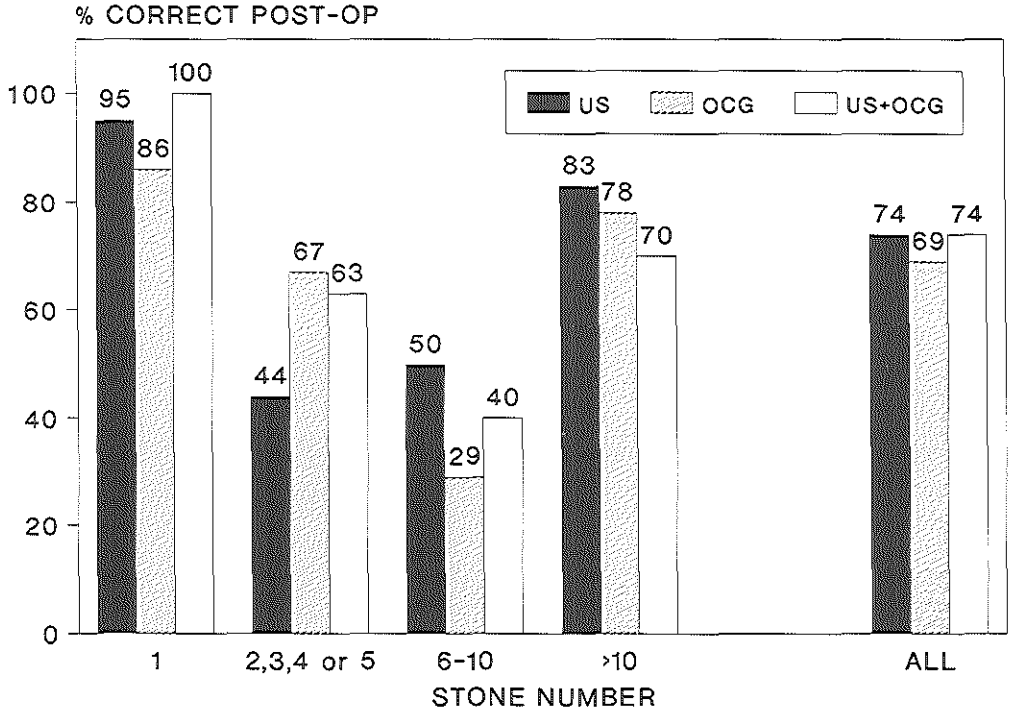

Figure 3.1 Percentages of correctly assessed numbers of gallstones on US (N=99), OCG (N=36) and combined US and OCG (N=34).

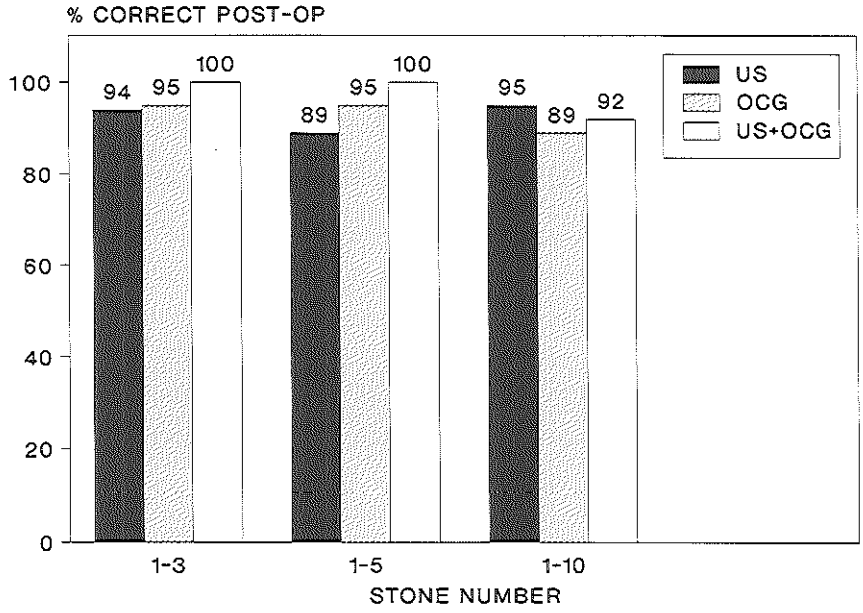

Figure 3.2 Percentages of correctly assessed presence of up to 3, 5 or 10 gallstones on US (N=99), OCG (N=36) and combined US and OCG (N=34).

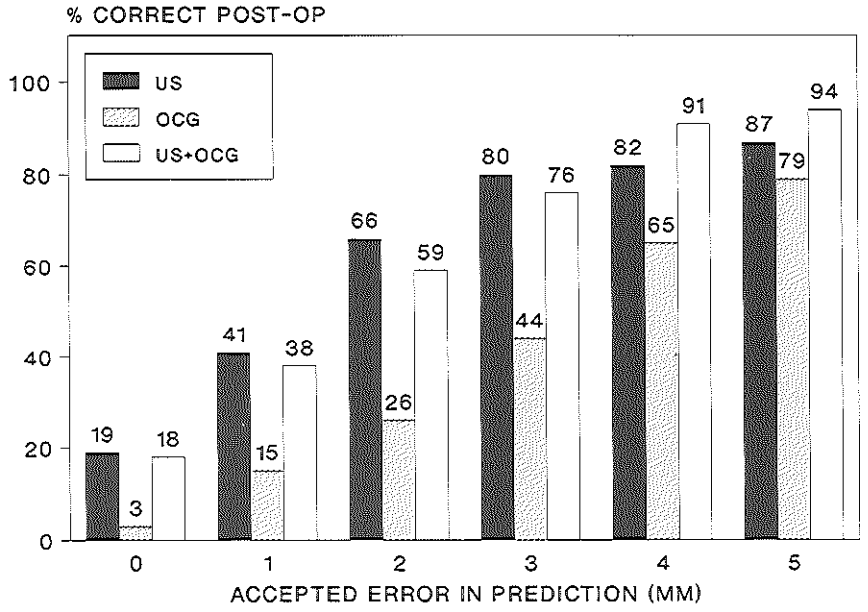

Figure 3.3 Percentages of correctly measured gallstone diameter on US (N=95), OCG (N=34) and combined US and OCG (N=34)

3.4 Results

The results are presented in Figures 3.1 to 3.5. Figure 3.1 shows the correctly assessed numbers of gallstones on US, OCG and the results of the combined techniques based on the examination revealing the largest number of stones. The number of gallstones was accurately estimated by US and OCG in 74% and 69% of the cases, respectively. In assessing the presence of 2, 3, 4 or 5 gallstones OCG was slightly, but not significantly, more accurate than US: 67% and 44%, respectively. The results did not improve significantly when US and OCG were used in combination.

In assessing the presence of up to 3, 5 or 10 stones the results obtained with US and OCG were similar. Again, combined US and OCG did not significantly improve the results (Figure 3.2).

Figure 3.3 shows accuracy of US and OCG in measuring gallstone diameter and the results of the combined techniques for which the largest measured diameter was used in the analysis. There was 19% accuracy with US compared to only 3% with OCG; with an accepted measurement error of 3 mm the percentage correct increased to 80% for US and 44% for OCG; with an accepted error of 5 mm the percentage increased to 87% for US and 79% for OCG. For up to 4 mm measurement error these results are significantly better for US compared to OCG ($p < 0.05$). The combination of US and OCG did not improve these results compared to either examination performed alone.

The results of the diameter measurements on US were independent of number of stones. Percentages correct of the predicted measurements on US were not significantly different when the gallstone population was divided into single vs multiple stones, up to 3 vs more than 3 stones, or up to 5 vs more than 5 stones. The stone population was also divided into stones up to 15 mm in diameter ($N = 58$) vs larger than 15 mm ($n = 37$). In assessment of stone diameter US was proved significantly better ($P < 0.05$) with stones up to 15 mm than for larger stones, irrespective of the accepted measurement error.

Figure 3.4 shows ROC graphs for discriminating gallstone size with US (Figure 3.4a) and OCG (Figure 3.4b) at various cut-off points. Since the entire curve for US lies closer to the upper left corner than the curve for OCG, US has more discriminating power than OCG, irrespective of the cut-off points. Nevertheless, US missed 2 out of 3 cases in detecting gallstones larger than 30 mm.

Figure 3.5 shows differences in postoperative measurements of gallstone diameter compared with US (Figure 3.5a) and OCG (Figure 3.5b). Both US and OCG underestimate gallstone size.

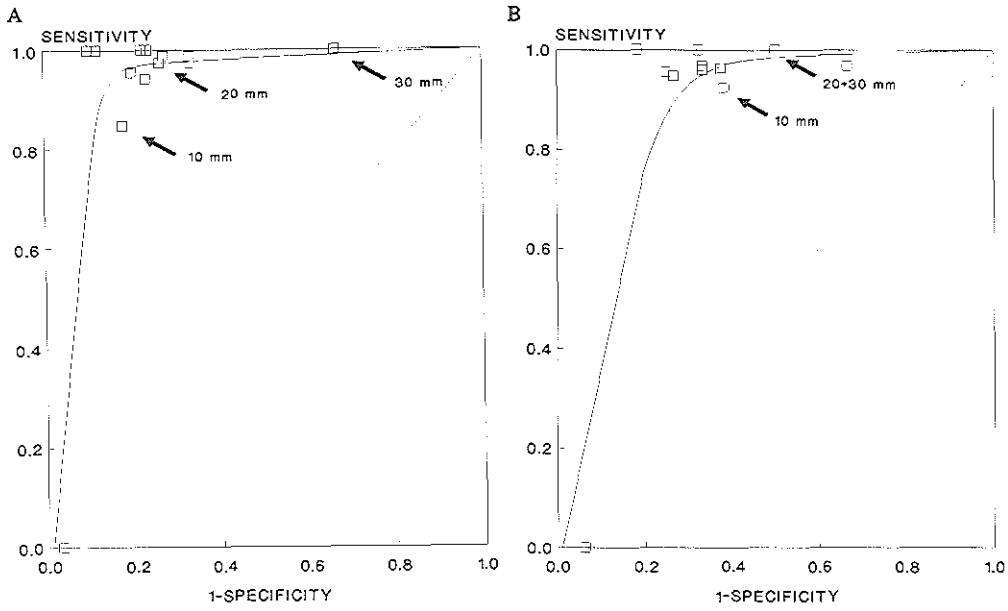

Figure 3.4 ROC graphs for discriminating gallstone diameter (a) with US (N=95) and (b) with OCG (N=34).

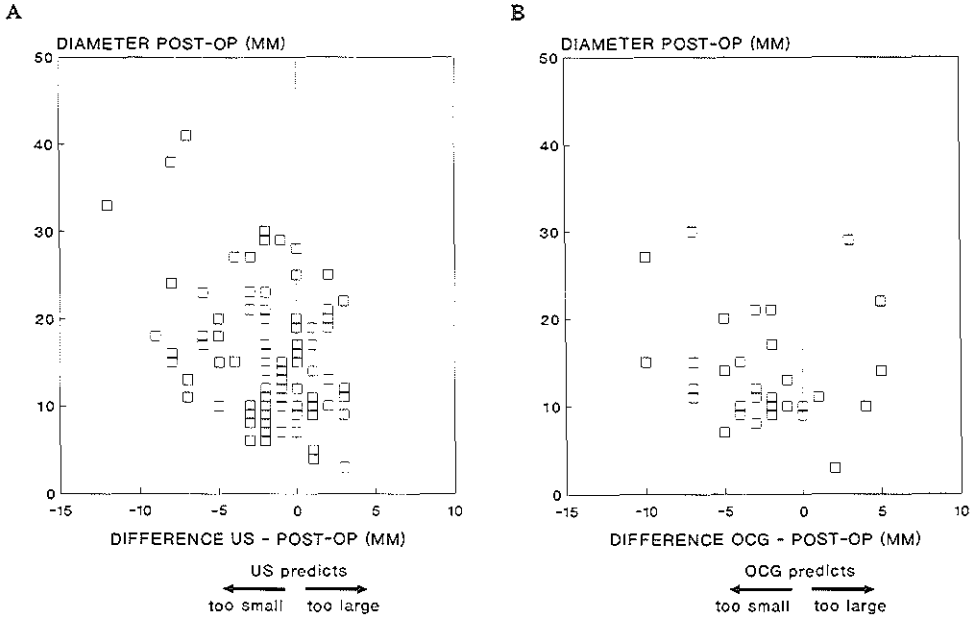

Figure 3.5 Postoperative measurement of gallstones compared (a) with US and (b) with OCG.

3.5 Discussion

This study compared the accuracy of US and OCG to assess the number and size of gallstones. To our knowledge this has not been described previously. The results show some limitations for both US and OCG, either alone or in combination.

With US there were problems in assessing the precise number of stones in the presence of 2 - 10 stones, which confirms the suggestion by other investigators [1] that US appears to be less accurate in counting stones. With OCG the estimation was slightly more accurate with 2 - 5 stones, but the overall results in assessing the number of gallstones were similar to those with US. Simeone and co-workers suggested to perform both US and OCG and to consider the examination revealing the largest number of gallstones to be correct. As the results of this study did not improve using this method, we can not support their conclusion. Selection criteria for biliary lithotripsy vary in the number of stones that can be treated [9,12-14]. Although in this study both US and OCG showed limitations in counting numbers of stones, these techniques can be used as tools to select patients, independent of the number of stones that are accepted for treatment. (Figure 3.2)

In assessing stone size, US becomes more reliable with an accepted measurement error of 3 mm, while OCG reaches a reliable standard only at an accepted error of 5 mm. When taking the largest measured diameter on US or OCG as the correct diameter, the results in this study did not improve, this in contrast to a report by others [1].

In measuring stone size both US and OCG underestimate size and detecting stones larger than 30 mm was problematic with US. This is important, because most protocols for biliary lithotripsy exclude stones larger than 30 mm. Unfortunately this study had no OCG examinations with stones larger than 30 mm, proven postoperatively. US and OCG accuracy to count and measure gallstones will be influenced by patient, technical and observer related factors. For example in obese patients the use of 5 MHz transducers in ultrasonography is limited and can be a cause of less accurate measurements [8]. Obesity will also influence the effect of radiographic magnification on OCG examinations.

In this study the measurements were corrected with a magnification factor of 1.3 for all OCG examinations, independent of the weight of the patient, which could have contributed to the less accurate measurements obtained on OCG. In addition the stone burden and composition of the stones can influence the level of accuracy. With US stones can be hidden in the acoustic shadow of other stones and axial measurements, which are more accurate than transverse measurements, are not always possible. Similarly OCG can miss small and slightly calcified stones or underestimate the size if a calcified rim is missed. The quality of US examination is highly dependent on the expertise of the investigator [7] as is OCG; moreover OCG has not been used during the last decade. All examinations

were made under routine conditions by different radiologists and therefore this study reflects common radiological practise.

Based on the results of this and a previously published study [15], some guidelines are suggested for imaging strategies in patient selection for biliary lithotripsy. In our opinion there are two main options:

1 Patient selection starts with US examination. Patients with a contracted gallbladder (11% in our previously published study) [15] are excluded because this US finding has proven to be highly specific in predicting non-visualization of the gallbladder on OCG- [15]. In case of stone impaction in the gallbladder neck or cystic duct (13% in our previously published study) [15] which also reliably predicts non-visualization on OCG, there could however be a role for lithotripsy, because this therapy could re-establish cystic duct patency. Patients with more than 3 (45% in this study), 5 (34%) or 10 (24%) stones are excluded depending on the chosen protocol for lithotripsy.
The remaining patients (44%, 55% or 65% according to the accepted number of stones) should undergo OCG for the following reasons:
   I To avoid false negative results concerning non-visualization of the gallbladder as predicted with US.
   II To get information about the chemical composition of gallstones, although OCG has limitations for this purpose. Buoyancy is a specific sign for cholesterol stones but unfortunately it is an infrequent finding. Radiolucency c.q. radiopacity is unreliable in distinguish cholesterol stones from pigment stones and computed tomography has proven to be more reliable for predicting gallstone composition [16].

2 The other option is to perform both US and OCG on the same day and consider it as one examination. Although this option has logistical advantages, the results of this study indicate that this will not improve the outcome and, therefore, some patients (44% - 65%) will be unnecessarily subjected to OCG.

It is concluded that 1) both US and OCG have some limitations in assessing the number and size of gallstones, 2) the combination of both examinations does not improve the results, 3) patient selection should start with US which would exclude $\pm$ 50% of the patients for biliary lithotripsy.

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CHAPTER 4

PREDICTING GALLSTONE COMPOSITION WITH CT: In Vivo and in Vitro Analysis

4.1 Abstract

Chemical composition of gallstones is of major importance in selecting patients for nonsurgical therapy. In a combined in vivo and in vitro study of predictive potential, 50 patients undergoing cholecystectomy were evaluated with computed tomography (CT) and either plain abdominal radiography or oral cholecystography (OCG). The largest stone surgically removed from each patient was subjected to in vitro CT and chemical analysis. The authors found an inverse relationship between CT attenuation numbers and cholesterol content and a good positive correlation between CT attenuation numbers and calcium content. In vivo CT analysis improved sensitivity, specificity, accuracy, and positive and negative predictive values compared to plain abdominal radiography and OCG in detection of cholesterol stones. Using their prediction rule (a CT number smaller than 140 HU indicates a pure cholesterol gallstone), the authors correctly classified gallstones in 17 (84%) of another 20 patients. In vivo CT analysis can enable reliable prediction of gallstone composition and should play an important role in the selection of patients for nonsurgical treatment.

4.2 Introduction

The success of nonsurgical treatment of gallstones is highly dependent on patient selection. One of the major selection criteria is the chemical composition of the stones. With the advent of oral and local contact dissolution agents, accurate estimates must be made regarding cholesterol and calcium content of the stones, because the best results are to be expected in stones with high cholesterol and low calcium content. Until now, the single radiographic criterion for assessment of cholesterol stones has been radiolucency. However, the predictive value of this feature is low [1].

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Therefore, investigators have been searching for radiographic features that can enable prediction of the composition of gallstones more precisely [2-9]. Ultrasonography seems to be of little value [3-4]. In vitro analysis with computed tomography (CT) is promising [6-9] and has encouraged us to perform a combined in vivo and in vitro study to evaluate the validity of in vivo CT analysis in predicting gallstone composition. In this report, results of in vivo and in vitro CT analysis are compared with findings from plain abdominal radiography and oral cholecystography (OCG). The chemical analysis of the gallstone composition served as the standard of reference.

4.3 Patients and Methods

Fifty consecutive unselected patients (37 women and 13 men aged 23-82 years; mean age 52 years, $\pm$ 12, (standard deviation, SD)) including one with congenital spherocytosis, underwent elective cholecystectomy between May 1988 and December 1988. All were evaluated preoperatively with plain abdominal radopgraphy (n = 29) or OCG (n = 21) and CT (n=50). After operation the largest gallstone was maintained in sterile saline solution and analyzed by means of CT. Thereafter chemical analyses were performed.

Patients followed diet instructions the day before all examinations and were in the fasting state, during all exminations.

Plain abdominal radiographs were made with the patient supine; collimated views of the right upper quadrant were obtained at a setting of 65-75 kV. OCG was performed after intake of eight tablets of 500 mg iocetamic acid (Cholebrine®, Mallinckrodt, St. Louis). No scout radiograph was obtained. Fluoroscopic examinations were made with the patients supine and erect to include spot images of the gallbladder. For plain abdominal radiography as well as for OCG, radiopacity was defined as present or absent without regard to location within the stones.

CT scans were obtained with a Tomoscan 350 (Philips Medical Systems, Eindhoven, The Netherlands), at settings of 120 kV and 200 mA and included contiguous sections of 12-mm thickness through the area of the gallbladder and, if stones were detected, contiguous sections of 3-mm thickness through the largest stone. No contrast material was given. In vitro CT examinations included contiguous sections of 3-mm and 1.5-mm thickness, made through a cylindric Plexiglass phantom containing eight chambers filled with physiologic saline solution.

At examination, gallstones were categorized as calcified or noncalcified. Calcified stones were subdivided into three groups: only a calcified rim (type I), only a calcified core (type II) or other (type III). Noncalcified stones were subdivided into two groups:

detectable (type IV) (including soft tissue attenuation, isoattenuating with a soft-tissue-attenuation rim and hypoattenuating) and nondetectable (type V) (isoattenuating with surrounding bile).

For both in vivo and in vitro CT studies, a reference calibration phantom containing water and serial dilutions of dipotassium hydrogen phosphate K_2HPO_4 [10] and a body phantom were used to compensate and/or correct for the different CT variables. For quantitative CT analysis we used a specially developed technical factor set.

Patients were scanned while they lay prone on the calibration phantom, which was in contact with the right upper abdominal wall. The calibration phantom was attached in vitro to the cylindric Plexiglass phantom. To enable comparison of our results with results from other CT systems, our CT numbers were converted to equivalent values of milligrams of K_2HPO_4 per milliliter, with the method described by Cann and Genant [10].

For CT analysis the following method was used (Fig.4.1). A 3-mm section with the maximum diameter of the largest stone was chosen for the assessment of the CT number. This ensures that, in analysis of stones with a calcified rim or core, a proportional part of the rim or core is included. After magnification of the image by a factor of four we chose a representative region of interest that encompassed the outline of the stone. The effect of volume averaging was minimized by avoiding the margins of the stone. However, for rimmed gallstones this would imply exclusion of the outerpart of the rim. Therefore we encompassed the complete outline of the rimmed stone.

Gallstones undetected at CT examination were considered to have attenuation values similar to those of bile (8 - 33 HU) (in vivo) or saline solution (10 - 15 HU) (in vitro).

CT analysis was carried out by one of the authors (K.B.). To estimate intraobserver variations, five randomly selected stones were analyzed 10 times at different dates. The coefficient of variation was below 5%.

4.3.1 Chemical analysis

Gallstones were washed, dried superficially, and weighted to the nearest 0.1 g. After drying to constant weight (48 hours at 37° C) the stones were weighed again to calculate water content. Gallstones were ground in a mortar, and 40 mg of the resulting powder was transferred to a 15-ml glass tube. Ten milliliters of ethanol was added, and the closed tubes were incubated at 50° C for 10 minutes to complete the dissolution of cholesterol. After standing at room temperature for another 10 minutes, the tubes were centrifuged at 2,000 g for 10 minutes. Then the cholesterol level was determined according to the method of Abell et al [11].

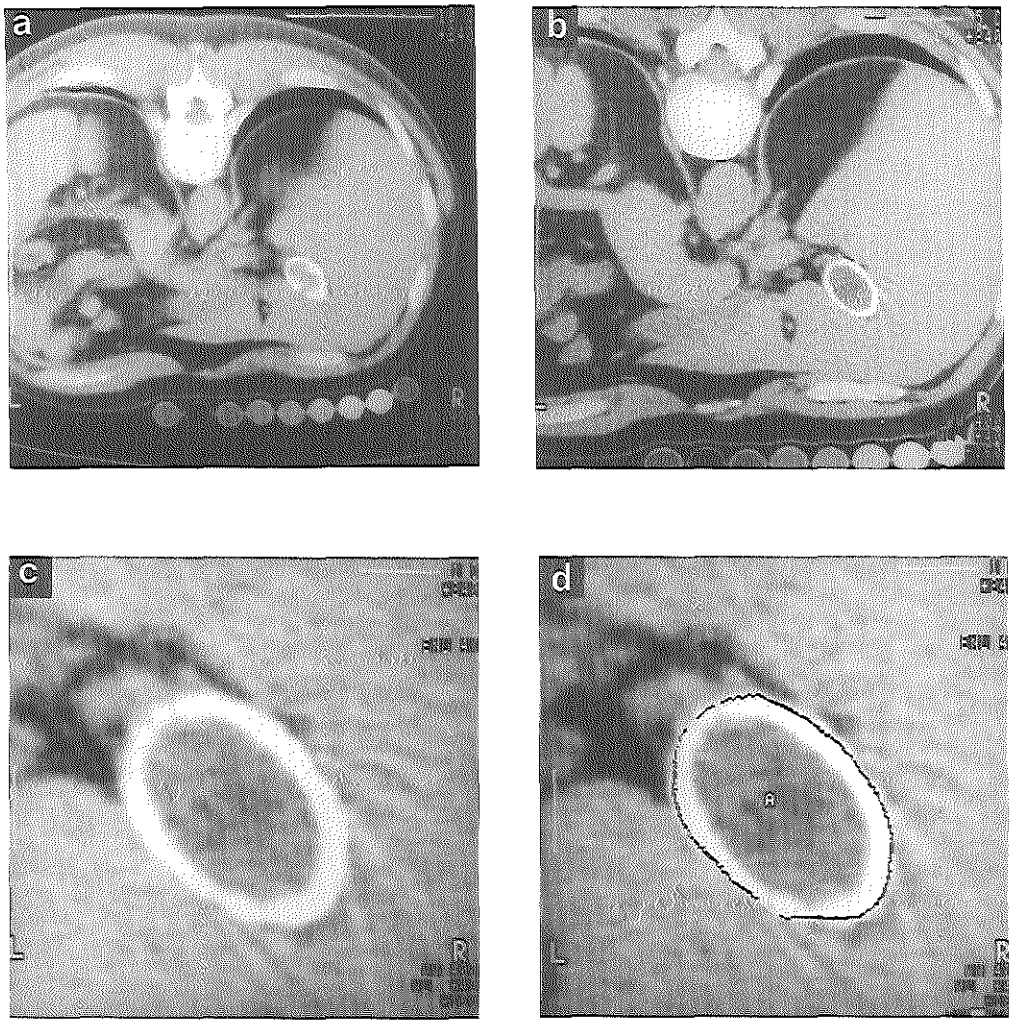

Figure 4.1 CT scans of patien in prone position illustrate our method of analyzing gallstones. Four steps are necessary to assess a CT number:(a) We obtained a 12-mm section through the area of the gallbladder that shows a gallstone. (b) Then we obtained a 3-mm section through the largest diameter of the gallstone. (c) We enlarged b four times. (d) Then we selected the region of interest (A).

Twenty-five milligrams of gallstone powder was transferred to a 50 ml volumetric flask. Five drops of concentrated HCl were added, and after 1 minute, 1 ml of water was added. After 1 more minute the flask was filled to volume with water. After filtration the calcium content was analyzed using an o-cresolphtalein complexion method [12] on an EPOS 5060 instrument (Merck, Eppendorf, Hamburg, Germany).

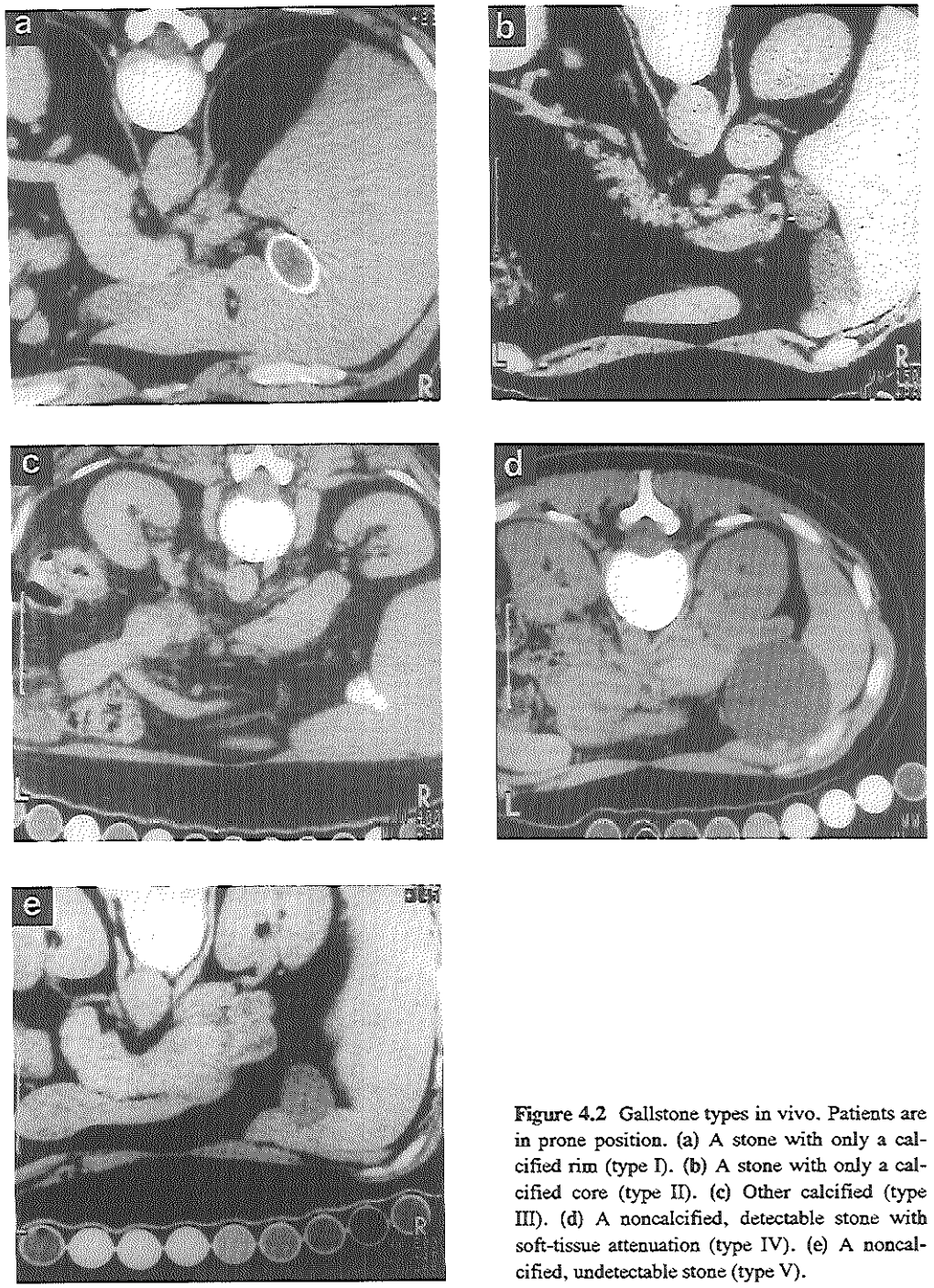

Figure 4.2 Gallstone types in vivo. Patients are in prone position. (a) A stone with only a calcified rim (type I). (b) A stone with only a calcified core (type II). (c) Other calcified (type III). (d) A noncalcified, detectable stone with soft-tissue attenuation (type IV). (e) A noncalcified, undetectable stone (type V).

4.3.2 Data analysis

Relationship between CT numbers and chemical composition were investigated with the Spearman's rank-correlation test. Receiver-operating characteristic graphs [13] were used for comparing tests. We chose this modus of presentation because it illustrates well the compromise one must make between the sensitivity and the specificity of different tests, both being independent of disease prevalence. The best test is the one lying closest to the upper left corner of the plot.

This study was approved in March 1988 by the Medical Ethics Committee of the Erasmus University / University Hospital Dijkzigt, Rotterdam, The Netherlands.

Table 4.1 Chemical analysis of gallstones in 50 patients

Type of gallstone	Number	Percentage of Cholesterol ± SD	percentage of Calcium ± SD
Pure cholesterol (≥80% cholesterol)	37	91.6 ± 5.3 (80-100)	2.0 ± 1.8 (0.0-7.4)
Mixed (≥25%-80% cholesterol)	5	68.0 ± 9.0 (55-78)	8.1 ± 5.8 (0.4-14.0)
Pigment stones (<25% cholesterol)	8	5.0 ± 7.8 (0-18)	16.1 ± 10.2 (0.0-28.5)

Note: Numbers in parentheses indicate range.

4.4 Results

The mean stone diameter was 15mm (range, 3-33). Table 4.1 shows the chemical analysis of the gallstones. We divided the stones into three groups, depending on cholesterol content: pure cholesterol gallstones (≥ 80% dry cholesterol weight), mixed gallstones (≥25% and <80%) and pigment gallstones (< 25%).

Table 4.2 shows the distribution of the different types of gallstone (I-V) in vivo (Fig. 2) and in vitro, with the average CT number for each type. The in vivo distribution closely resembles the in vitro distribution. Twelve stones were not detected in vivo (type V). Four of these were visualized in vitro and classified as type IV (noncalcified, detectable).
The individual CT numbers in vivo and in vitro showed a good correlation ($r = .98$) (Fig.4.3).

Table 4.2 Distribution of gallstone types at CT in vivo and in vitro

Type	Characteristic	No. of Gallstones* (n = 50) In Vitro	No. of Gallstones* (n = 50) In Vivo	Mean CT Numbers◇ (HU) In Vitro	Mean CT Numbers◇ (HU) In Vivo
I	Calcified rim	13 (26)	14 (28)	109 (62-303)	106 (40-309)
II	Calcified core	2 (4)	1 (2)	51 (42-64)	50 (50)
III	Other Calcified	17 (34)	17 (34)	392 (105-1028)	389 (83-1120)
IV	Noncalcified, detectable	10 (20)	6 (12)	56 (53-58)	49 (46-51)
V	Noncalcified, not detectable	8 (16)	12 (24)	12 (10-15)	18 (8-33)

* Numbers in parentheses are percentages.
◇ Numbers in parentheses indicate range.

Figures 4.4 and 4.5 show a good correlation between CT attenuation numbers and cholesterol and calcium content. The in vivo results are similar to the in vitro results. After analysis of these data, we defined a cutoff point for pure cholesterol stones at 140 HU with a range of 135-145 HU (the "safety zone"), so that the specificity and sensitivity were maximized.

No relationship was found between size of gallstones and ability to predict their compoition. The cholesterol content correlation coefficient of all stones (n = 50) was 0.80, and for stones 10 mm or larger(n = 37) it was 0.78. The calcium content correlation coefficient for all stones and for stones 10 mm or larger was 0.93.

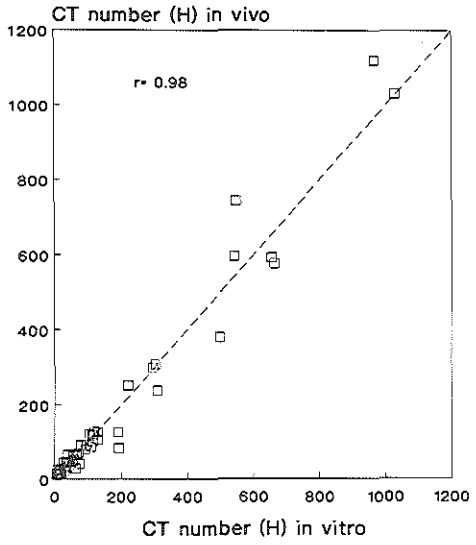

Figure 4.3 Comparison of the individual CT numbers in vivo and in vitro.

Table 4.3 shows the comparison of CT analysis with the classiccriteria of radiolucency and radiopacity. Both in vivo and in vitro CT analysis improved the predictability of gallstone composition in comparison with plain abdominal radiography or OCG. Most striking is the improvement in the negative predictive value: from 50% for plain radiograph or OCG to 83.3% for CT in vivo and even to 100% for CT in vitro.

Table 4.3 Results of radiologic examinations for classification of gallstones

Index	Plain Abdominal Radiography or OCG		CT in Vivo (mean total)		CT in Vitro (mean total)	
	Lucent	Opaque	≤140 HU	>140 HU	≤140 HU	>140 HU
Cholesterol content ≥80%	28	9	35	2	37	0
Cholesterol content <80%	4	9	3	10	3	10
Sensitivity (%)	75.7		94.6		100	
Specificity (%)	69.2		76.9		76.9	
Accuracy (%)	74.0		90.0		94.0	
Positive predictive value (%)	87.5		92.1		92.5	
Negative Predictive value (%)	50		83.3		100	

Because the prediction rule (a CT number smaller than 140 HU indicates a pure cholesterol stone) was determined retrospectively, we tested the usefulness of this rule prospectively in another 20 patients. Seventeen stones (84%) were correctly classified in vivo with this rule.

4.5 Discussion

To our knowledge, in vivo CT analysis of gallstones has not previously been described. Our in vivo results closely resemble in vitro results. This confirms the validity of the in vivo analysis.

Quantitative CT analysis for characterization of gallstones, like all quantitative CT studies, is complicated by CT number instability due to technical and geometrical factors [14]. The use of a reference calibration phantom compensates for the instability of our CT numbers over time. We measured the beam-hardening effect and scatter with a body phantom. The correction was subsequently applied empirically. We standardized the position (level) of the examination table, the reference calibration phantom, and the patients' position (we had them all lie prone), so that variabilities in CT numbers due to

nonuniformity of the scan field were negligible.

Comparison of our cutoff point at 140 HU (range 135-145 HU) to that of other CT systems is possible with conversions to equivalents of milligrams of K_2HPO_4 per milliliter. In this study 135-145 HU was equivalent to 90-100 mg of K_2HPO_4 per milliliter.

Because of the above-mentioned limitations in quantitative CT analysis, it is not possible to compare our cutoff point (140 HU) in differentiating cholesterol stones from mixed and pigment stones with the cutoff point (50 HU) in the study of Hickman et al [8], since no data on these variabilities were given. Nevertheless, the previously reported inverse relation between CT attenuation numbers and cholesterol content [5,9] is confirmed by our in vitro and in vivo study. A discrepancy between the results of Baron et al[9] and ours is the good correlation we found between CT attenuation numbers and calcium content. We found a correlation for calcium as good as for cholesterol, so we could not endorse their conclusions that calcium content plays a smaller role than cholesterol content in CT attenuation of gallstones.

Aware of the difficulties in analysis of rimmed stones, we included these gallstones in our study because they form a clinically important group (28% in our study). Our data show that the attenuation values of such stones correlate with cholesterol and calcium content as well as do values of the unrimmed stones (Figs.4.4 - 4.5).

The CT patterns of our group of gallstones are similar to those in the in vivo study of Barakos et al [15] and the in vitro study of Baron et at al [9]. The percentage of undetectable stones in vivo (24%) is comparable to the percentage (21%) found by Barakos et al [15] and emphasizes the limitations of CT in the detecting of gallstones. Our assumption that these stones have attenuation numbers equal to that of surrounding bile is confirmed by our in vitro study, in which all gallstones had attenuation numbers below 30 HU except one that had a dense core and a CT number of 46 HU. Because the various types of gallstones showed a great range in their CT numbers, it is not sufficient to make a reliable prediction of gallstone composition based on CT patterns.

In comparing the accuracy of different radiographic tests, it is important to realize that for predicting cholesterol stones there is a prior probability of 74%. This percentage is similar to the one in the study by Whiting et al [16] (75%). When there is a high prior probability, the negative predictive value is more important than the positive predictive value. Table 4.3 shows that in this regard CT analysis (negative predictive value in vivo, 83.3%, in vitro, 100%) is superior to plain abdominal radiography or OCG (negative predictive value of 50%).

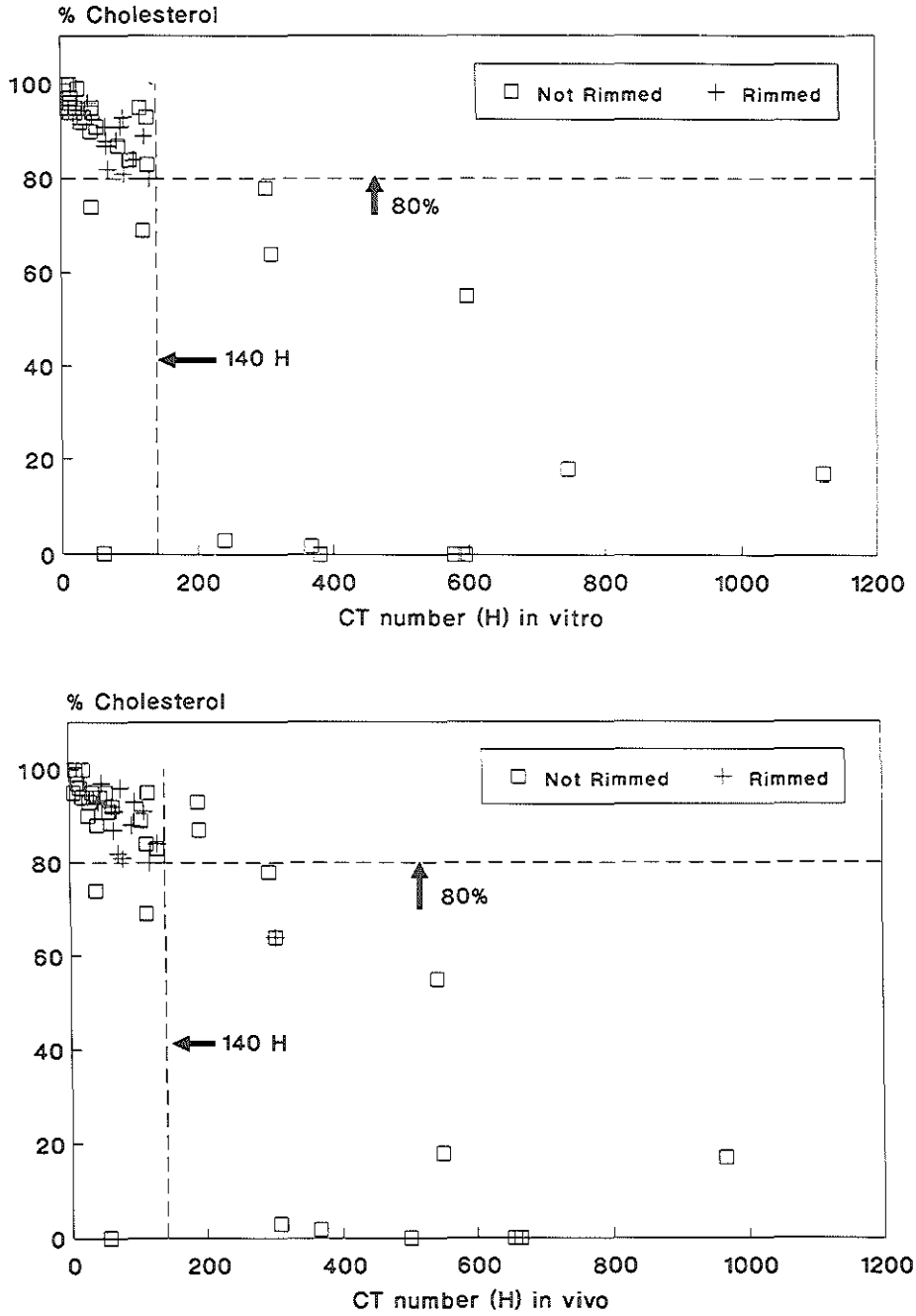

Figure 4.4 Diagrams show correlation between cholesterol content and CT attenuation numbers in vitro (r=-0.83)(top) and in vivo (r=-0.80)(bottom).

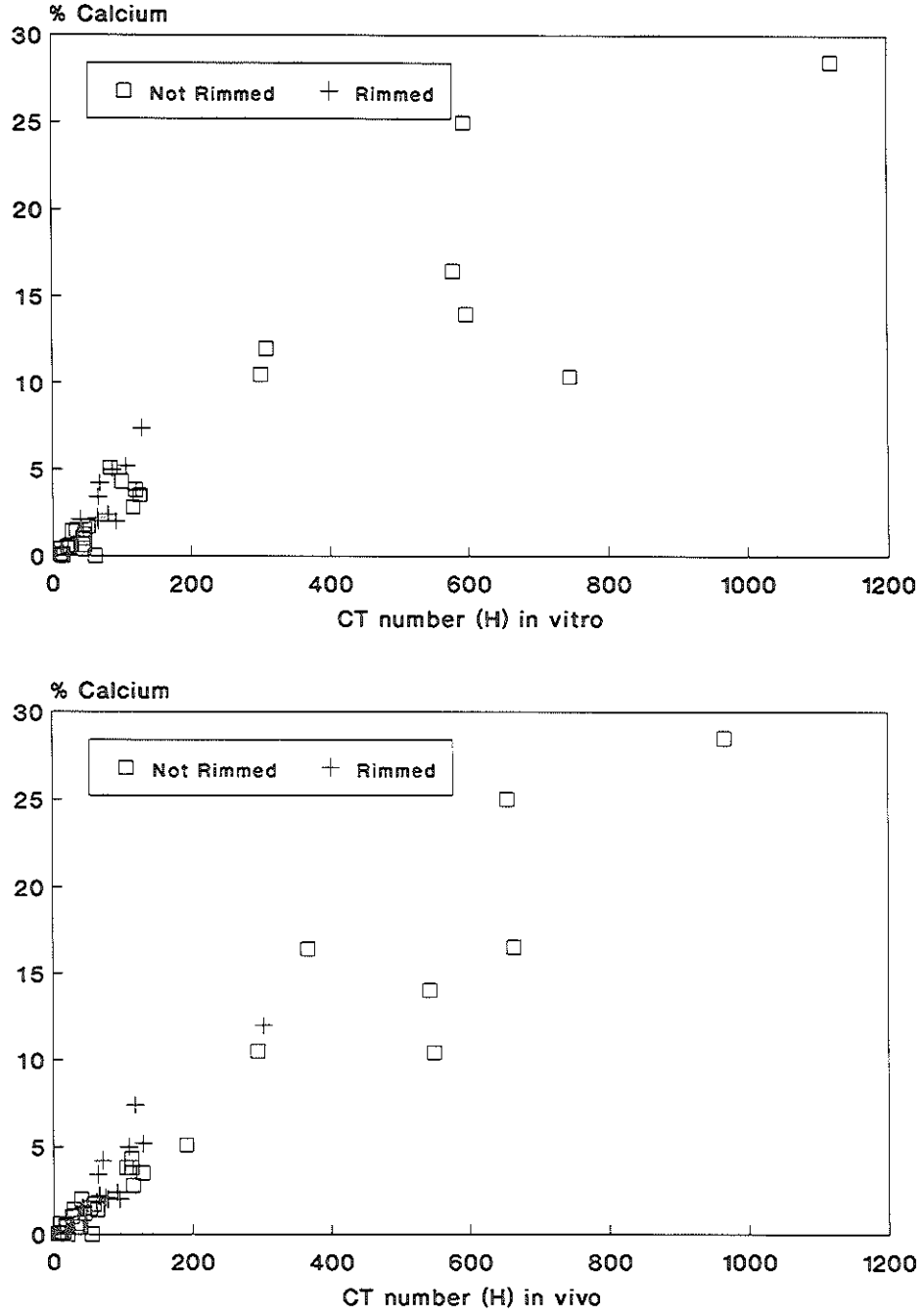

Figure 4.5 Diagrams show correlation between calcium content and CT attenuation numbers in vitro (r=0.91)(top) and in vivo (r=0.93)(bottom).

We also used receiver-operating characteristic graphs [13] to compare our results with those of published data (Fig.4.6). These graphs show that plain abdominal radiography (in this study and studies by Trotman et al [1] and Whiting et al [16]) is far inferior to CT and the discriminant analysis made by Dolging et al [5], because the position of these points is closer to the nondiscriminating diagonal. The comparison of CT analysis in vivo with the analysis by Dolgin et al [5] reveals similar results in sensitivity (both 95%), specificity (Brakel et al 77%, Dolgin et al 82%), accuracy (90 vs 91%), positive predictive value (92 vs 93%) and negative predictive value (83 vs 88%). Nevertheless, there are important differences between the two studies. Dolgin et al [5] based their discriminant analysis on gallstone characteristics seen at OCG. OCG is less expensive than CT and is essential in selecting patients for nonsurgical gallstone therapy because visualization at OCG ensures cystic duct patency [17]. On the other hand, the method of discriminant analysis is unwieldy. Moreover, 15 (27%) of 56 gallstones were considered indeterminate.

One has to take a "safety zone" [14] into account in CT analysis. In our study we based this zone on variations inherent in the CT system and on intraobserver variation. We believe a zone between 135 and 145 HU is safe. None of the 50 stones we analyzed had a CT number in this zone. In our prospective test of 20 patients, one showed findings in this range.

Our data show that in vivo CT analysis can enable prediction of gallstone composition more precisely than plain abdominal radiography or OCG and therefore should play an important role in patient selection for nonsurgical treatment of gallstones.

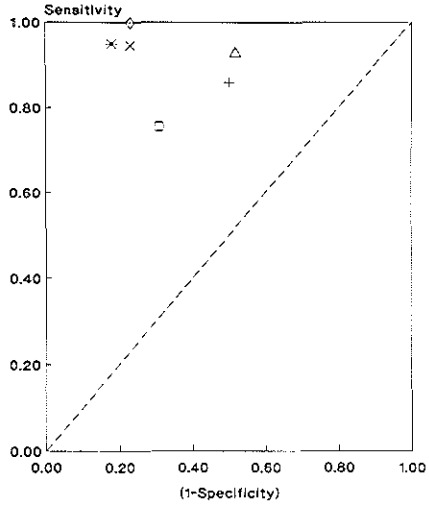

Figure 4.6 Receiver-operating characteristic graph of radiologic examinations for classification of gallstones. □ = plain abdominal radiography in our study, + = plain abdominal radiography in reference 16, △ = plain abdominal radiography in reference 1, ◇ = CT in vitro, x = CT in vivo, * = discriminant analysis with OCG [5].

4.6 References

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CHAPTER 5

ELECTROMAGNETIC SHOCKWAVE LITHOTRIPSY OF GALLSTONES IN VITRO: The role of different stone characteristics and treatment variables

5.1 Abstract

From 40 sets of five human gallstones obtained at cholecystectomy, four stones were subjected to either 125/250 (maximum generator output) or 250/500 (half-maximum generator output) electromagnetic shockwaves; the fifth stone was used for computed tomography (CT) and chemical analysis. Overall, 130 (81%) of 160 stones fragmented, including 72 (45%) adequately (fragments ≤ 5 mm). After application of 250 shockwaves (maximum generator output), the percentages overall and adequate fragmentation amounted to 95% and 70%, respectively. A significantly higher overall fragmentation rate was obtained in pure cholesterol stones ($p<0.01$), in stones with a mean CT density ≤ 110 HU ($p<0.001$), and in stones with a calcified rim ($p<0.05$). The success of fragmentation was significantly associated with stone weight and diameter ($p<0.001$), bilirubin content ($p<0.02$), and calcium content ($p<0.05$). A weight >500 mg and a diameter >10 mm could be defined as stone characteristics being significant negative predictors of adequate fragmentation. High correlations between mean CT attenuation numbers (HU) and cholesterol ($r=-0.87$; $p\leq 0.001$) or calcium ($r=0.92$; $p\leq 0.001$) content were found. Using a cutoff point of 110 HU, pure cholesterol ($\geq 80\%$ cholesterol) and noncholesterol stones could be discriminated by CT with an overall accuracy of 95%.

5.2 Introduction

From 1986 extracorporeal shockwave lithotripsy (ESWL) has been expanding as a nonsurgical treatment for selected patients with gallstone disease [1-3]. Biliary lithotripsy has been performed with electrohydraulic [4-6], electromagnetic [7,8] or piezoelectric [9, 10] lithotriptors. The acoustic energy output of the respective systems, however, can vary considerably [11].

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This depends on the employed techniques of shockwave generation and focusing. It is thus conceivable that the performance of different types of ESWL devices may vary.
In contrast to the electrohydraulic and piezoelectric systems [12-14], gallstone fragmentation and the role of different stone characteristics have not been systematically studied in vitro for electromagnetic systems. The aims of the present study were to evaluate the potential for gallstone lithotripsy of a recently developed electromagnetic shockwave source under various treatment regimens and to assess the significance of different stone characteristics in predicting stone fragmentation in vitro.

5.3 Methods

Stones

Forty sets of five gallstones were obtained from 40 patients who underwent elective cholecystectomy for symptomatic gallbladder stones. By gross observation the stones comprising one set were comparable in morphology and size and were assumed to be of similar chemical composition, because they came from the same patient. The stones were stored at 4°C in phosphate buffered saline (PBS), containing 50 000 IU/l penicillin and 50 000 μg/l streptomycin. One stone from each set was used for examination by computed tomography followed by chemical analysis. The remaining four stones from each set were used for lithotripsy experiments.

Computed Tomography

Computed tomography (CT) was performed with a Somatom CR (Siemens AG, Erlangen, Germany) at settings of 125 kV and 450 mAs. Contiguous sections of 2-mm-thickness were made through a cylindric plexiglas phantom containing eight chambers filled with physiologic saline, in which the stones were immersed individually. For each stone, mean CT attenuation values, expressed in Hounsfield Units (HU), were obtained by the method described by Brakel et al [15].

At CT examination, gallstones were categorized as calcified or noncalcified according to Brakel et al [15]. Calcified stones were subdivided into three groups: calcified rim (type I), calcified core (type II), or other pattern of calcification (type III). Noncalcified stones were subdivided into two groups: detectable (type IV), and nondetectable (type V) (isoattenuating with surrounding fluid).

Chemical Analysis

Gallstones were washed, dried superficially, and weighed to the nearest 0.1 g. After drying to constant weight (48 hours at 37°C), the stones were weighed again to calculate water content. Gallstones were ground in a mortar, and the resulting powder was used for

analysis of cholesterol, calcium, and bilirubin. The methods of determination of cholesterol, calcium, and bilirubin contents have been described elsewhere [15,16].

Shockwave Device

For shockwave lithotripsy of the gallstones the Lithostar Plus (Siemens AG, Erlangen, Germany) was used. This lithotriptor is based on the electromagnetic principle. At maximum generator output setting, the Lithostar Plus generates shockwaves with a maximum positive focal pressure of about 65 MPa in vitro; the focal zone (i.e., the zone within which more than 50% of maximum focal pressure occurs) has a length of 40 mm and a width of 3 mm [17]. The maximum acoustic energy output (total energy delivered into the focal plane by a single shockwave generated at maximum generator power) amounted to 70 mJ in vitro [17].

Lithotripsy Experiments

The shockwave applicator was coupled by means of ultrasound coupling gel to a nonattenuating elastic membrane sealing off a window of a water-filled test basin. After measurement of the maximum diameter and weight, individual stones were placed in a small plastic net (1.5 mm meshes) suspended in the water such that the stone was exactly focused. The four stones of each set used for in vitro lithotripsy were subjected to different numbers of shockwaves, generated at a generator voltage setting of either 20.3 kV (maximum focal shockwave pressure [100%]) or 16.9 kV (half-maximum focal shockwave pressure [50%]):

treatment I : 125 shockwaves, focal pressure 100% (20.3 kV);
treatment II : 250 shockwaves, focal pressure 100% (20.3 kV);
treatment III : 250 shockwaves, focal pressure 50% (16.9 kV);
treatment IV : 500 shockwaves, focal pressure 50% (16.9 kV).

Application of shockwaves was stopped before completing the intended number of shockwaves when the net was completely emptied. If necessary, the net was gently shaken during lithotripsy to allow the fragments to pass through the meshes. Fragments remaining in the net after maximum shockwave application were sieved using a metal sieve with a 2.5 mm grid. All fragments not passing through this grid were collected and their diameters measured. Fragmentation was considered to be adequate when all remaining fragments measured ≤ 5 mm in their largest diameter, and was considered unsatisfactory if fragmentation did not occur, or if at least one particle was larger than 5 mm at the end of the experiment. If all treatment regimens failed to fragment the stones, a total of 1500 shockwaves generated at maximum generator output setting was administered.

Data Analysis

Differences between diameter or weight between stone sets, and differences between chemical composition or CT density versus treatment regimen were analyzed with the Kruskal Wallis (multiple comparison) test. Relations between CT density and chemical composition were examined with Spearman's rank-correlation test. Categorized fragmentation results were compared using the Chi-square test or Mann-Whitney U-test, where appropriate. The determination of the optimal cutoff point for CT density in predicting chemical composition was performed using ROC-analysis [18].

Table 5.1 Chemical and CT analysis of 40 human gallstones

Type of Gallstone	No	Cholesterol[a] (%)	Calcium[b] (%)	Bilirubin[c] (%)	Mean CT density[d] (HU)
All	40	93.2 (0.0-99.9)	0.7 (0.0-32.7)	0.0 (0.0-23.6)	41 (7-584)
Pure cholesterol (≥80%)[e]	30	95.4 (82.3-99.9)	0.2 (0.0- 3.9)	0.0 (0.0- 1.8)	29 (7-111)
Mixed (≥25%-80%)[e]	4	54.7 (38.0-64.9)	14.7 (3.3-19.3)	0.0 (0.0-11.4)	273 (117-516)
Pigment (≥25%)[e]	6	0.0 (0.0-11.4)	2.1 (0.8-32.7)	10.2 (1.2-23.6)	179 (84-584)
Calcified[f]	22	84.1 (0.0-96.4)	1.6 (0.2-32.7)	0.0 (0.0-23.6)	106 (21-584)
Noncalcified[f]	18	96.2 (91.8-99.9)	0.1 (0.0- 1.2)	0.0 (0.0- 0.5)	21 (7- 41)
CT pattern I	8	91.9 (11.4-96.4)	0.8 (0.2-16.0)	0.0 (0.0-23.6)	79 (21-284)
II	4	91.8 (85.8-94.7)	0.8 (0.6- 1.3)	0.0 (0.0- 1.3)	56 (49- 63)
III	10	19.9 (0.0-90.0)	3.0 (0.8-32.7)	4.0 (0.0-22.1)	155 (102-584)
IV	16	96.2 (91.8-99.9)	0.1 (0.0- 1.2)	0.0 (0.0- 0.5)	22 (13- 41)
V	2	97.7 (95.5-99.9)	0.1 (0.0- 0.1)	0.0 (0.0- 0.0)	8 (7- 8)

NOTE: Data are given as median values with ranges in parentheses.

[a,b,d] pure vs mixed, [a-d] pure vs pigment, [c] pure vs pigment: $p < 0.05$.

[a-c] calcified vs noncalcified: $p < 0.05$.

[a,b,d] I vs IV/V, [b] II vs IV, [a,d] II vs V, [a-d] III vs IV/V: $p < 0.05$.

[e] percentage of cholesterol.

[f] on CT scan.

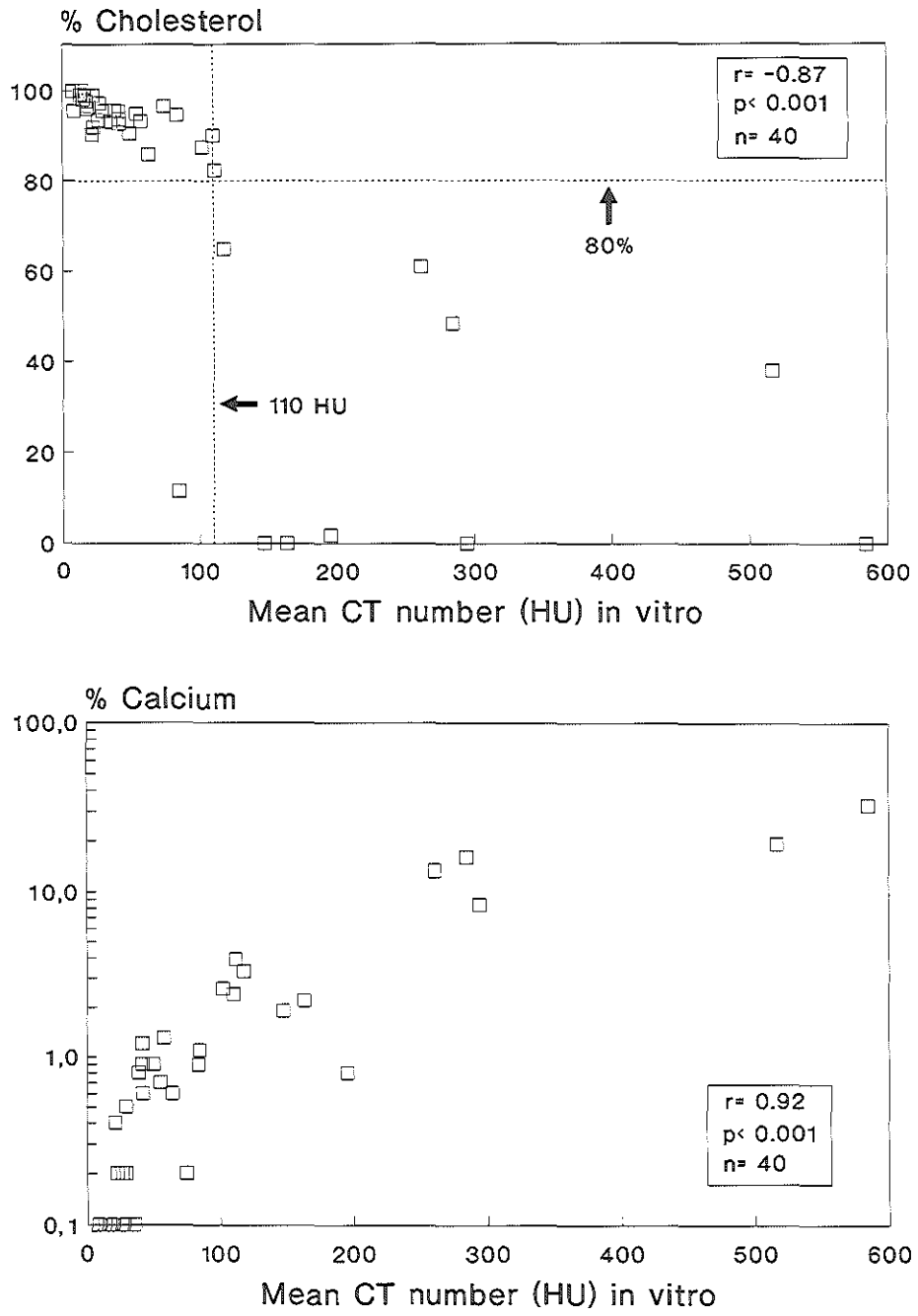

Figure 5.1 Correlation between cholesterol (top) respectively calcium (bottom) content and mean CT attenuation numbers (HU) in vitro of 40 gallstones.

5.4 Results

The median diameter and weight of the 160 stones used for lithotripsy were 8 mm (range: 6-17) and 230 mg (range: 20-1840), respectively. Diameters and weights of the 40 subsets of stones allocated to the different treatment regimens were equal. Taken together, within particular sets of four stones the diameters and weights differed on average 1.0 mm (range: 0-6) and 72 mg (range: 0-870), respectively.

Chemical and CT analysis of single gallstones of the 40 stone sets are given in Table 5.1. The stones were divided into three groups, depending on cholesterol content: pure cholesterol (≥80% dry cholesterol weight), mixed (≥25% and <80%), and pigment stones (<25%). From the 22 stones (55%) which were calcified at CT, 8 stones (20%) were classified as type I, 4 stones (10%) as type II, and 10 stones (25%) as type III. From the 18 stones (45%) categorized as noncalcified, 16 stones (40%) were of type IV and 2 stones (5%) of type V. Stones of type II as well as noncalcified stones (types IV and V) were pure cholesterol stones, but cholesterol stones could also present CT patterns of type I and III. Pigment and mixed stones assorted to type I (n=2) and type III (n=8).

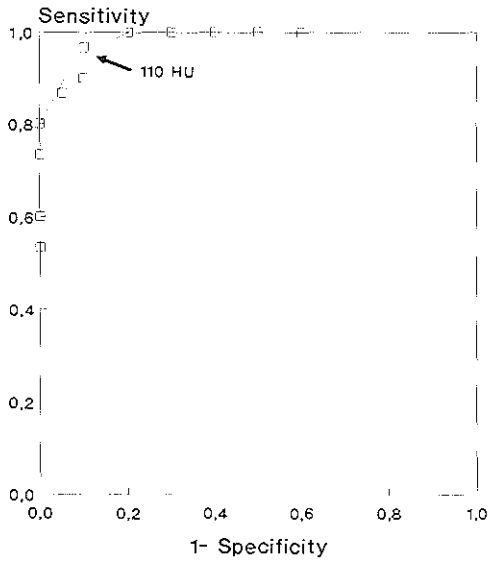

Figure 5.2 Receiver-operating characteristic graph of CT attenuation cutoff numbers for classification of gallstones. Specificity and sensitivity of CT to discriminate in vitro between pure cholesterol (≥80% cholesterol) and noncholesterol stones were maximized using a cutoff point of 110 HU.

Figure 5.1 shows a high correlation between mean CT attenuation numbers and cholesterol ($r=-0.87$; $p\leq 0.001$) and calcium ($r=0.92$; $p\leq 0.001$) content, respectively. The optimum cutoff point for pure cholesterol stones was defined by receiver-operating characteristic (ROC) analysis at 110 HU (Fig. 5.2), because at this value specificity and sensitivity were maximized[18]. Using this cutoff point, CT discriminated between pure cholesterol and noncholesterol (<80% cholesterol) stones with a specificity of 0.90, a sensitivity of 0.97, a positive predictive value of 0.97, a negative predictive value of 0.90, and an overall accuracy of 0.95.

Irrespective of treatment regimen, 130 (81%) of 160 stones fragmented. Adequate fragmentation (all fragments ≤5 mm) was achieved in 72 stones (45%).

Table 5.2 Results of in vitro ESWL of gallstones according to treatment regimen.

Treatment Regimen	No	Fragmentation	Maximum Particle Size at End of Experiment *		
			≤2.5 mm	>2.5 mm and ≤5 mm	>5 mm
I	40	32 (80%)	7 (18%)	8 (20%)	25 (62%)
II	40	38 (95%)	14 (35%)	14 (35%)	12 (30%)
III	40	28 (70%)	3 (8%)	9 (22%)	28 (70%)
IV	40	32 (80%)	11 (27%)	6 (15%)	23 (58%)
Overall	160	130 (81%)	35 (22%)	37 (23%)	88 (55%)

NOTE: Data are given as numbers of stones with percentages in parentheses.
* I vs II, II vs III/IV: $p < 0.05$.

Unsatisfactory results were obtained in 88 calculi (55%), including 30 stones (19%) which did not fragment at all. The results of the various treatment regimens according to different categories of remaining particle size are given in Table 5.2.

Table 5.3 Characteristics of gallstones according to results of in vitro ESWL, irrespective of treatment regimen

Stone Characteristics	Maximum Particle Size at End of Experiment		P Value
	≤5 mm (n=72)	>5 mm (n=88)	
Diameter of implant (mm)	7.7 ± 0.2	9.5 ± 0.3	< 0.001
Weight of implant (mg)	228 ± 25	470 ± 46	< 0.001
Cholesterol (%)	77.6 ± 3.7	75.3 ± 3.9	NS
Bilirubin (%)	0.8 ± 0.4	3.5 ± 0.7	< 0.02
Calcium (%)	5.1 ± 1.1	1.2 ± 0.2	< 0.05
Mean CT density (HU)	128 ± 20	70 ± 8	NS

NOTE: Data are given as mean ± SEM values.

Figure 5.3 depicts the percentage overall as well as adequate and unsatisfactory fragmentation. The highest percentage of (adequate) fragmentation was achieved at a generator voltage setting of 20.3 kV (focal pressure 100%) with 250 shockwaves (treatment II). At this generator voltage, significant better results were obtained after application of 250 (treatment II) *versus* 125 (treatment I) shockwaves ($p<0.05$). At 16.9 kV (focal pressure 50%), doubling the number of shockwaves from 250 (treatment III) to 500 (treatment IV) also improved the results albeit not significantly. Halving of the focal pressure was not fully compensated for by administration of twice as many shockwaves as evidenced by comparing the results of treatment I and IV, for instance; the number of shockwaves must be increased four-fold to achieve comparable results.

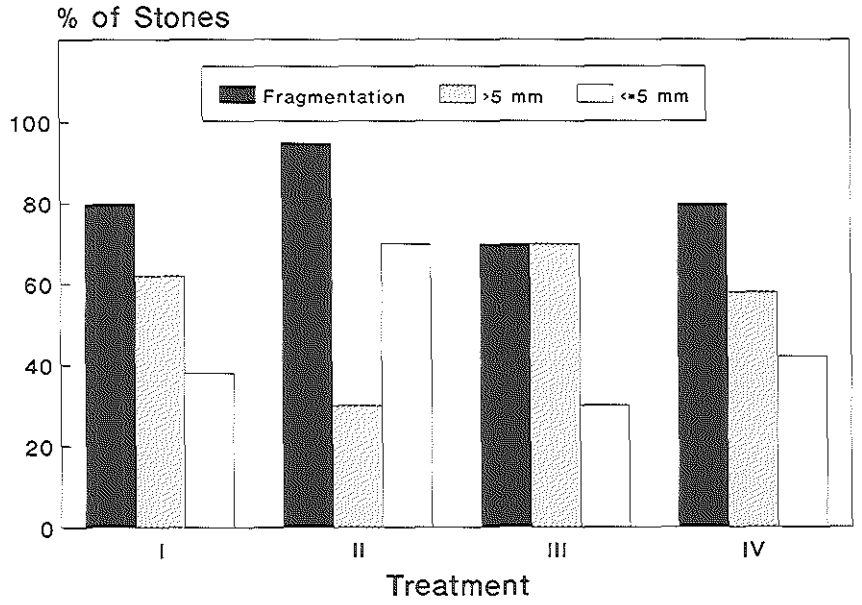

Figure 5.3 Percentage of total, adequate (fragments ≤5 mm), and unsatisfactory (fragments >5 mm) in vitro fragmentation of 40 sets of gallstones for 4 different treatment regimens (I: 125 shockwaves, 100% focal pressure; II: 250 shockwaves, 100% focal pressure; III: 250 shockwaves, 50% focal pressure; IV: 500 shockwaves, 50% focal pressure).

Table 5.3 shows different stone characteristics according to results of fragmentation, irrespective of treatment regimen. Only the stone diameter and weight ($p<0.001$) as well as the bilirubin content ($p<0.02$) and calcium content ($p<0.05$) were significantly associated with adequate fragmentation. Independent of treatment regimen and without

regard to fragmentation outcome, a significantly higher percentage of pure cholesterol stones ($p<0.01$), stones with a mean CT density ≤ 110 HU ($p<0.001$), and stones with a calcified rim ($p<0.05$) fragmented as shown in Table 5.4.

Table 5.4 Results of in vitro ESWL according to different stone categories

Stone Categories	No	Fragmentation ◇	Maximum Particle Size at End of Experiment * ≤5 mm (n=72)	Maximum Particle Size at End of Experiment * >5 mm (n=88)	P Value
Weight:					
≤ 500 mg	126	105 (83%)	67 (53%)	59 (47%)	NS
> 500 mg	34	25 (74%)	5 (15%)	29 (85%)	< 0.001
Diameter:					
≤ 10 mm	129	107 (83%)	66 (51%)	63 (49%)	NS
> 10 mm	31	23 (74%)	6 (19%)	25 (81%)	< 0.001
Cholesterol:					
≥ 80%	120	104 (87%)	53 (44%)	67 (56%)	NS
< 80%	40	25 (65%)	19 (48%)	21 (52%)	NS
Mean CT density:					
≤ 110 HU	120	105 (88%)	53 (44%)	67 (56%)	NS
> 110 HU	40	25 (63%)	19 (48%)	21 (52%)	NS
Calcified on CT:					
+	88	68 (77%)	37 (42%)	51 (58%)	NS
-	72	62 (86%)	35 (49%)	37 (51%)	NS
CT pattern:					
I	32	29 (91%)	15 (47%)	17 (53%)	NS
II + III	56	39 (70%)	22 (39%)	34 (61%)	NS
II	16	14 (88%)	5 (31%)	11 (69%)	NS
I + III	72	54 (75%)	32 (44%)	40 (56%)	NS

NOTE: Data are given as numbers of stones with percentages in parentheses.

* cholesterol ≥80% vs <80%, mean CT density ≤110 HU vs >110 HU, CT pattern I vs II + III: $p<0.05$.

◇ weight ≤500 mg vs >500 mg, diameter ≤10 mm vs >10 mm: $p<0.05$.

Except for a stone weight >500 mg and a diameter >10 mm, other stone characteristics which were significant negative predictors of adequate fragmentation, however, could not be identified.

Thirty-two stones from 14 different stone sets did not fragment, but in only 3 sets fragmentation failed with treatment II. In 2 sets (pigment stones, CT type III) all treatment regimens failed to fragment the stones. In these cases, application of 1500 shockwaves (focal pressure 100%) was still insufficient in the one, whereas this resulted in adequate fragmentation in the other case.

5.5 Discussion

In this study a single stone of each set from one patient was used for chemical and CT analysis because we assumed that this stone would be representative. This is justified by the observation that the chemical composition of multiple stones obtained from the same patient varied with only 2.5% [19].

The utility of computed tomography for predicting gallstone composition is an unsettled issue yet [20,21] In the present study, however, pure cholesterol stones were reliably identified (overall accuracy 95%) by mean CT attenuation numbers using a cutoff point of 110 HU. Brakel et al. achieved a similar overall accuracy using a cutoff point for pure cholesterol stones of 140 HU [15] Because HU values are device-dependent, the cutoff points for different CT systems cannot be compared unless a reference calibration phantom is used by which CT numbers can be converted to equivalent values of milligrams of K_2HPO_4 per ml [15]. We found an inverse relation between CT attenuation numbers and cholesterol content, confirming earlier in vitro as well as in vivo observations [13,15,22-24]. Unlike Baron et al., but corroborating other studies, we also found a good correlation between CT attenuation and calcium content [13,15,24,25].

The various CT patterns of the gallstones in this study were similar to those described previously [13,15,22,25,26] Stones which were noncalcified by CT appearance (type IV and V) and stones with a calcified core (type II) invariably were pure cholesterol stones, in accordance with the findings of Baron et al [22] The other CT patterns (type I and III), however, may correspond with cholesterol as well as with mixed and pigment stones. Therefore, qualitative CT analysis of gallstones based on different CT patterns provides some insight into the chemical composition, but does not allow a definite distinction in stones with a high cholesterol content and those with a low cholesterol content.

Evaluating our results, it should be considered that the use of a net to contain the gallstones and the encouragement of the passage of the fragments through the mesh during in vitro lithotripsy is not fully representative of the situation in vivo. During in vivo lithotripsy fragments are known to impede both the visualization and possibly the transmission of the shockwaves. Therefore clearance of these fragments during in vitro analysis probably artificially improves the results obtained.

We defined the endpoints of fragmentation as adequate (all remaining particles ≤ 5 mm) versus unsatisfactory (no fragmentation or at least one residual particle >5 mm). The rationale for this stratification is based on the observation that spontaneous passage of fragments up to 5 mm through the cystic duct and the papilla of Vater appears to be possible and rarely causes clinical and/or biochemical symptoms [28]. Furthermore, post-ESWL oral dissolution therapy resulted in a significantly higher stone-free rate when all residual fragments measured ≤ 5 mm [5]

Comparable in vitro gallstone fragmentation studies have been performed using both electrohydraulic [12,13] and piezoelectric shockwave devices [14] Schachler et al. achieved adequate fragmentation (≤ 5 mm) in 42 of 51 solitary stones (82%) after application of at most 1500 shockwaves [12] In the study of Barkun et al. a mean number of more than 2000 shockwaves was administered to achieve fragmentation in 68 of 85 stones (80%), adequate fragmentation (≤ 5 mm) occurring in only 27 stones (32%) [13] Ell et al. applied a maximum of 4000 shockwaves which effected fragmentation of all stones ($n=177$), 86% of which fragmented "appropriately" (≤ 4 mm) [14]. In the present study overall fragmentation was attained in 81% and adequate fragmentation in 45% of the stones. However, it must be emphasized that in our study 4 different treatment regimens were followed, applying considerably lower numbers of shockwaves than in the aforementioned studies. We are aware that the number of shockwaves used is not representative for the number of shockwaves normally used in the clinical setting. The reason that we have decided to use such a small number of shockwaves is that otherwise it might have been impossible to establish any relationship between energy setting and the number of shockwaves. Considering only the results of treatment II (highest effectiveness), 38 out of 40 stones (95%) fragmented, including 28 (70%) adequately. It is thus conceivable that these results would have been even better if a higher number of shockwaves had been applied.

There are several possible explanations for the varying results obtained in the various in vitro experiments. Firstly, the employed shockwave devices differ in acoustic energy output which is directly related to the effectiveness [11]. As shown in this experiment,

lower energy settings (resulting in lower focal shockwave pressures) can be compensated for by increasing numbers of shockwaves, but the relation between the energy and the number of shockwaves required for stone fragmentation seems to be not linear but exponential [27]. Secondly, the respective stone populations are not fully comparable with respect to stone size. Particularly in the present study, the median stone diameter was relatively small, probably because these stones were collected from patients with multiple stones. This is of interest because stone size is shown to be an important determinant of the outcome of fragmentation, which became also apparent from this study [4,5,10,12-14]. Thirdly, it cannot be excluded that the treatment geometries in the various fragmentation experiments have been different [29]. Finally, the differing numbers of shockwaves applied in the various studies might have been of importance in determining the results.

Confirming previous observations [12-14], we did not find any relationship between chemical composition, mean CT density, or CT pattern and adequate fragmentation except that bilirubin and calcium content may play a certain (minor) role. Nevertheless, some stone categories (pure cholesterol stones, stones with a CT number $\leq$ 110 HU,and stones with a calcified rim) seem to fragment easier than other ones (Table 5.4).

Barkun et al. established a stone diameter $\leq$ 15 mm, the presence of an angular stone shape and a stone density distribution index $\geq$ 60 HU as strong determinants of satisfactory fragmentation ($\leq$ 5 mm) [13]. In our study, a stone weight $>$ 500 mg and a stone diameter $>$ 10 mm were identified as categorical variables determining the result of fragmentation in a negative way.

In conclusion, the fragmentation efficacy of electromagnetic ESWL is mainly determined by the energy output of the lithotriptor and by the size, but not by chemical composition and CT characteristics of the stones. Quantitative CT analysis can provide reliable prediction of gallstone composition and therefore may play an important role in the selection of patients where primary or adjuvant chemolitholysis is considered as nonsurgical treatment. The present data warrant further clinical validation.

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CHAPTER 6

THE VALUE OF ULTRASOUND IN THE FOLLOW-UP OF PATIENTS TREATED WITH BILIARY LITHOTRIPSY: Implications for Monitoring Patients after Nonsurgical Therapy of Gallbladder Stones

6.1 Abstract

Both ultrasound (US) and oral cholecystography (OCG) can be used for monitoring patients after nonsurgical therapy of gallbladder stones. US is most preferred. In order to establish the value of US in the follow-up of patients treated with extracorporeal shockwave lithotripsy (ESWL), the results of 484 US examinations from 87 patients were analyzed and related to the results of ESWL. Reliability of US to assess efficacy was investigated by comparing consecutive US examinations. Unreliable US results were found in 36 patients (41%); in 7 patients US failed to demonstrate fragments; in 19 patients there was an inaccurate measurement of the largest fragment size and 13 patients had nondiagnostic US examinations. In 9 patients (10%) unreliable US findings contributed to delayed retreatment with ESWL. To avoid errors in treatment regimen, verification of US findings is advised in case of demonstrating no fragments or fragments < 5 mm.

In 22 patients (25%), US findings appeared indicative for hampered stone migration: a contracted gallbladder in 15 patients, a common bile duct > 7 mm in 6 patients, hydrops and signs of pancreatitis in one patient each. Only 2 of these 22 patients (9.1%) became free of stones compared to 32 of the remaining 65 patients (49.3%)) ($p < 0.01$) even though both groups had similar initial stone characteristics and similar time of follow-up. Therefore US findings such as a contracted gallbladder or a CBD > 7 mm indicate poor efficacy of ESWL.

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6.2 Introduction

In contrast with cholecystectomy, nonsurgical gallstone therapies affects gallstones only. Meticulous follow-up of patients treated in this way is necessary in order to assess stone fragmentation and/or clearance and possible recurrence. As a result of this follow-up, clinicians have to decide whether to cease or continue therapy or to retreat patients. For follow-up, both ultrasound (US) and oral cholecystography (OCG) can be used. US is preferred because it is harmless, cheap and highly sensitive in the detection of gallstones or its fragments. Nevertheless US has shown to be of limited value to assess precisely the number and size of gallstones [1-4]. Furthermore, in case of fragmentation treatments such as extracorporeal shockwave lithotripsy (ESWL), fragments may clump together and this also may lead to less accuracy [3,5].

Follow-up is also necessary to be informed about possible complications of nonsurgical gallstone therapy. These complications are on the one hand related to the migration of stone fragments from the gallbladder to the duodenum and on the other hand to the therapy itself, for instance energy trauma in case of ESWL. US should be able to provide information concerning possible complications.

To evaluate the value of US in the follow-up of patients treated with ESWL, the following questions were addressed:

1. What is the reliability of US in the assessment of stone fragmentation and/or clearance following treatment with ESWL?
2. In which way, decisions concerning the treatment regimen are affected by unreliable US results?
3. Can US indicate hampered migration of stone fragments and therefore indicate poor efficacy of ESWL?
4. What complications caused by shockwave lithotripsy itself are detected with US?

For these purposes we analyzed retrospectively in 87 patients the post-ESWL US findings and related them to the results and complications of ESWL.

6.3 Materials and Methods

From April 1988 to July 1991, 87 patients with symptomatic gallbladder stones (27 males, 60 females, mean age 48.1 years, ± 12.1 SD; range 28-81) underwent 203 treatments with an electromagnetic lithotriptor. (Lithostar® and Lithostar plus®, Siemens AG, Erlangen, Germany) as part of an ongoing trial [6]. Only patients with follow-up in our hospital were included in this study. All patients received a combination of urso- and

cheno-desoxycholic acid 7-8 mg/kg bodyweight in one dose in the evening) as an adjuvant treatment.

The in- and exclusion criteria were comparable with other ongoing trials for lithotripsy with one major difference that patients were included with up to 10 stones and without being limited by the size of the stones. Forty-five patients (52%) had a solitary stone, 27 (31%) had 2 or 3 stones and 15 (17%) had 4-10 stones prior to ESWL. The mean diameter of the largest stone was 17.4 mm $\pm$ 7.2 SD (range 5-35).

US examinations were performed 7-10 days after lithotripsy. Retreatment by lithotripsy was carried out if fragments of 5 mm or larger were present. After successful treatment (fragments reduced to $<$ 5 mm) US was repeated every 3 months. When US revealed complete clearance of the stones, the adjuvant therapy with oral bile acids was continued for 3 months and subsequently stopped if the next verifying US again showed the absence of fragments in the gallbladder.

US was performed by several radiologists, not associated with the lithotripsy trial. It was performed in the fasting state on real time equipment with 3.5 MHz or 5.0 MHz curved array or sector transducers. Sections of the gallbladder were obtained in different planes with patients in supine, left posterior oblique and erect positions. The following US findings were recorded on standardized forms:

1. The size and shape of the gallbladder, i.e. normal, contracted or hydropic. A gallbladder was considered contracted when the lumen of the gall bladder contained only calculi without normal surrounding bile. Hydrops was assumed when the transverse diameter of the gallbladder measured more than 4.5 cm [7].
2. The number and size of gallstones or fragments. Only stones with a diameter of 3 mm or larger were counted. Stones or fragments smaller than 3 mm were considered to be grit (sand). The number of stones was categorized as 1, 2, 3, 4, 5, 6-10 or more than 10 stones. Only the size of the largest stone or fragment was recorded.
3. Other US findings concerning the gallbladder and bile ducts such as: a generally thickened gallbladder wall, impaction of stones or fragments in the cystic duct or gallbladder neck; sludge, a diameter of more than 7 mm of the common bile duct, dilatation of intrahepatic bile ducts.
4. Abnormalities appearing in the liver parenchyma, the pancreas and the right kidney were also recorded.

US was considered unreliable to evaluate the number and size of gallstones when:

1. An US examination in which stones or residual fragments could not be demonstrated, was followed within 3 months by US in which stones or fragments were demonstrated, obviously not due to stone recurrence.

2. Two consecutive US examinations within 3 months, in which the last examination revealed a largest fragment diameter to be more than 3 larger than was measured in the former examination.
3. An examination was recorded as nondiagnostic concerning the number and size of gallstones or fragments, e.g. in case of a contracted gallbladder or aggregation of stone fragments.

The following US findings were recorded as indicative for hampered migration of stone fragments: a contracted gallbladder, hydrops of the gallbladder, diameter of common bile duct larger than 7 mm and signs of pancreatitis, such as enlargement and echopoor aspect of the pancreas or fluid collections around the pancreas.

Data analysis

Results are given as mean (range) or mean $\pm$ SD, as indicated. Continuous data were compared with the Mann-Whitney U-test. Proportions were compared using a standard test assuming two binominal distributions or with the Chi-square test.

Table 6.1 US examinations with unreliable results concerning the stone fragmentation and/or clearance in 87 patients

	number of patients	contributed to delay in retreatment with ESWL
incorrect stone free	7	-
inaccurate measurement	19	8
nondiagnostic because of:		
- contracted gallbladder	9	1
- aggregation of stone fragments	4	-
	36 * (41%)	9 (10%)

* three patients had a combination of two examinations with unreliable results.

6.4 Results

Eighty-seven patients underwent 464 post-ESWL US examinations. US examinations in 36 patients (41%) were considered unreliable concerning the assessment of stone fragmentation and/or clearance (Table 6.1). In 19 cases this was due to inaccurate measurements. In 7 patients US incorrectly did not demonstrate stones or fragments. In 9 patients an unreliable US examination contributed to delay in retreatment with ESWL of at least 3 months.

Table 6.2 Ultrasound findings indicative for hampered migration of stone fragments

		FOLLOW-UP		
US findings	patients	stone free	transient	cholecystectomy
contracted gallbladder	15	1	7	4
hydrops of the gallbladder	1	-	-	1
common bile duct >7 mm	6	1	4	1
pancreatitis	1	-	-	1
	22 *	2	11	7

* one patient had a combination of US findings.

The US findings of 22 patients (25%) indicative for hampered migration of stone fragments are listed in Table 6.2. The most frequent findings were a contracted gallbladder in 15 patients (17%) and a common bile duct larger than 7 mm in 6 patients (7%). In 11 patients the US findings returned to normal. Seven patients underwent cholecystectomy either because ESWL was considered inadequate or because of complications of ESWL.

Among the patients a statistically significant difference in the percentage who were free of stones ($p < 0.01$) was found between the group of 22 patients with US findings indicative for hampered stone migration (9.1%) and the remaining 65 patients without these findings (49.3%). The two groups of patients did not significantly differ in baseline stone characteristics or time of follow-up (Table 6.3).

Table 6.3 Comparison of stone characteristics, results and complications in 2 groups of patients with and without US findings indicative for hampered stone migration

	group of 22 patients with US findings indicative for hampered stone migration	group of 65 patients without US findings indicative for hampered stone migration	P value
baseline stone characteristics:			
·solitary stone	10 (45.5)*	35 (53.9)	n.s.
·2-3 stones	8 (36.3)	19 (29.3)	
· > 3 stones	4 (18.2)	11 (16.9)	
·diameter largest stone (mm)	20.8 ± 7.8	16.2 ± 6.7	n.s.
mean time follow-up (months)	10.5 ± 6.7 (range 1-21)	12.8 ± 8.5 (range 1-36)	n.s.
therapeutic results:			
·no fragmentation	2 (9.1)	2 (3.1)	< 0.01
· < 50% decrease in diameter of the largest stone	6 (27.2)	11 (16.9)	
· > 50% decrease in diameter of the largest stone	9 (40.9)	11 (16.9)	
·grit (sand)	3 (13.6)	9 (13.8)	
·free of stones	2 (9.1)	32 (49.3)	
complications:			
·colics	9 (40.9)	22 (33.8)	n.s.
cholecystectomy	7 (31.8)	6 (9.2)	< 0.01

* percentages in parentheses

In two patients, the US examination one week after ESWL, showed an echo poor focal lesion of ± 2 cm of the liver adjacent to the gallbladder, which was considered to be a hematoma. There were no clinical or laboratory signs of damage to the liver in these patients and the lesions disappeared spontaneously and could not be demonstrated on the next follow-up US examination.

6.5 Discussion

This study demonstrate some limitations of US to assess stone fragmentation and/or clearance in patients treated with ESWL. Limitations of US in assessing the number and size of gallstones and fragments have been ascribed to patient, technical and observer related factors [8]. ESWL itself also induces additional diagnostic problems [5]. In this study 13 patients (15%) had nondiagnostic US examinations concerning the assessment of efficacy because of side effects that were induced by ESWL. In 9 cases this was caused by a contracted gallbladder. In 4 patients reliable interpretation of the US examination was not possible due to clumping of fragments. Although we did not use "rollover maneuvres" to prevent clumping as advised by Khouri et al [5], patients were examined in different positions including the erect position. Because the phenomenon of clumping is most evident on US within 24 hours of ESWL, we started US evaluation 7-10 days after ESWL. Therefore clumping plays a minor role in the problems associated with imaging after ESWL.

Interpretation of post-ESWL US examinations may be influenced by the so-called comet-tail artifact [9]. However this artifact is only observed on US within a few days after ESWL and was not observed in this study, probably because we started evaluation after 7-10 days.

In evaluating the efficacy of ESWL two major questions should be addressed. Firstly to determine the necessity for retreatment with ESWL. In most protocols patients are eligible for retreatment if residual stone fragments are larger than 5 mm.

Retreatment with ESWL was delayed in 9 patients (10%), because the fragment size was underestimated in 8 patients and US was nondiagnostic in 1 patient.These findings support the results of a study by Baumgartner et al [10] in which oral cholecystography (OCG) proved more reliable than US in deciding patient eligibility for repeated ESWL. They therefore proposed that OCG should be an integral part of follow-up evaluation in ESWL.

In our opinion the use of OCG is only beneficial when the first US examination in follow-up evaluation reveals fragments smaller than 5 mm. In this situation a verification

OCG or US within a short period of time should be performed in order to decide whether or not to cease ESWL.

The second question concerning efficacy is the assessment of complete disappearance of stones and/or grit (sand) to cease further adjuvant therapy. In our protocol, patients free of stones continue adjuvant oral bile acid medication for three months, after which US is performed to verify the absence of stones. The necessity of this verification is proven by the outcome of this study in which the verification US examinations revealed grit or even fragments in 7 patients (8%), in spite of the former US examination in which no stones or fragments could be demonstrated. Because the verification US was performed within 3 months during oral medication of bile acids, recurrence of stone formation is unlikely[11].

The reliability of US to assess stone fragmentation and/or clearance was investigated in this study by comparing consecutive US examinations. Of course, this method have limitations because a gold standard is not available. These patients normally do not undergo cholecystectomy.

This study shows that US may provide important information concerning the ultimate stone clearance after ESWL. The 22 patients with US findings indicative for hampered stone migration had significantly lesser percentages of complete stone clearance compared with the group of patients without these US findings. The most frequent US finding in these 22 patients was a contracted gallbladder in 15 patients. A contracted gallbladder as assessed with US is highly specific in predicting non-visualization of the gallbladder on oral cholecystography [12]. Gallbladder visualization on OCG is required for oral treatment with bile acids because this ensures both cystic duct patency and concentration capability of the gallbladder. The utility of continuing oral medication of bile acids in patients with a contracted gallbladder is therefore very doubtful.

In this study a contracted gallbladder was found in 15 of 87 patients (17%). This is similar to the frequency of non-visualization of the gallbladder on post-ESWL OCG in 5 of 39 patients (13%) as reported by Baumgartner et al [10], however more than Sackmann et al [13] who reported a contracted gallbladder on US and a non-visualized gallbladder on OCG in only 5 of 175 patients (3%). Maybe this is due to the extended inclusion criteria for stone characteristics in our protocol [6].

Complications of ESWL as a result of shockwave therapy, i.e. energy trauma, are mostly mild and limited to transient microscopic hematuria and skin petechia. More serious complications that could be assessed with US are extremely rare and limited to one case report [14]. Our findings of two cases with suspected liver hematoma are hard to prove, because of the absence of clinical and laboratory signs in these patients, although the temporary nature of these findings is circumstantial evidence for trauma.

We conclude that US has some limitations in assessing the efficacy of ESWL. These limitations can influence clinical management in two ways:

1. Overestimation of efficacy by incorrectly demonstrating no fragments. Therefore a verification US is advised and claims regarding success without a verification US should be regarded with caution.
2. Delay in retreatment with ESWL by underestimation of the fragment size. Therefore a verification OCG or US is advised if US reveals fragments smaller than 5 mm.

It is expected that these limitations also affects the follow-up of other nonsurgical treatment of gallbladder stones such as oral and local contact dissolution therapies.

It is furthermore concluded that US findings indicative for hampered stone migration indicate poor efficacy of ESWL. In patients with a contracted gallbladder continuing oral medication with bile acids is doubtful.

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CHAPTER 7

PERCUTANEOUS CHOLECYSTOSTOMY FOR TREATMENT OF GALLBLADDER STONES

7.1 Introduction

Percutaneous cholecystostomy was initially introduced to decompress the gallbladder and/or bile ducts in case of acute cholecystitis and (malignant) obstruction of the common bile duct [1-7]. The percutaneous approach has proven to be a viable alternative for surgical cholecystostomy in severely ill patients with high-risk for general anesthesia. With increasing experience, percutaneous cholecystostomy was also used as a diagnostic procedure to assess biliary obstruction and as a method to enable percutaneous treatment of gallstones [8-13]. This chapter presents an outline of the technical aspects of percutaneous cholecystostomy and discusses the most important percutaneous techniques for the treatment of gallbladder stones.

7.2 Technical aspects of percutaneous cholecystostomy

7.2.1 Access route to the gallbladder

To obtain access to the gallbladder, a transhepatic and a subhepatic route are available. Most investigators prefer the transhepatic route to the upper one third of the gallbladder where it is attached to the liver surface ("bare area"). Theoretically, risk of bile leakage into the peritoneal cavity is reduced using this approach [4,5]. However this advantage is still unproven, as the reported frequency of bile leakage for the different access routes is very low (about 1%) [12]. Catheters used for the transhepatic approach have to be limited in size because of the risk of damage to liver tissue. Another potential drawback of the transhepatic route is that it may be difficult or even impossible to avoid the pleural space. A transpleural puncture can cause additional pain and creates an artificial connection between the peritoneal and pleural cavities.

The second approach is the direct transperitoneal subhepatic puncture to the fundus of the gallbladder. This route avoids the pleural space and avoids unnecessary damage to the liver. Ultrasonography is generally adequate to ensure a safe subhepatic route, although it is sometimes difficult to avoid the colon. For this reason and because of large variations in right upper quadrant anatomy, computed tomography is advocated by some as a better method to assess a safe access route [14,15]. A potential risk of the direct subhepatic route is that contact with the gallbladder can be lost during dilatation of the tract. The develop-

ment of a removable anchor device [10] that fixes the fundus of the gallbladder to the anterior abdominal wall seems to have solved this problem. This creates a safe and short track to the gallbladder which allows introduction of large catheters and stone removal devices.

7.2.2 Puncture techniques

The initial puncture of the gallbladder is usually performed under ultrasound guidance. For subsequent catheter placement fluoroscopy is preferable, although a bedside procedure using only ultrasound guidance is feasible [4]. In case of doubt concerning a safe puncture route, computed tomography is indicated. There are several methods described for catheter placement and the "best" method is dependent on personal experience and preference. Many investigators prefer the Seldinger technique. A thin needle (22-gauge) is used for initial puncture of the gallbladder after which a guide-wire (0.018 inch) is inserted. Over the guide-wire a combination of an 18-gauge needle and a 6-F catheter is introduced. After dilatation of the track the final catheter is installed. If unsuccessful, the initial puncture with the thin needle can safely be repeated, which is an advantage over other methods. Because this method uses exchanges over a guide-wire, the risk of leakage of a small amount of bile is present. Another drawback of the Seldinger method is that contact with the gallbladder during exchange and dilatation can be lost, with subsequent failure of the procedure. Therefore others advocate the Trocard method [6]. This method is a single-step procedure in which the puncture is performed with a thick needle with a preloaded catheter. After introduction of the needle into the gallbladder, the catheter is pushed off; this method avoids bile leakage and catheter positioning problems. The initial puncture, however, cannot be repeated without serious risks of liver damage or bile leakage.

7.2.3 Complications of percutaneous cholecystostomy

Recently, Teplick and colleagues [12] reviewed the results of successful percutaneous cholecystostomy in 252 patients that were reported in literature, including their own patients. The indications for percutaneous cholecystostomy were acute cholecystitis and desobstruction of bile ducts in, mostly, severely ill patients. The complication rate was 8%. The most serious complications were peritonitis caused by bile leakage (4 cases, one of which was fatal [5]), hemobilia (5 cases) and severe vasovagal reactions (4 cases, one of which led to a nonfatal cardiac arrest [16]).

One cause of bile leakage is early removal or dislodgement of the cholecystostomy catheter. Therefore the catheter has to remain in situ for at least 7-10 days, the time in

which a tract develops. If early removal is desired gelfoam, or other material, to plug the puncture site should be used. The cause of vasovagal reactions is unknown but the severe reactions mentioned above were only seen in patients with an underlying cardiac disease. Prophylactic use of atropine and minimizing manipulations with guide-wires and catheters in the gallbladder are advocated to prevent these vasovagal reactions.

7.2.4 Patient care around the procedure

Commitment to patient care around interventional procedures is essential for the radiologist [17]. Before the procedure is performed, screening for bleeding disorders is necessary. Solid food is withheld for 8-12 hours prior to the procedure. Patients should receive prophylactic antibiotics in case of infectious disease of the gallbladder or bile ducts.
Pain and anxiety are treated with local anesthetics (lidocaine) and an i.v. combination of an opium derivate and a benzodiazepine (common practise is a combination of fentanyl and midazolam). Atropine is administered to prevent vasovagal reactions. During the procedure, monitoring the patient by means of oxymetry, electrocardiography and continuous bloodpressure measurements, is strongly advised.

7.3 Percutaneous contact dissolution of gallbladder stones by methyl tert-butyl ether

7.3.1 Dissolution solvent

At present methyl tert-butyl ether (MTBE) is the only solvent used for percutaneous contact dissolution of gallbladder stones. MTBE is an alkyl ether similar to diethyl (anesthetic) ether which was known to dissolve cholesterol gallstones rapidly. Diethyl ether was used to dissolve retained bile duct stones until the 1950s, but it produced serious side effects owing to the volatilization of ether at body temperature [18]. The boiling point of MTBE is 55.2°C, it remains liquid at body temperature and is therefore less volatile.

In the past decades several cholesterol solvents has been used to dissolve cholesterol bile duct stones, such as mono-octanion [19,20], limolene [21] and mixtures of limolene and mono-octanion [18]. In vitro tests have shown that MTBE dissolves cholesterol stones 50-200 times faster than mono-octanion [22-23] and 10 times faster than limolene or a mixture of limolene and mono-octanion [23]. Thus MTBE is the most potent cholesterol solvent now available. MTBE is also able to completely dissolve stones with only 40% cholesterol [22]. Vergunst and colleagues [23] reported partial dissolution of pigment stones in vitro by MTBE. Encouraging clinical results are reported with 1% EDTA (a calcium chelating agent) solutions in combination with bile acids and mono-octanion to

dissolve brown pigment stones in the bile ducts [24]. However, it seems that black pigment stones in the gallbladder are practically insoluble [18]. Clinically successful dissolution of calcified pigment stones in the gallbladder is limited to one case report [25].

7.3.2 Patient selection for MTBE therapy

Selection of patients for MTBE therapy is based on two major issues: (1) the composition of gallstones and (2) the patency of the cystic duct. Only patients with cholesterol stones, irrespective of the number and size, are eligible. The classic radiographic criterion for assessment of cholesterol stones has been radiolucency on plain abdominal radiography or oral cholecystography (OCG). The predictive value of this feature is low [26,27]. Additional computed tomography is advised to predict gallstone composition more precisely [27,31] and to ensure the absence of calcifications in gallstones [28-30].

Protocols in the two largest studies of MTBE therapy [29,30] include only patients with a patent cystic duct as assessed by visualization of the gallbladder on OCG. This issue is disputed by others [32,33]. Cystic duct patency is desirable to enable the migration of residual debris from the gallbladder to the intestine. However, patients have been treated successfully with MTBE in the presence of an occluded cystic duct [34]. These patients suffered from acute cholecystitis and underwent percutaneous cholecystostomy to decompress the gallbladder. After regression of the signs of inflammation subsequent dissolution of the gallstones by MTBE was achieved.

7.3.3 Method of solvent delivery

MTBE has some qualities that need special care and attention. MTBE is a foul-smelling, volatile, inflammable liquid that is anesthetic at high concentrations. Therefore MTBE therapy should be carried out in a well-ventilated room, preferably with external exhaust ventilation [29]. In addition to its superb properties to dissolve cholesterol, MTBE also macerates and destroys plastics and synthetics [35]. Therefore catheters must be made of teflon, polyethylene or polyurethane; only glass syringes and metal stopcocks can be used.

Usually the percutaneous transhepatic approach is used for insertion of a catheter into the gallbladder. The technique was discussed in section 7.2.2. Some authors advocate an endoscopic retrograde cannulation of the gallbladder to instill MTBE [36,37]. Technical difficulties to pass the spiral-shaped Heister valves in the cystic duct and the inability to manipulate the catheter when introduced in the gallbladder, impedes extended clinical application of this method.

Several factors will influence the dissolution rate of cholesterol stones by MTBE. These factors include [34]:

1 the viscosity of MTBE, which is very low and therefore contributes to its excellent dissolution properties,
2 the contact time of the solvent with the stones
3 stirring or agitation of the solvent. (this is necessary because MTBE floats on bile and gallstones sink in bile).

The ideal method to dissolve gallstones with MTBE will be achieved with a catheter position surrounding the gallstones and with continuous infusion and aspiration of MTBE. Overflow of MTBE from the gallbladder to the bile ducts can cause serious side effects such as ulcerative duodenitis and hemolysis. The "overflow volume" can be assessed by injecting a contrast agent in the gallbladder under fluoroscopic control before the therapy is started. This should be repeated periodically during the therapy because the volume of the gallbladder can change in time. Until now, treatment in most patients has been by manual instillation and aspiration of small volumes (2 - 15 ml) of MTBE 4 - 6 times a minute [29,30]. As this method is tedious and labour intensive, automatic solvent delivery systems have been developed. Zakko designed a pressure controlled pump [38,39] (Lithox Systems, Salem, Mass. USA) that regulates instillation and aspiration volumes of the solvent by a pressure monitor. The pump automatically responds to changes in gallbladder volume, so changes in the "overflow volume" are corrected. The Mayo group designed a volume-controlled pump [40] (Baxter Health Care, Irvine, Calif. USA) that fixes instillation and aspiration volumes of the solvent, which is set after assessment of the "overflow volume". Preliminary results in patients showed that efficacy was identical to the manual syringe method but the working time of an operator was reduced with 70% [41]. It is expected that both pumps will soon be commercially available.

7.3.4 Results of contact dissolution therapy by MTBE

7.3.4.1 Efficacy of MTBE therapy

Thistle and co-workers from the Mayo Clinic [29] reported a success rate of 96% (72 of 75 patients). Success was defined as a complete dissolution (N=21) or more than 95% dissolution (N=51). More than 95% dissolution was estimated on the basis of the change in stone size, as determined by catheter cholecystography. In the 51 patients with more than 95% dissolution, residual debris (fragments not larger than 5 mm in diameter) was detected by Ultrasonography. Only 15 of these 51 patients became ultimately stone free

after 6 - 35 months. A group from Frankfurt, Germany [30] also reported a success rate of 96% (48 of 50 patients). However, criteria for success were not defined in this study. In an updated preliminary report from this group that to date have treated 231 patients, the success rate was still 96%. However, 40 - 50% of the patients had "some sludge" in the gallbladder after successful stone dissolution [41]. The treatment time usually ranges over 1 - 3 days with about 5 hours treatment each day. The total treatment time averaged between 9.5 hours (range 2.5 to 21 hours) [30] and 12.5 hours (range 3.8 - 30.8 hours) [29]. In 90% of the patients hospitalization is limited to 3-4 days [41].

7.3.4.2 Side effects of MTBE therapy

Puncture related complications have been discussed in section 7.2.3. Percutaneous transhepatic placement of a 5-F catheter for MTBE therapy is reported to be successful in most patients [29,30].

Reported side effects related to MTBE include: nausea with or without emesis, sedation, and the odour of MTBE on the breath. These symptoms are related to systemic absorption of MTBE. Approximately one third of the treated patients complained of these side effects [29,30,42,43]. All patients responded rapidly to anti-emetic drugs or transient cessation of solvent infusion. In most patients burning pain in the right upper quadrant required i.v. analgesics during the first hours of therapy [29]. Other causes of pain are postulated by Mueller [34]: extravasation of bile or MTBE along the catheter track, biliary colic due to stone fragments that may be displaced into the cystic or common duct during MTBE therapy, and catheter manipulations for optimal repositioning of the catheter.

Serious side effects related to overflow of MTBE from the gallbladder to the bile ducts and duodenum are extremely uncommon. Thistle [29] reported one case with clinical signs of ulcerative duodenitis and intravascular hemolysis. Ponchon [43] described one patient who went into coma for 4 hours and subsequently developed acute renal failure. Hemolysis was suspected to have caused the renal failure. No deaths have been reported related to percutaneous contact dissolution by MTBE.

7.3.4.3 Follow-up of MTBE therapy

Data are sparse on long-term results after MTBE treatment. Only preliminary results from the Mayo Clinic are available [44]. They followed 117 patients treated with MTBE for 6 - 48 months. Complete dissolution of stones was achieved in 36 patients (31%). In 8 of these 36 patients, recurrence of gallstones was documented. Residual debris was present in 81 patients; 15 of 81 patients became ultimately stone free and 34 other patients had doubled their residual debris ("regrowth").

7.3.5 Conclusions

In his leading article "Nonsurgical treatment of gallstones: many contenders but who will win the crown?" Bouchier [45] gives his opinion on MTBE therapy: "This treatment is not for the faint hearted". With this statement Bouchier refers to the side effects of MTBE, such as nausea, vomiting and pain that makes this therapy uncomfortable for many patients. Moreover MTBE therapy is tedious, labour intensive and more invasive than other nonsurgical treatments such as ESWL and oral bile acids. On the other hand, rapid dissolution of cholesterol stones, irrespective of their number or size, can be achieved more effectively and quicker with MTBE than with oral bile acids or ESWL therapy. The reported high success rate of dissolution (96%) [29,30] includes residual debris in most patients. In a comment on the work of Thistle and co-workers at the Mayo Clinic, Auteri and Malet [46] take the view that the ultimate fate of this residual debris is the key question for the role of MTBE therapy. Questions that have to be answered are: to what extent will residual debris cause biliary symptoms? Will it spontaneously pass out the gallbladder or does it provide a nidus for rapid recurrence ("regrowth")? Can residual debris be avoided by a more precise selection of patients, perhaps by computed tomography? Further studies on these issues should define the potential role of percutaneous local contact dissolution by MTBE for the treatment of gallstone disease.

7.4 Percutaneous techniques for fragmentation and removal of gallbladder stones

7.4.1 Introduction

Interventional radiology of the biliary tract first attracted the attention of the lay press when Burhenne percutaneously removed a retained gallstone from the bile duct of the exiled Shah of Iran in 1979 [47]. In the following decade a plethora of percutaneous techniques for the management of gallstones became available. This section discusses the most important techniques for fragmentation and removal of gallbladder stones.

Percutaneous techniques may be used in severely ill, high-risk patients with acute cholecystitis who need decompression of the gallbladder. If, after resolution of the inflammation, cholecystectomy remains contraindicated, the gallstones may be removed through a dilated cholecystostomy tract. Indications for elective removal of gallstones by percutaneous techniques are usually confined to morbidly obese patients and patients with high risk for anesthesia. In most cases there are no restrictions regarding the size, number and composition of the gallstones. Patient selection only requires the assessment of a safe access route to the gallbladder, as discussed in section 7.2.

Table 7.1 Percutaneous fragmentation and removal of gallbladder stones

Series	No	Indication	Anesthesia
(1) Rotational contact lithotripsy			
Miller 1991[50]	10	elective	local anesthesia i.v. analgesics i.v. sedatives
(2) Percutaneous cholecystolithotomy			
Cope 1988[10], 1990[54]	20	elective	epidural
Lees,Kellet 1988[11], 1989[56]	61	elective	general
Hruby 1989[57]	11	elective	general
Grifith 1990[58]	13	elective	general
Akiyama 1990[55]	28	elective	no data
Kerlan 1985[52]	3	acute	local anesthesia i.v. analgesics i.v. sedatives
Picus 1989[53]	11	acute	local anesthesia i.v. analgesics i.v. sedatives
(3) Combined surgical and radiological intervention			
Burhenne 1985[59], Gibney 1987[60]	36	acute	local anesthesia i.v. analgesics i.v. sedatives
Total	193		

NOTE: number of patients in parentheses

Access route	Maximal diameter tract	No of patients stone free	Complications
transhepatic	10-F	7	access loss (1) biloma (1) bile leakage (1) Instrumental failure (1)
subhepatic anchor	14-24-F	17	access loss (1) vasovagal reaction (1) retained anchor (3)
subhepatic	28-F	56	cholecystectomy due to failure (4)
subhepatic	24-F	9	access loss (1) cholecystitis (1) stone fragmentation failed (1)
subhepatic	25-F	11	access loss (1) bile leakage (1) inability to access (1)
transhepatic	26-F	20	bile leakage (2) bleeding (1) stone impaction cystic duct (2)
transhepatic	24-F	3	-
transhepatic	18-F	11	wound infection (1) bileperitonitis † (1)
subhepatic	24-F	35	access loss (1) colon injury (1)
		169	

Table 7.1 gives an outline of three groups of procedures which includes:
1. percutaneous rotational lithotripsy [48-51]
2. percutaneous cholecystolithotomy [10,11,52-58] and
3. combined surgical and radiological intervention [59-60].

7.4.2 Percutaneous rotational lithotripsy

A new method to fragment and remove gallstones was developed by Kensey and Nash who designed a device to pulverize calculi in a manner similar to that of a household blender [48]. The Kensey Nash lithotrite (Kensey Nash, Exton, PA,USA) consists of a six-pronged basket which surrounds a 3 mm impeller mounted on a cable in a 7-F catheter. The basket protects the gallbladder wall from the impeller. An electric motor drives the impeller to rotate up to 30.000 RPM. A strong fluid vortex pulls the stones automatically into the basket and fragmentation to sizes mostly smaller than 2 mm is achieved within minutes [48,49]. Percutaneous cholecystostomy by means of a 10 F introducer sheath is performed to allow the introduction of the lithotrite into the gallbladder. General anesthesia is not necessary, but as the procedure may be painful, adequate i.v. analgesics and sedation are required. After the procedure a 10 F catheter is left in place for 7-10 days to flush the gallbladder with saline and to aspirate residual debris. Moreover, in this period a tract develops which is required for safe removal of the catheter (section 7.2).

Miller et al reported the first clinical experience with the lithotrite in 10 patients [50]. The selection criteria for the treatment included: no limitations in the number of stones, but stone volume may not exceed 75% of the volume of the gallbladder. This restriction is necessary because the device must be able to open freely in the gallbladder. Stones up to 25 mm in size, can be treated; the gallbladder should be visualized on oral cholecystography (this criteria lapses in a sequel study [51]). The number of calculi varied between 1 to more than 25. In 9 of 10 patients the treatment was completed; in one patient access to the gallbladder was lost. The rotation time varied between 5-39 minutes. At the termination of the procedure 7 of 9 patients were stone free. Complications occurred in three patients: one patient with an infected biloma due to catheter dislodgement 12 hours after the procedure; one patient with transient bile leakage after removal of the catheter 9 days after the procedure and in another patient an instrumental failure occurred without injury to the gallbladder.

The hospital stay ranged from 2-3 days. In the follow-up after 3-6 weeks, ultrasonography showed aggregates (3-4 mm) in three patients who were initially considered to be stone free at the end of the procedure. This phenomenon was explained by the authors according to observations in animal studies [48,49], that showed mucosal trauma with an

irregular gallbladder wall and some blood clots after treatment. Some stone fragments will temporarily adhere to the mucosa and will not be detected until they drop into the bile and clump together. Flushing with saline for some days after the procedure cannot totally prevent this phenomenon. In a preliminary report, results of 32 patients treated at 6 centres were presented [51] and these results did not differ essentially from the first 10 patients.

Like local contact dissolution by MTBE, local contact lithotripsy with the Kensey Nash lithotrite has to deal with the consequence of residual debris. Nevertheless, compared to MTBE therapy, treatment with the lithotrite appeared to be more attractive. Differences between the two treatment modes are shown in Table 7.2.

TABLE 7.2 Comparison between MTBE and Lithotrite treatment

	MTBE	Lithotrite
Stone composition	cholesterol	all stones
Stone number and size	no limitation	< 30 mm: < 75% gallbladder volume
Treatment time	hours-days	minutes
Catheter size employed	5-F	10-F

7.4.3 Percutaneous cholecystolithotomy (PCCL)

This method consists of a heterogeneous group of treatments with many modifications [10,11,52-58] (Table 7.1). They have the following steps in common: (1) percutaneous access to the gallbladder (2) dilatation of the tract (3) introducing instruments to fragment and remove gallstones (4) leaving a drainage tube in the gallbladder for a period of time. The access route to the gallbladder is discussed in section 7.2.1. Dilatation of the tract can be performed with fascial dilatators, co-axial systems or by balloon dilatation. The dilatation is painful and is a risk, particularly when a large tract is needed and a transhepatic route is chosen. Therefore multiple sessions for gradual dilatation may be necessary. When a subhepatic route is chosen and general anesthesia is used, dilatation of a large tract can be achieved in one step [11,56-58]. If the final tract to the gallbladder is established, small stones will leave the gallbladder spontaneously. Medium sized stones can be removed under fluoroscopic guidance with the use of baskets, graspers or forceps. Larger stones must be fragmented by techniques such as intracorporeal electrohydraulic lithotriptors, ultrasound lithotriptors or laser. For these fragmentation techniques, direct visualiza-

tion is enabled using flexible choledochoscopes [10,53-55], or rigid nephroscopes [11,56-58]. Multiple sessions may be needed to extract all stones. Good results (Table 7.1) were reported (127 of 147 stone free = 86%), with relatively few complications. One death due to bile leakage after withdrawal of the catheter in a severely ill high-risk patient was reported [53]. Although these procedures are complex and technically demanding, percutaneous cholecystolithotomy appeared to be a safe and effective procedure in high-risk patients, especially in those patients with acute cholecystitis in whom percutaneous decompression of the gallbladder is indicated. Some authors [11,56-58] advocate a one-step procedure under general anesthesia as an elective treatment for patients who refuse surgery to avoid a prolonged hospital stay or a large abdominal scar. With the introduction of laparoscopic cholecystectomy this is no longer a viable alternative.

7.4.4 Combined surgical and radiological intervention

This technique, introduced by Burhenne [59], is an example of good cooperation between surgeon and interventional radiologist. After localizing the gallbladder with ultrasonography, the surgical part consists of a minicholecystostomy performed under local anesthesia. A small ($\pm$ 5 cm) abdominal incision is made over the marked gallbladder fundus and a pursestring suture is made in the fundus of the gallbladder. Within this suture a small incision is made to introduce a 24-F catheter in the gallbladder. The fundus of the gallbladder is than stitched on each side of the combined peritoneum and posterior rectus sheet layer, thus creating a short surgical tract. After 7-10 days the radiological intervention for stone removal can be performed, using techniques similar to those employed for PCCL. This method is claimed to be safe and effective (Table 7.1). Burhenne preferred it for high-risk patients for the following reasons [60]: (1) the surgical procedure avoids the painful and hazardous dilatation of a percutaneous track (2) in case of recurrence, subsequent percutaneous cholecystostomy is easy because of the superficial location of the fixed fundus of the gallbladder (3). Vaso-vagal reactions following percutaneous cholecystostomy are avoided. Nevertheless this technique has not gained widespread acceptance.

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CHAPTER 8

SCLEROTHERAPY OF THE GALLBLADDER IN PIGS: Development of a balloon catheter for a single-step procedure

8.1 Abstract

Gallbladder sclerotherapy after permanent cystic duct occlusion, to prevent gallstone recurrence in nonsurgical gallstone therapy, is at least a two-stage procedure. A balloon catheter was developed to perform gallbladder sclerotherapy with only temporary occlusion of the cystic duct, and the efficacy and safety of this method was subsequently investigated. Twenty pigs underwent cholecystostomy for positioning of a 7-F triple lumen balloon catheter with proximal side holes. Sclerotherapy with 96% ethanol and 3% sodium tetradecyl sulfate for 20 minutes was performed.

The animals were killed 24 hours, two, six and 12 weeks after the procedure. The balloon catheter functioned well and seems suitable for procedures in which a temporary occlusion of the cystic duct is required.

Although gallbladders after six and 12 weeks were shrunken and fibrotic, a single treatment of gallbladder sclerotherapy with subsequent catheter removal and no permanent cystic duct occlusion, as performed in this experiment did not produce complete gallbladder ablation. In this study, sclerotherapy proved safe in the short term, but long-term effects remain to be assessed.

8.2 Introduction

The introduction of extracorporeal shockwave lithotripsy (ESWL) of gallstones has stimulated interest in other nonsurgical treatment modalities for gallstone disease. Radiological intervention techniques play a major role in this field, including several techniques for fragmentation and percutaneous removal[1-4] or direct contact dissolution [5-8] of gallbladder stones, and also ablation of the gallbladder.

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Several authors have reported results of in situ gallbladder ablation. Permanent occlusion of the cystic duct preceding chemical sclerosing of the gallbladder mucosa has been reported as successful [9-11], but have been unable to reproduce this method successfully [12].

Good results also have been reported without permanent occlusion of the cystic duct [13]. Because permanent cystic duct occlusion followed by gallbladder sclerosing is at least a two-stage procedure, we have attempted to develop a one-step procedure in which stone treatment and gallbladder sclerosing could take place.

This study was initiated to test a balloon catheter developed for radiological interventional procedures with temporary cystic duct occlusion, and to investigate the safety and efficacy of gallbladder sclerotherapy with only temporary occlusion of the cystic duct.

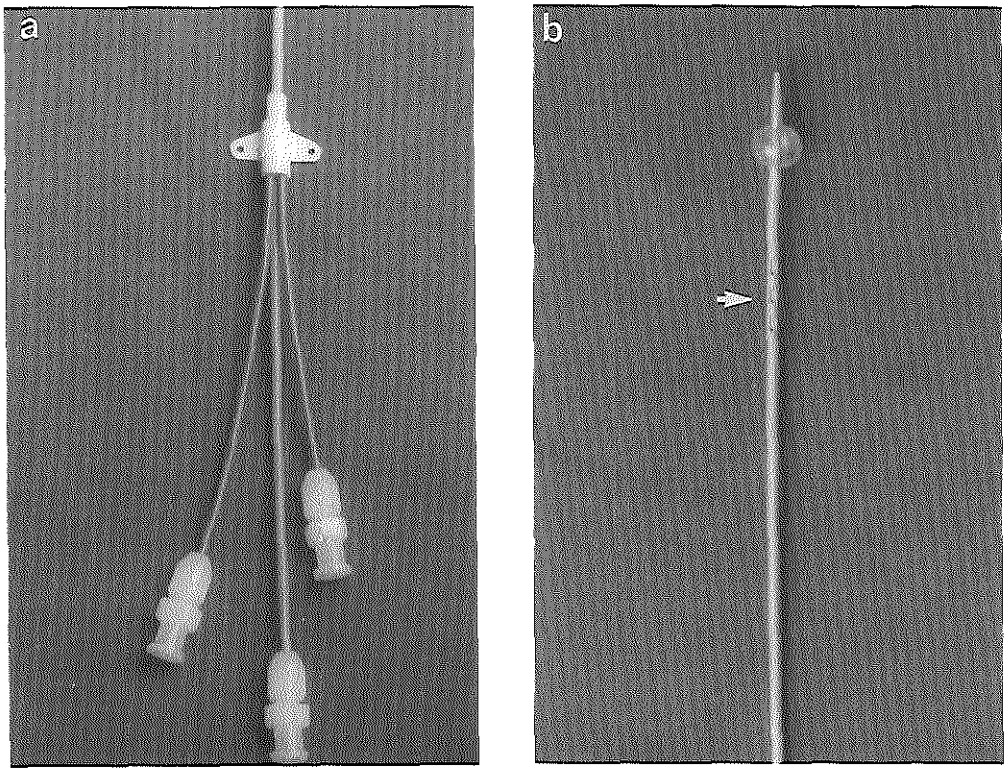

Figure 8.1 The 7-F triple-lumen balloon catheter. (a)Proximal portion with three separate lumina. (b)Distal portion with proximal side holes (arrow), balloon, and an end hole.

8.3 Materials and Methods

Animals

Twenty young Yorkshire pigs (average weight 28 kg) were used for the experiments. Before the procedure, they were fasted overnight. After premedication with ketamine IM (30 mg/kg) and intratracheal intubation, inhalation anesthesia was maintained with oxygen, nitrous oxide and enflurane. Fentanyl citrate and pancuronium bromide were used for IV analgesia and muscle relaxation, respectively. A single IM dose of 2.0 to 2.5 ml Depomycin 20/20® (penicillin G 200,000 U/ml, streptomycin 200 mg/ml, Mycofarm, de Bilt, The Netherlands) was given as antibiotic prophylaxis.

Positioning of the balloon catheter

After localizing the gallbladder with sonography, a median longitudinal incision (7-10 cm) at the level of the gallbladder was made. The gallbladder was mobilized and a small pursestring suture with proleen 3.0 was made in the fundus of the gallbladder. Within this suture the gallbladder was punctured to evacuate bile and to introduce a specially designed 7-F triple lumen balloon catheter with proximal side holes and an end hole (Cook Company, Eindhoven, The Netherlands; designed by J.S. Laméris, MD) (Fig. 8.1).

After flushing and filling the gallbladder with saline through the catheter, a J-shaped guide wire (0.035 inch) was inserted into the cystic duct to enable positioning of the balloon in the cystic duct. The balloon was then insufflated with air and the gallbladder was emptied and completely filled with contrast (16-20 ml Telebrix, Guerbet, Aulnay S/Bois, France) to control the position of the balloon and complete occlusion of the cystic duct (Fig. 8.2).

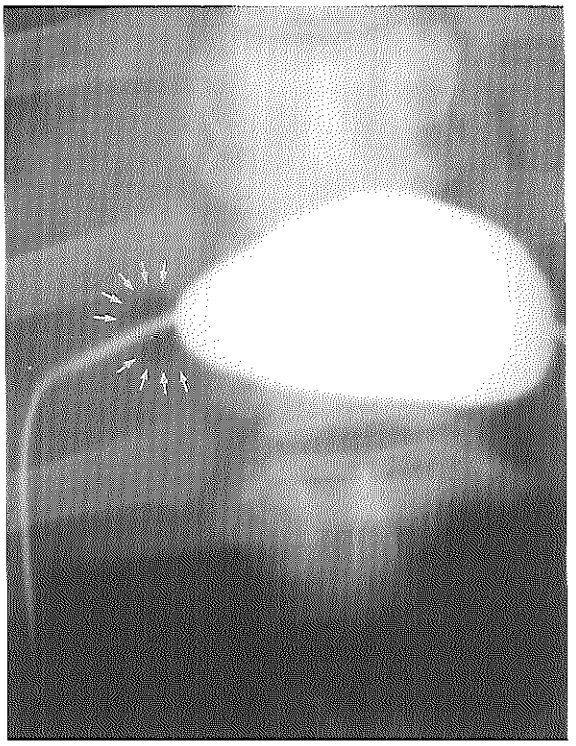

Figure 8.2 Radiograph of the abdomen after filling the gallbladder with contrast to control the position of the balloon (arrows). The cystic duct is completely occluded; there is no leakage of contrast in the bile duct.

In the event of leakage at the introduction site of the catheter in the fundus of the gallbladder, the fluid was cleared with gauze steeped in saline.

Sclerotherapy

After evacuating the contrast, the gallbladder was filled with a similar amount of sclerosing agent (96%
ethanol with 3% sodium tetradecyl sulfate) over the course of 20 minutes. Thereafter the sclerosing agent was aspirated, and the gallbladder was flushed with saline. After withdrawal of the catheter, the gallbladder pursestring and the abdomen were closed. Blood samples (white blood count, aspartate aminotransferase, alanine-aminotransferase, alkaline phosphatase, amylase) were taken before and after the procedure and just before the animals were killed. Serum ethanol levels were determined immediately before the removal of the sclerosing agent.

Macroscopic studies

The pigs were divided into four groups of five animals each; these were killed after 24 hours, two weeks, six weeks and 12 weeks.

Ultrasonography was performed before the procedure and before autopsy. At autopsy, the intra-abdominal organs were carefully inspected for macroscopic lesions. The liver, biliary tract, and gallbladder were resected en bloc and fixed in phosphate buffered formalin. Specimens for histologic investigation were obtained from the fundus and corpus of the gallbladder, the transitional zone of gallbladder neck and proximal cystic duct, and the distal cystic duct, common bile duct and porta hepatis, all with adjacent liver tissue. A control specimen was taken from a distant liver area. Sections were stained with hematoxylin-azophloxin-saffron (HAS).

Microscopic studies

Histologic data were recorded on standardized forms by a experienced hepatobiliary pathologist (FJWK), who was uninformed about the assigned group.

Data analysis

Statistical evaluation of the laboratory data was performed by the Mann-Whitney U test.

This protocol was approved by the committee on Animal Research of the Erasmus University, Rotterdam, The Netherlands.

8.4 Results

8.4.1 Balloon Catheter

There were no catheter-related problems during the procedure. The cystic duct could be

completely occluded by the balloon in all cases.
In one animal, killed after 2 weeks, the cystic duct displayed localized deep inflammation of the wall with necrosis and fibrosis, probably related to mechanical injury from the balloon. No other lesions were found in the cystic duct.

8.4.2 Sclerotherapy of the gallbladder

Safety

In 11 of 20 procedures, at maximal filling of the gallbladder, leakage of some drops of gallbladder content (saline, contrast, sclerosing agent) occurred at the introduction site of the balloon catheter in the fundus of the gallbladder. The serum ethanol concentration did not reach the detection rate (0.1 gr/l) in any animal. Each pig served as its own control for evaluation of laboratory parameters. A minor increase in mean white blood count ($P < 0.05$) was observed one day after the procedure. The mean serum activity of aminotransferase aspartate was elevated in all groups of animals immediately after the procedure (maximum increase 1.9-fold) ($P < .05$), but was restored to baseline values at the time of killing. No other significant changes in laboratory findings were observed.
All pigs survived the procedures and were in good health until they were killed.
At autopsy, no free fluid was present in the abdomen. In the 11 animals with gallbladder leakage, mild adhesions in the pericholecystic area and small superficial lesions on the liver surface were observed. Two pigs suffered from an intraperitoneal encapsulated abscess, one as a result of a gauze that was left behind, the other with a fistula from the gallbladder. No other macroscopic lesions were found.

At microscopic investigation, bile duct specimens showed nonspecific mild chronic inflammation. Damage to the liver was restricted to a small region of the gallbladder fossa, and was most clearly seen in the group killed at 24 hours, showing as mild to moderate acute inflammation in four of the five animals. In the other groups (killed at 2 weeks, 6 weeks, 3 months) only three of the 15 pigs showed mild fibrosis and/or mild to moderate chronic inflammation. All liver specimens, included those from a distant liver area, showed very mild chronic portal inflammation.

Efficacy

At autopsy, all gallbladders were shrunken, with a mean volume of 2.5 ml (range: 0.5-7.5 ml) while the mean volume before the procedure was 18 ml (range: 16-20 ml). Most of the gallbladders contained solid material, with fibrin, mucin, and bile. The results of the histologic investigations of the gallbladder are shown in Table 8.1. Following sclerotherapy in each group of animals, a characteristic sequence of changes in the gallbladder wall was observed.

In the group of animals killed after 24 hours, the predominant finding was edema of the entire gallbladder wall (Fig. 8.3a). In two pigs from this group there were signs of necrosis and extensive proliferation of fibroblasts (active fibrosis). Local regeneration of the epithelial lining had started in the form of a monolayer of cylindrical mucus secreting cells.

In the group of animals killed after two weeks, coagulation necrosis of the mucosa, which was rejected as a membrane, was prominent (Fig. 8.3b). Regeneration was also present, starting from isolated islands of intact mucosa. In the groups killed after six and 12 weeks, in seven of eight pigs moderate to strong fibrosis was observed. A regenerated epithelial lining was evident, consisting of a monolayer of cylindrical mucus secreting cells covering the atrophic mucosa (Figure 8.3c).

Table 8.1 Histologic appearance of the gallbladder after sclerotherapy*

	group No.	edema	necrosis	inflammation	active fibrosis	regeneration mucosa	inactive fibrosis
24 hrs	1	+++	0	+	0	0	0
	2	++	++	+	++	+	0
	3	+++	0	+	0	0	0
	4	++	++	+	+	+	0
	5	+++	0	+	0	0	0
2 wks	1	0	+++	++	+++	+	0
	2	0	+++	++	++	+	0
	3	0	+++	++	+++	+	0
	4	0	+	+	++	+	0
	5	+	+++	+	+++	+	0
6 wks	1	0	0	0	0	+++	++
	2	0	0	+	0	+++	++
	3	0	0	+	0	+++	+++
	4	-	-	-	-	-	-
	5	0	0	0	0	+++	+
12 wks	1	0	0	+	0	0	+
	2	0	0	0	0	+++	+++
	3	0	0	+	0	+++	++
	4	-	-	-	-	-	-
	5	0	0	0	0	+++	++

*) 0:absent; +:mild; ++:moderate; +++:strong; -:not available for analysis due to autolysis of histologic material

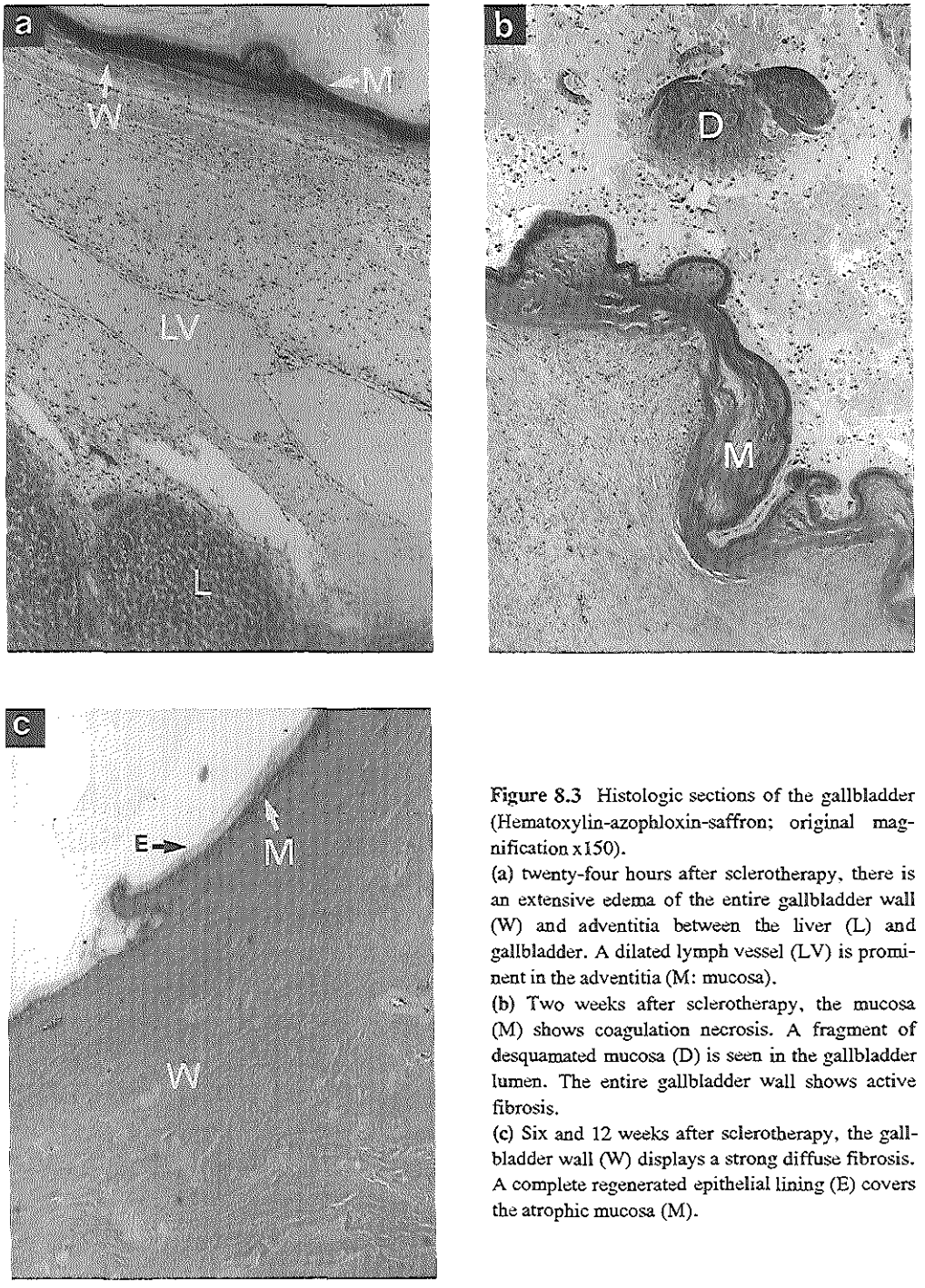

Figure 8.3 Histologic sections of the gallbladder (Hematoxylin-azophloxin-saffron; original magnification x150).
(a) twenty-four hours after sclerotherapy, there is an extensive edema of the entire gallbladder wall (W) and adventitia between the liver (L) and gallbladder. A dilated lymph vessel (LV) is prominent in the adventitia (M: mucosa).
(b) Two weeks after sclerotherapy, the mucosa (M) shows coagulation necrosis. A fragment of desquamated mucosa (D) is seen in the gallbladder lumen. The entire gallbladder wall shows active fibrosis.
(c) Six and 12 weeks after sclerotherapy, the gallbladder wall (W) displays a strong diffuse fibrosis. A complete regenerated epithelial lining (E) covers the atrophic mucosa (M).

8.5 Discussion

We developed and tested a balloon catheter to investigate the efficacy and safety of gallbladder sclerosing with only temporary occlusion of the cystic duct.

The specially designed balloon catheter for temporary cystic duct occlusion proved to be effective in our pig model. The catheter can serve as a useful tool for interventional procedures such as sclerotherapy of the gallbladder and local contact dissolution of gallstones. During the sclerotherapy, the cystic duct was occluded completely without leakage of gallbladder content into the bile ducts.

The diameter of the balloon (8 mm) was sufficient to occlude the cystic duct without tissue damage. The side holes situated 30 mm proximal to the balloon functioned efficiently for both installation and evacuation of the sclerosing agent. We are currently developing a modification of the catheter in which the proximal side holes are situated in an additional loop of the catheter; this will be especially suitable for local dissolution therapy. The third lumen with the end hole is used for insertion of the guide wire and can also be used for flushing the bile duct during deflation of the balloon at the end of the procedure.

To gain access to the gallbladder, we performed a cholecystotomy after a minilaparotomy, because the porcine gallbladder is situated subhepatically and is very mobile [14]. In 11 of 20 procedures with this method, leakage of some drops of gallbladder content occurred at the gallbladder fundus, where the balloon catheter was inserted. In humans, leakage can be prevented by percutaneous transhepatic access, or by a subhepatical approach using a currently available anchoring device [15].

Our findings indicate that sclerotherapy of the gallbladder with only temporary occlusion of the cystic duct is a safe procedure. No toxic effects or hepatic injury related to the sclerotherapy were found.

Although the one-step procedure with a balloon catheter for gallbladder sclerotherapy resulted in a shrunken fibrotic and defunctionalized gallbladder in all animals, we did not succeed in destroying the mucosa completely, and therefore ablation was not achieved. In our opinion this can be explained by the following observations.

First, the regenerative capacity of the gallbladder mucosa plays an important role. In this animal model it was remarkable how quickly (within 24 hours) extensive mucosal regeneration occurred from little islands of still-viable mucosa. Although there might be further refinements in sclerotherapy, such as longer duration of the therapy or different administration regiments with different sclerosing agents, we consider it virtually impossible to achieve total destruction of the mucosa. In this study, introduction of even a small air bubble in the gallbladder during installation of the sclerosing agent was sufficient to cause such islands of undestroyed mucosa. Becker et al [11], who reported very good

results of sclerotherapy in pigs, also found occasional "nests" of epithelium in five of 16 animals. Perhaps their use of a 22-F cholecystotomy catheter with a large balloon situated in the gallbladder fundus made it impossible for the sclerosing agent to reach the mucosa at that site, and contribute to the creation of "nests" of epithelium.

Further, in humans with almost inaccessible sinuses of Aschoff-Rokitansky, these remnants of undestroyed mucosa seem to be an even greater problem [16]. Therefore it is not surprising that Becker and coworkers in humans [17] were unable to reproduce the good results as they achieved in animals [11].

The long term effects of remnants of undestroyed mucosa remain unknown, and the potential risk for malignant transformation should be considered. A second possible explanation for failure to achieve total mucosal destruction in this study is that the cystic duct was not permanently occluded. Although, in contrast to Getrajdman et al [10], we did not observe mucosal regeneration from the cystic duct, almost all gallbladders in our study contained material with fibrin, mucin and bile. Thus, as suggested by Becker et al [11], obliteration of the gallbladder lumen will be hampered. On the other hand, leaving a catheter in the gallbladder for a certain time period could have been an appropriate solution for this problem. We chose temporary occlusion with a balloon catheter, and subsequent catheter removal, in the search for a single-step procedure. The ultimate goal of this therapy is to achieve gallbladder ablation, which prevents recurrence of gallstones and avoids risks such as mucocele and malignancy, because ablation implies that no endothelium or adenomatous remnants remain.

Since gallstone recurrence is a problem predominantly in young people, this therapy offers most to this age group. However, as the long-term effects of this treatment are unclear, the indication for sclerotherapy is, especially for young people, doubtful. Moreover in this group of patients this therapy has to "compete" with surgical therapy, of which laparoscopic cholecystectomy seems to be a less invasive and promising therapy [18].

We conclude that:

1) The triple lumen balloon catheter is suitable for radiological interventional procedures in which a temporary occlusion of the cystic duct is required.
2) A single treatment of gallbladder sclerotherapy with subsequent catheter removal and no permanent cystic duct occlusion as performed in this experiment does not produce complete gallbladder ablation.
3) Although sclerotherapy is proven safe in the short term, long-term effects on remnants of undestroyed mucosa remain to be assessed.

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CHAPTER 9

FINAL REMARKS
An imaging strategy for patients suspected of gallstone disease

The management of gallstone disease has changed rapidly during the last few years. Studies described in this thesis were initiated four years ago, when first reported results of gallstone lithotripsy aroused hopes for a new era in the management of gallstone disease. Because ESWL fell short of these high expectations and laparoscopic techniques made surgical therapy more attractive, it is now expected that nonsurgical gallstone treatment will play only a limited role. Nevertheless, most of these nonsurgical treatments have proven to be safe and effective in selected patients. Therefore nonsurgical treatment modalities should be part of the armamentarium in the management of gallstone disease.

The treatment of choice for patients with symptomatic gallstone disease depends on: (1) the patient's state of health, (2) the need for emergency or elective treatment, (3) radiological selection criteria and (4) the preference of the patient.

One of the aims of this thesis was to design an imaging strategy for patients with symptomatic gallstone disease. The ideal imaging strategy consists of an efficient sequence of imaging modalities, able to assess selection criteria for the different gallstone treatment modalities in a reliable, safe and cost effective manner. Success of nonsurgical treatment is highly dependent on precise selection. Therefore the cost of the selection procedure should be outweighed against costs generated by ineffective treatment in patients not selected properly. For an effective patient selection it is essential to be aware of the selection criteria at the time of diagnosis. Ultrasonography (US) is the first diagnostic modality to detect gallbladder stones. Once the diagnosis of gallstones is made by US, additional information for selection purposes should be obtained during the same examination.

The value of US in providing this information was a subject of study in this thesis (chapters 2 and 3):

In chapter 2, the value of US in providing information concerning the so-called "function" of the gallbladder was investigated. Oral cholecystography (OCG) is considered to be the standard test for this selection criterion. Gallbladder visualization on OCG is required for most nonsurgical treatments of gallstones because it ensures both cystic duct patency and concentration capability of the gallbladder. The results presented

in chapter 2 show that US findings such as a contracted stone-filled gallbladder or an impacted gallstone in the cystic duct or the gallbladder neck are highly specific in predicting non-visualization of the gallbladder on OCG. Therefore patients with these findings are not eligible for most nonsurgical treatments. Nevertheless in case of stone impaction there could be a role for ESWL, since such therapy may re-establish cystic duct patency.

In chapter 3, the accuracy of US and OCG in assessing the number and size of gallstones was investigated. From this study it is concluded that, although both US and OCG have some limitations in assessing the number and size of gallstones, both US and OCG are suitable for selection purposes concerning this selection criterion. However, with respect to US, one has to be aware of the following restrictions:
- In case of more than one stone, US can only roughly estimate the total number of stones.
- US will mostly underestimate the size of the gallstones and detection of gallstones larger than 30 mm has proved problematic with US.

With careful attention to these selection criteria, a major part of the information that is needed for proper selection can be obtained with US at the time that the diagnosis of gallstone disease is made. The next step in the sequence of imaging modalities depends on the treatment options that remain eligible and that will be preferred.

The sequence of imaging modalities needed for proper selection for each treatment option are now discussed separately:

1 **(Laparoscopic) cholecystectomy**
US alone is sufficient. No further radiological selection is needed.
2 **Percutaneous techniques for fragmentation and removal of gallstones**
US alone is sufficient. Only in rare cases when there is doubt concerning a safe percutaneous puncture route, computed tomography (CT) will provide additional information.
3 **Oral bile acid therapy, ESWL**
Visualization of the gallbladder on OCG is mandatory for these treatments. Therefore, the next imaging modality that should be performed is OCG.
4 **Oral bile acid therapy, local contact dissolution with methyl tert-butyl ether (MTBE)**
For these treatments, one has to be informed about the chemical composition of the gallstones because only cholesterol stones will be dissolved.

OCG has limitations in discriminating between cholesterol and pigment stones. Floating gallstones at OCG is considered a specific sign for cholesterol stones [1], but is unfortunately an infrequent finding (35% of cholesterol stones [1]; 19% of radiolucent stones [2]). The classic radiographic criterion to distinguish cholesterol from pigment stones is radiolucency c.q. radiopacity on plain abdominal radiography or OCG. This criterion is unreliable and CT has proven to be more reliable in predicting gallstone composition (chapter 4). Nevertheless, the use of CT for stone characterization has not gained widespread application. Reasons for this were summarized by Brink and Ferrucci [3]: including, variable accuracy, cumbersome interpretive algorithms and high costs.

Indeed the CT defined cutoff point to discriminate between cholesterol and pigments stones varies in different studies from 50 to 140 HU. However, comparison of CT numbers from different studies without the use of a reference calibration phantom is impossible (chapter 4). Different CT systems produce different CT numbers, which is illustrated in chapter 4 and 5. In these studies CT scans were obtained with different CT systems (chapter 4: Tomoscan 350, Philips Medical Systems, Eindhoven, The Netherlands; chapter 5: Somaton CR, Siemens AG, Erlangen, Germany). For the rest, the studies described in chapter 4 and 5 have identical study designs with respect to CT and chemical analysis. The results were similar with respect to the high correlation between the mean CT numbers and the cholesterol or the calcium contents, but differed with respect to the defined cutoff point to discriminate between pure cholesterol and non-cholesterol stones (140 HU in chapter 4 vs 110 HU in chapter 5).

Besides these practical problems it is still uncertain to what extent CT is able to predict successful outcome of nonsurgical therapy. To solve this problem one has to deal with the question: which type of stones will be most amenable for a successful treatment (i.e. complete stone clearance)? It seems that the classic distinction between cholesterol stones and pigment stones is not sufficient for this purpose.

Using oral bile acid therapy, several authors [4-6] reported significant higher dissolution rates for floating stones as assessed with OCG compared to non-floating stones. Malet and co-workers [2] hypothesized that this was due to their findings that buoyancy of gallstones indicates a subset of cholesterol stones with relatively low content of calcium salts.

A comparable subset of gallstones was defined with the use of CT. Baron and co-workers [7] reported a good correlation between CT patterns and in vitro MTBE dissolution rates. Highest dissolution rates were achieved in gallstones with faint or isodense CT patterns (these patterns are comparable with detectable and nondetectable noncalcified gallstones as described in chapter 4).

In vitro studies did not shown any relationship between quantitative CT analysis or CT patterns and adequate fragmentation of gallstones by ESWL (chapter 5). Nevertheless, Ell and co-workers [8] reported in a recent study some interesting findings with respect to the utility of CT as selection tool for patients treated with ESWL and adjuvant oral bile acid therapy. In this study 111 patients with solitary radiolucent stones underwent CT examination before treatment. Based on maximum CT numbers, patients were categorized into three groups: group A, < 50 HU, group B > 50 HU and < 90 HU, group C > 90 HU. A significant higher degree of stone disintegration and stone clearance was found in gallstones of group A compared to groups B and C. Because group A represents noncalcified gallstones at CT and groups B and C represent calcified gallstones at CT, quantitative CT analysis seems not necessary to distinguish group A from groups B and C.

In conclusion, adequate treatment results of nonsurgical gallstone therapy may only be expected with a subset of cholesterol stones with low or absent contents of calcium salts. If this is the case one can formulate two criteria to select this subset of cholesterol stones:
(1) buoyancy as assessed with OCG (20% of radiolucent stones) (2) noncalcified stones on CT ($\pm$ 50% of radiolucent stones).

Finally, an imaging strategy to diagnose and select patients suspected of gallstone disease is summarized in the following flow chart (figure 9.1):

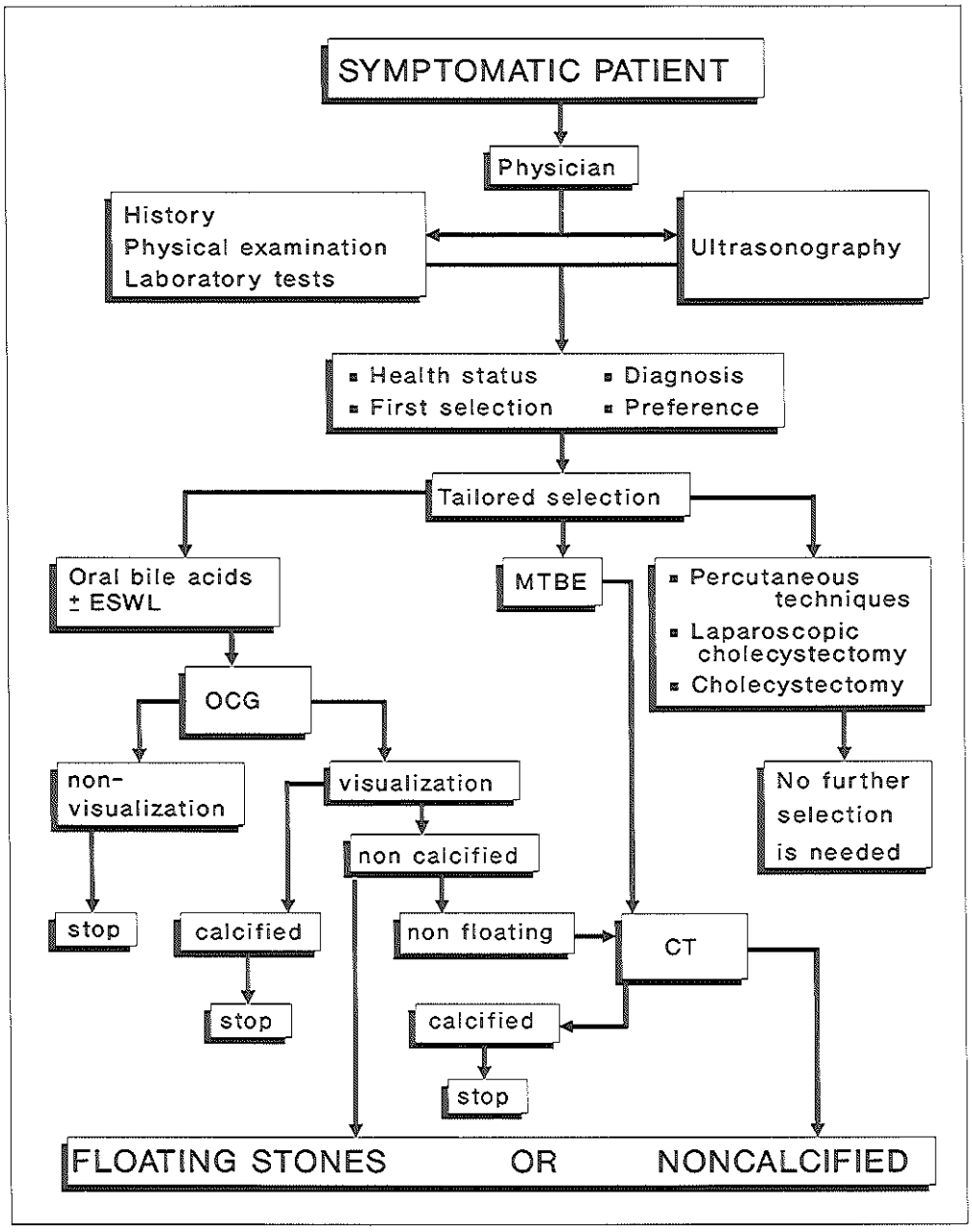

Figure 9.1 flow chart of an imaging strategy to diagnose and select patients suspected of gallstone disease

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SUMMARY

Nonsurgical therapy of gallbladder stones has fundamently changed the role of radiology in the management of gallstone disease. Aspects of this new role, both in diagnostic imaging and in interventional radiology are the subjects of this thesis.

Chapter 1 gives an outline of the currently available surgical and nonsurgical treatment modalities for the management of symptomatic gallbladder stones, and the aims of the thesis are formulated.

Chapter 2 presents the results of a study in which we attempted to establish sonographic criteria which will predict non-visualization of the gallbladder on oral cholecystography (OCG). Ultrasound (US) and OCG findings have been compared in 171 patients with symptomatic gallstones. The results show that US findings, such as a contracted gallbladder or an impacted gallstone in the cystic duct or in the gallbladder neck, are highly specific in predicting non-visualization of the gallbladder on OCG. Patients with a contracted gallbladder on US are not suitable for nonsurgical therapy of gallbladder stones. In case of an impacted gallstone, there could be a role for extra corporeal shockwave lithotripsy (ESWL) because this therapy may re-establish cystic duct patency.

Chapter 3 reports on the accuracy of US and OCG in assessing the number and size of gallstones. The results show that both US and OCG have some limitations to count and measure gallstones. Combining examinations does not improve the results. Both US and OCG are suitable for selection purposes, but one has to be aware of the following restrictions: 1) In case more than one stone is present, US can only roughly estimate the number of stones. 2) US proves more reliable than OCG in discriminating gallstones smaller or larger than 10 mm and smaller or larger than 20 mm, but with US detection of gallstones larger than 30 mm has proved problematic. 3) With both US and OCG the size of the gallstones are underestimated.

Chapters 4 & 5 are devoted to the potential role of computed tomography (CT) in the prediction of the chemical composition of gallstones.
Chapter 4 presents the results of in vitro and in vivo CT analysis of gallstones which have been compared with plain abdominal radiography or OCG. Chemical analysis of

the gallstone composition served as the standard of reference. High correlations between mean CT attenuation numbers (HU) and either cholesterol or calcium content are found in vitro as well as in vivo. Using a cutoff point of 140 HU, pure cholesterol stones (≥ 80% cholesterol) and noncholesterol stones can be discriminated far more accurately by in vitro and in vivo CT compared to plain abdominal radiography or OCG.

Chapter 5 describes a similar study design with respect to the relationship between in vitro CT characteristics and chemical gallstone composition. The CT system (Somaton CR, Siemens AG, Erlangen, Germany) differs from the one used in the study described in chapter 4 (Tomoscan 350, Philips Medical Systems, Eindhoven, The Netherlands). The results reveal similar high correlations between mean CT attenuation numbers and either cholesterol or calcium content. Only the defined cutoff point to discriminate between pure cholesterol stones and noncholesterol stones differs: from 140 HU in chapter 4 versus 110 HU in chapter 5. This illustrates that different CT systems produce different CT attenuation numbers.

The study described in chapter 5 also examines the relationship between in vitro CT characteristics and in vitro fragmentation by ESWL; no relationship was found.

Chapter 6 discusses the follow-up of patients after nonsurgical therapy of gallbladder stones. In order to establish the value of US in the follow-up of patients treated with ESWL, the results of 484 US examinations of 87 patients are analyzed and related to the results of ESWL. The reliability of US to assess stone fragmentation and/or clearance following treatment with ESWL is investigated by comparing consecutive US examinations. In 7 patients the efficacy of ESWL is overestimated by US due to incorrectly demonstrating no fragments. In 9 patients delay in retreatment with ESWL was due to underestimation of the fragment size by US. It is also found that US findings indicative for hampered stone migration, such as a contracted gallbladder or a common bile duct diameter > 7 mm, indicates poor efficacy of ESWL.

Chapter 7 gives a review of the literature of percutaneous techniques for the treatment of gallbladder stones. The technical aspects of percutaneous cholecystostomy and the possibilities and limitations of the currently available techniques for percutaneous fragmentation and removal, or direct contact dissolution of gallbladder stones, are discussed.

Chapter 8 deals with the problem of gallstone recurrence following nonsurgical therapy of gallbladder stones. This can be prevented by chemical ablation of the gallbladder by

percutaneous administration of sclerosing agents. A triple lumen balloon catheter was developed to perform gallbladder sclerotherapy with only temporary occlusion of the cystic duct, and the efficacy and safety of this method is subsequently investigated in the pig model. The balloon catheter functioned well, the procedure was safe on a short-term basis, but complete ablation of the gallbladder is not achieved. Long-term effects on remnants of undestroyed mucosa remain to be assessed.

Chapter 9 discusses the results from the studies described in the chapters 2, 3 and 4 and recent reported data within the scope of an imaging strategy for patients suspected of gallstone disease.
Finally a flow chart for an imaging strategy is presented.

SAMENVATTING

Niet chirurgische behandeling van galblaasstenen, heeft de rol van de radiologie in de diagnostiek en behandeling van galsteenziekte fundamenteel veranderd.
Aspecten van deze nieuwe rol, zowel op het gebied van de beeldvormende diagnostiek als op het gebied van de interventie radiologie zijn het onderwerp van deze studie.

Hoofdstuk 1 geeft een overzicht van de op dit moment beschikbare chirurgische en niet chirurgische behandelingsmethodes voor symptomatisch galsteenlijden. De doelstellingen van het onderzoek worden geformuleerd.

Hoofdstuk 2 geeft de resultaten weer van een studie waarin getracht is echografische criteria vast te stellen voor het voorspellen van een niet visualiseerbare galblaas op een oraal cholecystogram (OCG). Hiertoe werden bij 171 patiënten met symptomatisch galsteenlijden de echografische en OCG bevindingen met elkaar vergeleken. Echografische bevindingen zoals geschrompelde galblaas, geimpacteerde steen in de ductus cysticus of in de galblaashals, zijn specifieke tekenen die het niet zichtbaar worden van de galblaas op een OCG kunnen voorspellen. Patiënten waarbij deze tekenen worden gevonden komen niet in aanmerking voor niet chirurgische behandeling van galblaasstenen. Alleen wanneer een geimpacteerde steen aanwezig is zou behandeling met extracorporele schokgolf lithotripsie (ESWL) een gunstig resultaat kunnen hebben zodat de ductus cysticus weer normaal doorgankelijk wordt.

Hoofdstuk 3 behandelt de nauwkeurigheid waarmee echografie en OCG het aantal en de grootte van galstenen kan vaststellen. Zowel echografie als OCG kunnen het aantal stenen en de grootte daarvan slechts in beperkte mate vaststellen. Ook met beide onderzoeksmethoden samen wordt het resultaat er niet beter op. Niettemin kunnen zowel echografie als OCG worden toegepast voor selectie doeleinden, mits men zich bewust is van de volgende beperkingen: 1) Indien meer dan één steen aanwezig is, kan het aantal aanwezige galstenen slechts ruwweg geschat worden d.m.v. echografie.
2) Echografie is betrouwbaarder dan OCG in het onderscheid maken tussen galstenen kleiner of groter dan 10 mm en kleiner of groter dan 20 mm; echter, het vaststellen van galstenen groter dan 30 mm is echografisch moeilijk. 3) De ware grootte van de galstenen wordt zowel met behulp van echografie als met behulp van OCG onderschat.

De *Hoofdstukken 4 & 5* behandelen de rol van computer tomografie (CT) in het voorspellen van de chemische samenstelling van galstenen.
Hoofdstuk 4 toont de resultaten van in-vitro en in-vivo CT analyse welke wordt vergeleken met bevindingen bij het blanco buikoverzicht of het OCG. De uitkomst van de chemische analyse van de samenstelling van de galstenen diende als gouden standaard. De gemiddelde CT getallen (HU) en zowel het cholesterol- als het calcium gehalte van de galstenen zijn zowel in-vitro als in-vivo, sterk gecorreleerd. Bij een "cutoff point" van 140 HU kunnen met behulp van CT pure cholesterol stenen (> 80% cholesterol) en "noncholesterol" stenen veel nauwkeuriger van elkaar worden onderscheiden dan met behulp van het blanco buikoverzicht of het OCG.
Hoofdstuk 5 beschrijft een studie met een identieke opzet voor wat betreft de relatie tussen bevindingen bij in-vitro CT analyse en de chemische samenstelling van galstenen. De CT analyse werd in hoofdstuk 5 uitgevoerd op een Somaton Plus (Siemens AG, Erlangen, Duitsland) en in hoofdstuk 4 op een Tomoscan 350 (Philips Medical Systems, Eindhoven, Nederland). De gevonden correlaties tussen de gemiddelde CT getallen en zowel het cholesterol- als het calciumgehalte van de galstenen zijn identiek aan de gevonden correlaties in hoofdstuk 4. Alleen het "cutoff point" om onderscheid te kunnen maken tussen pure cholesterol stenen en "noncholesterol" stenen is in de studie beschreven in hoofdstuk 4 vastgesteld op 110 HU in plaats van 140 HU, zoals in de studie beschreven in hoofdstuk 5. Hiermee wordt geïllustreerd dat verschillende CT apparaten verschillende CT nummers voortbrengen.
In hoofdstuk 5 werd ook de relatie onderzocht tussen in-vitro CT analyse en in-vitro vergruis resultaten; er kon geen relatie worden aangetoond.

Hoofdstuk 6 heeft betrekking op de follow-up van patiënten die behandeld zijn met een niet chirurgische therapie voor galsteenlijden. Wij beperkten ons tot de bestudering van de waarde van echografie in de follow-up van patiënten behandeld met ESWL. Voor dit doel werden de resultaten van 484 echo onderzoeken bij 87 patiënten geanalyseerd en vergeleken met de behandelresultaten van ESWL. De betrouwbaarheid van echografie voor het vaststellen van de behandelingsresultaten van ESWL werd onderzocht door de opeenvolgende echografische onderzoeken met elkaar te vergelijken.
Op basis van deze echografische bevindingen zijn 7 patiënten ten onrechte steenvrij verklaard. Bij 9 patiënten is een noodzakelijke herbehandeling met ESWL pas later uitgevoerd omdat aanvankelijk de steenfragmenten echografisch ten onrechte te klein zijn gemeten.
Uit deze studie blijkt ook dat echografische bevindingen, zoals een geschrompelde of

samengevallen galblaas of een ductus choledochus met een diameter van meer dan 7mm een indicatie zijn voor slechtere behandelingsresultaten van ESWL.

Hoofdstuk 7 geeft een overzicht van de literatuur met betrekking tot percutane technieken voor de behandeling van galsteenlijden. Eerst worden de technische aspecten van percutane cholecystostomy beschreven. Hierna worden de mogelijkheden en beperkingen besproken van de op dit moment beschikbare technieken voor percutane vergruizing en verwijdering of oplossing van galblaasstenen.

Hoofdstuk 8 heeft betrekking op het probleem dat hernieuwde galsteenvorming na een niet chirurgische behandeling van galblaasstenen kan optreden. Een methode ter voorkoming hiervan is de chemische ablatie van de galblaas d.m.v. percutane toediening van scleroserende stoffen.
Een speciale balloncatheter werd door ons ontwikkeld om de ductus cysticus tijdens de sclerotherapie tijdelijk af te sluiten. De veiligheid en effectiviteit van de methode werd onderzocht bij varkens. De balloncatheter functioneert goed en de gevolgde methode is veilig, hoewel het niet lukte om een volledige ablatie van de galblaas tot stand te brengen. De gevolgen van het achterblijven van resten niet vernietigde galblaasmucosa op langere termijn dienen nog nader te worden bestudeerd.

Hoofdstuk 9 bespreekt de resultaten van de studies beschreven in de hoofdstukken 2,3 en 4 en recent gepubliceerde gegevens. Een radiologisch protocol ten behoeve van diagnostiek en selectie van patiënten verdacht voor galsteenlijden wordt gegeven. Tot slot wordt een stroomschema van dit protocol gepresenteerd.

EPILOOG

Dit proefschrift is tot stand gekomen in goede samenwerking tussen de afdelingen Radiodiagnostiek en Heelkunde van het Academisch Ziekenhuis Dijkzigt te Rotterdam. Een deel van de studie werd uitgevoerd op het laboratorium voor Experimentele Chirurgie van de Erasmus Universiteit te Rotterdam.

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