

Acute Cholecystitis: Delayed Surgery or Observation. A Randomized Clinical Trial

M. Vetrhus, O. Søreide, I. Nesvik & K. Søndena

Rogaland Central Hospital, Stavanger, Norway, and SMM/SINTEF UNIMED, Oslo, Norway

Vetrhus M, Søreide O, Nesvik I, Søndena K. Acute cholecystitis: delayed surgery or observation. A randomized clinical trial. *Scand J Gastroenterol* 2003;38:985–990.

Background: The aim of the present study was to compare the risk of observation versus that of cholecystectomy in acute cholecystitis in patients randomly allocated to delayed operation or conservative treatment. **Methods:** One-hundred-and-eighty patients were considered for participation in the study; 71 were excluded according to predefined criteria and 45 did not join for other reasons. The remaining 64 patients were randomized to cholecystectomy ($n = 31$) or observation ($n = 33$). Randomized patients were contacted regularly and followed up for a median of 67 months. All gallstone-related hospital contacts were registered in both randomized and excluded patients. **Results:** Gallstone-related complications or emergency admissions for pain occurred in six patients in the operation group (19%; 95% CI 5%–33%) and in 12 patients (36%; 9% CI 20%–53%) in the observation group. Twenty-seven of 31 patients randomized to cholecystectomy had a cholecystectomy at a median of 3.6 months after randomization, and, of these, 3 (11%; 95% CI 0%–23%) suffered a major and 7 (26%; 95% CI 9%–42%) a minor complication. Ten patients randomized to observation later had their gallbladders removed, 1 (10%; 95% CI 0%–29%) patient had a major and 1 (10%; 95% CI 0%–29%) a minor complication. We found no mortality after cholecystectomy. **Conclusions:** We found a certain risk of subsequent gallstone-related events following conservative treatment of acute cholecystitis, but the data also show that cholecystectomy should not necessarily be compulsory after acute cholecystitis.

Key words: Acute cholecystitis; cholecystectomy; complications; observation; randomized clinical trial

Morten Vetrhus, M.D., Rogaland Central Hospital, P.O. Box 8100, NO-4068 Stavanger, Norway (fax. +47 51519919, e-mail. mvetrhus@chello.no)

Acute cholecystitis (AC) was earlier synonymous with symptomatic gallbladder stone disease, but is today considered a separate disease entity and a complication to gallbladder stone(s). Sub-acute (generally within 72 h) or delayed cholecystectomy (within 3 months) is commonly recommended as standard treatment following AC (1).

The treatment policy of most hospitals in Norway (including the hospitals participating in this study) has been to treat patients with AC with antibiotics and subsequently a delayed cholecystectomy. Some reports have questioned whether cholecystectomy is necessary after AC, because 12%–22% of patients do not turn up for their cholecystectomy (2–4). The risk of recurrent AC may seem to increase with age and frequency of symptoms (5).

A randomized clinical trial (RCT) comparing expectant treatment with cholecystectomy has never been carried out. Such research information would provide information on the full risk of observation with regard to recurrent gallstone symptoms and complications, and whether a recurrent cholecystitis would be more harmful to the patient than a cholecystectomy. We have performed a RCT to address these questions.

Patients and Methods

Patients

Consecutive patients admitted with AC (see later) were recruited by two consultant surgeons in two hospitals from October 1991 to May 1994. The participating hospitals (Haukeland University Hospital in Bergen ($n = 38$) and Rogaland Central Hospital in Stavanger ($n = 26$)) are first-line treatment centres for defined catchments areas, and the study population was representative for patients admitted for surgical treatment.

Disease definition

AC was defined by three criteria: Acute abdominal pain, commonly in the right subcostal or midline epigastric area with a duration of more than 8–12 h and tenderness on clinical examination in the upper right quadrant were compulsory. AC was then confirmed by the presence of gallbladder stones and signs of inflammation on ultrasonography (US) and in clinical biochemistry data, including an elevated temperature.

Ultrasonography

US signs as outlined in a consensus paper supported the

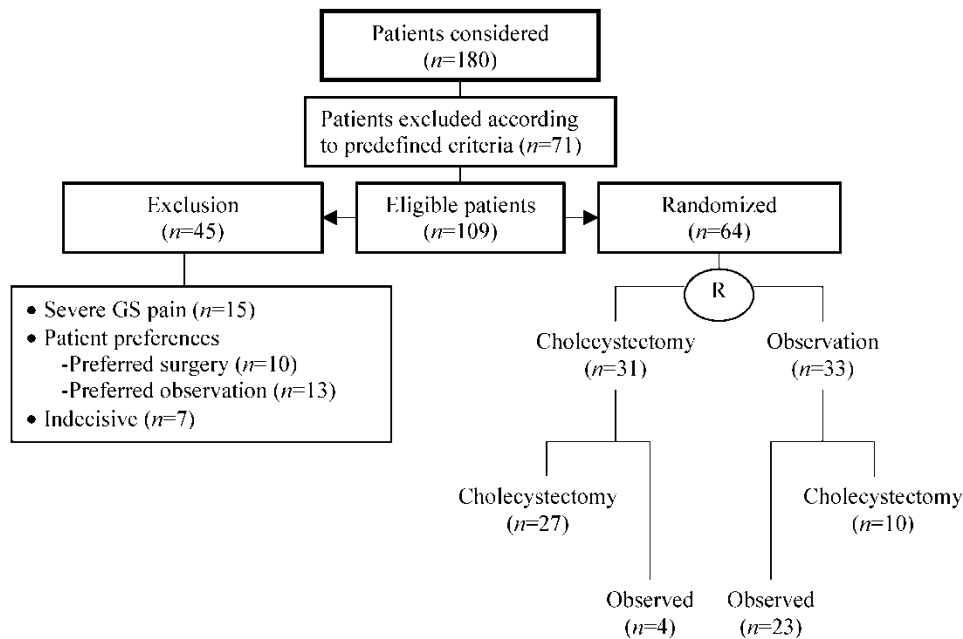


Fig. 1. Acute cholecystitis study population.

clinical diagnosis (6). Gallstones or non-visualization of the gallbladder were considered major signs, and gallbladder wall thickening (>4 mm), a positive sonographic Murphy sign, GB enlargement (>5 cm in any dimension), a round gallbladder shape or pericholecystic fluid constituted minor or supportive signs of AC.

Clinical biochemistry

An elevated C-reactive protein (CRP) and/or a white blood cell (WBC) count or a temperature exceeding 37.8 °C were signs of infection.

Patients with increased liver function tests (bilirubin, alkaline phosphatase, gamma glutamyl-transferase or alanine aminotransferase) suggestive of common bile duct (CBD) obstruction or a CBD cross-section diameter of >6 mm at US were investigated further with ERCP if appropriate.

Eligibility, randomization and ethics

After the diagnosis was established, patients were considered for the study (7). Those ($n=71$) with defined exclusion criteria (age <18 or >80 years ($n=33$), severe concomitant disease ($n=12$), suspected CBD stone ($n=5$), acalculous cholecystitis ($n=9$) or patients with localized peritonitis suggesting gallbladder perforation or gangrenous cholecystitis ($n=12$) were treated at the discretion of the attending surgeon.

Eligible patients ($n=109$) were asked to join the study. Of the 45 patients who did not join, 23 (51%) had a personal preference regarding choice of treatment. Other reasons for exclusion are given in Fig. 1. The remaining 64 patients were randomized in blocks of five using opaque, sealed and

numbered envelopes. Participation was confirmed by the patient by signing an agreement form.

Thirty-one patients were randomized to cholecystectomy and 33 to observation (Fig. 1). All patients were treated with antibiotics and best supportive care. After symptom resolution all were discharged and those randomized to operation (see later) were put on a regular waiting list and operated on as soon as capacity permitted. Those randomized to observation were given information about the nature of their disease, and were advised to avoid food, which from their experience provoked abdominal pain. Otherwise, no food restrictions were imposed.

The study was approved by the Regional Ethics Committee (Health Region 3) and the National Surveillance Bureau of Data Registries in Norway.

Follow-up

After discharge, patients were given the opportunity to contact the local study coordinator if needed, and all subsequent gallstone-related incidents were recorded. They responded to questionnaires on symptoms at the time of randomization and later at regular intervals (6, 12 and 60 months). In the case of new events of gallstone (GS) complications or symptoms of unacceptable intensity and/or frequency, the surgeon in conjunction with the patient decided further treatment (cholecystectomy). At around 60 months all patients attended a final outpatient consultation.

Excluded patients were not followed-up regularly. After a minimum follow-up period of 60 months, hospital notes were checked and relevant new events (admissions for abdominal pain, complications of GS disease, cholecystectomy, etc.)

Table I. Patient characteristics

		Randomized patients (n = 64)		Excluded patients (n = 116)	
		Cholecystectomy group (n = 31)	Observation group (n = 33)	Cholecystectomy (n = 43)	Observation (n = 73)
Women	No. of patients	17	20	25	36
	Median age (range)	58 (27–77)	47 (29–71)	67 (27–81)	79 (27–91)
Men	No. of patients	14	13	18	37
	Median age (range)	64 (41–77)	64 (29–73)	69 (36–85)	71 (17–99)

were recorded. Official population registries were consulted to record the time and cause of death for deceased patients.

Outcome

The main outcome measure was the number of patients and cumulative risk of having a cholecystectomy in each group, and the type and time of appearance of GS related complications in the two groups.

Statistics

Due to lack of background data, estimation of sample size based on assumptions on hypothesis testing and statistical power was not formally carried out. Arbitrarily, it was assumed that a minimum of 200 patients should be enrolled.

Analyses were done by reporting frequency distributions with 95% confidence intervals and cross-tabulations. The cumulative probability of having a cholecystectomy was studied using time-to-event analysis and presented as the reciprocal of the Kaplan-Meier survival analysis plot. The difference between the two groups was examined using a log-rank (Mantel-Cox) test. The Fisher exact test and Kruskal-Wallis test were used to compare the frequencies of events in the two randomized groups.

Results

Patient characteristics

Gender and age characteristics for randomized and excluded patients are given in Table I and the clinical biochemistry and US findings of randomized patients in Table II. Gallbladder stones were found in all patients. Thirty-seven of

Table II. Clinical biochemistry and ultrasonographic (US) findings in randomized patients. Median values (range) for laboratory data. No. of patients (%) with US findings

	Cholecystectomy group (n = 31)	Observation group (n = 33)
Clinical biochemistry		
Temperature (°C)	38.2 (36.5–39.3)	38.0 (36.9–40.1)
CRP (mg/L)	82 (3–317)	70 (4–376)
WBC (*10 ⁹ /L)	14.3 (8.5–30.6)	12.2 (5.8–31.2)
Ultrasound		
Gallbladder stones	31 (100%)	33 (100%)
Murphy's sign	24 (77%)	14 (42%)
GB diameter >5 cm	2 (6%)	3 (9%)
GB wall >4 mm	19 (61%)	14 (42%)

64 (58%) randomized patients were women. The AC was the debut of GS disease in 21 patients (33%), 43 patients (67%) had past symptoms (median duration 7 months) compatible with GS disease and 6 of these had had an earlier attack of acute cholecystitis. Twelve patients had concomitant heart disease, diabetes or obstructive lung disease (9 in the operation group and 3 in the observation group). No patients were lost to follow-up and the median follow-up time was 67 months (range 56–98) in the 60 patients who lived through the trial.

Outcome

Four (13%; 95% CI 1%–25%) of the patients randomized to cholecystectomy refused operation on the grounds of freedom from symptoms. In the remaining 27 patients the median time from randomization to cholecystectomy was 3.6 months (range 0.5–12.8). Ten of 33 patients (30%; 95% CI 15%–46%) randomized to observation (Fig. 1) and 43 of 116 excluded patients (37%, 95% CI 28–46%) later had their gallbladders removed.

The cumulative proportion of patients in each group (cholecystectomy versus observation) having a cholecystectomy is illustrated in Fig. 2. A log-rank test showed a significant difference in the cholecystectomy rate in the two

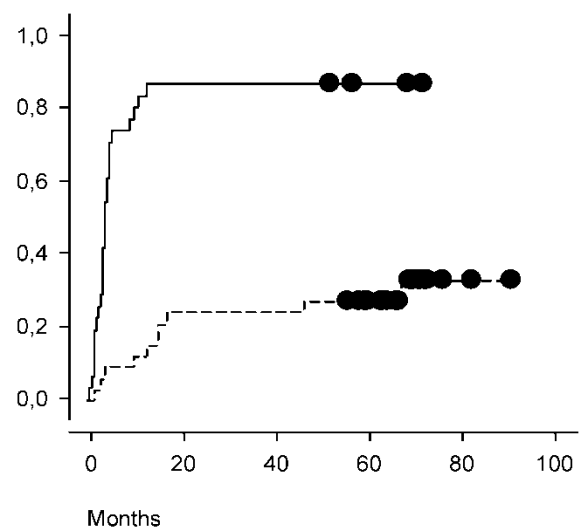


Fig. 2. Cumulative risk of having a cholecystectomy (— operation group, ---- observation group, ● censored).

Table III. Gallstone-related events after randomization; numbers in parentheses refer to late complications occurring after cholecystectomy

	Cholecystectomy group		Observation group		
	Cholecystectomy <i>n</i> = 27	Observation (withdrawal) <i>n</i> = 4	Observation only <i>n</i> = 23	Cholecystectomy (withdrawal) <i>n</i> = 10	Excluded patients <i>n</i> = 116
Admission for pain	3	–	1	3	7
Acute cholecystitis	1	–	6	3	4
CBD stone(s)	(1)	–	2	1+(1)	7+(3)
Acute pancreatitis	1	–	–	–	1

groups ($P < 0.0001$). In the observation group the cumulative proportion of patients having a cholecystectomy was 24% at 5 years (95% CI 10%–39%) and 30% at 8 years (95% CI 15%–46%). The risk increased gradually up to 1.5 years, but then appeared to taper off.

Events during follow-up

Table III gives GS-related events in randomized and excluded patients; late complications (CBD stone) were detected in 5 patients 14, 22, 23, 37 and 85 months after cholecystectomy. Emergency admissions for biliary pain occurred in 3 of 31 patients (10%; 95% CI 0%–20%) in the operation group, in 4 of 33 patients (12%; 95% CI 1%–23%) in the observation group and in 7 of 116 excluded patients (6%; 95% CI 2%–10%). Three of 31 patients (10%; 95% CI 10%–20%) in the operation group had a GS-related complication (AC, CBD stone or acute pancreatitis), while 13 GS-related complications occurred in 10 of the 33 patients (30%; 95% CI 15%–46%) in the observation group, and in 15 of 116 excluded patients (13%; 95% CI 7%–19%). No significant difference (Fisher exact test, $P = 0.13$) was found between numbers of patients with complications in the operation and observation group.

A combined total of 6 admissions for all GS-related events (pain attacks and complications) were registered in 6 of 31 patients (19%; 95% CI 5%–33%) in the operation group. Seventeen occurrences of GS-related events were found in 12 of 33 patients (36%; 95% CI 20%–53%) in the observation group, and 22 occurrences in 19 of 116 excluded patients (16%; 95% CI 10%–23%). The difference in number of patients with GS-related events in the two randomized groups was not significant (Fisher exact test, $P = 0.16$), nor with respect to number of events (Kruskal-Wallis test, $P = 0.09$). The time interval from randomization to first GS-related event in patients randomized to observation is illustrated in Fig. 3.

Operative complications

Three of 27 patients (11%; 95% CI 0%–23%) in the operation group had a major complication, including 1 patient with bile duct injury in need of biliodigestive anastomosis 2 years after laparoscopic cholecystectomy. One patient in the observation group (10%; 95% CI 0%–29%) had two major complications and five excluded patients (12%; 95% CI 2%–21%) had six major complications. Minor complications occurred in 7 (26%; 95% CI 9%–42%), 1 (10%; 95% CI

0%–29%) and 3 patients (7%; 95% CI 0%–15%), respectively. The difference in number of patients with post-operative complications in the two randomized groups was not significant (Fisher exact test: major complications, $P = 1.00$; minor complications, $P = 0.66$). Two of 43 excluded patients (5%; 95% CI 0%–11%) had to be re-operated because of bowel obstruction ($n = 1$) and a left-behind operation swab ($n = 1$).

In randomized patients, there was no mortality related to cholecystectomy or GS disease. No deaths occurred in the observation group, but 4 of 31 patients (13%; 95% CI 1%–25%) in the group allocated to cholecystectomy died of heart disease or cancer; all but one of these had had a cholecystectomy.

Forty-four of 116 excluded patients (38%; 95% CI 29%–47%) died, 2 of these during conservative treatment of AC. Two patients aged 79 and 89 were diagnosed with pulmonary embolus and myocardial infarction and both were considered high operative risk. The remaining 42 patients died of unrelated disease.

Discussion

The natural course after conservative treatment for AC has, to our knowledge, never been investigated prospectively after the introduction of modern investigative technologies (US,

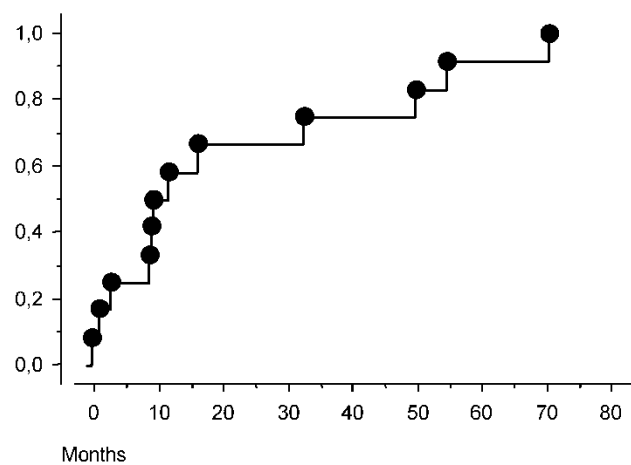


Fig. 3. The time interval from randomization to first GS-related events in patients randomized to observation.

Table IV. Complications in 80 patients undergoing cholecystectomy

	Randomized patients		Excluded patients
	Cholecystectomy group	Observation group	
No. of patients undergoing cholecystectomy	27	10	43
Laparoscopic/open /converted cholecystectomy	19/ 4/ 4	8/ 2/-	10/ 28/ 5
Complications – major			
– Intraabdominal infection / bile leakage	1	1	2
– Wound infection / dehiscence	–	–	3
– CBD stone / bile duct injury / pancreatitis	2	1	1
Complications – minor			
No. of re-operations	–	–	2

ERCP) allowing for specific categorization of GS-related disease. The existing studies were uncontrolled, mostly from the pre-ultrasonographic and ERCP era (8, 9), and generally conclude that cholecystectomy is warranted in all patients with symptomatic gallstones. The general consensus has been that 10%–15% of patients initially treated with antibiotics and scheduled for delayed cholecystectomy will have recurrent disease (4, 10). It has been argued that delayed operation carries an increased risk of complications and mortality and that cholecystectomy is warranted as soon as possible (11). Consequently, most studies have concentrated on the timing of cholecystectomy (acute, subacute or delayed) rather than on the necessity of cholecystectomy.

Even though the majority of professionals advocate cholecystectomy after AC, some studies have shown that a significant proportion of patients (12%–22%) do not show up for elective cholecystectomy (2, 3). In our material, 13% (4/31) of patients randomized to operation and 29% (13/45) of eligible, but excluded, patients favoured conservative treatment. On the other hand, only 30% of patients (10/33) in the group randomized to observation subsequently had a cholecystectomy. The corresponding percentage in another study with patients suffering from symptomatic, but uncomplicated GS disease was 50% (12). The substantial number of patients in any group that opted not to have a cholecystectomy indicates that freedom from symptoms (pain) after conservative treatment of AC is not an exception.

The frequency of all GS-related admissions for pain and complications in the group randomized to observation was 36% (95% CI 20%–53%) during follow-up. In patients allocated to operation the median time from randomization to cholecystectomy was relatively short (3.6 months). Albeit small numbers, even in these patients GS events occurred in 19% and corresponds with that of others (1, 11). Although more events occurred in the observation group, no significant difference was found between the two groups.

It is worth noting that the risk of experiencing new GS-related episodes decreased over time, thus the majority of events (>70%) occurred within 20 months after randomization (Fig. 3). Similar results have been found with regard to the development of complications in patients with sympto-

matic, uncomplicated GS (13). Others have demonstrated that the incidence of AC and subsequent complications following AC is higher in older people (14), but interestingly the median age of the randomized patients that had a GS-related complication was only 41 years (compared to a median age of 58 in all randomized patients).

Relatively few events were encountered in excluded patients (16%), although only 37% of these eventually had a cholecystectomy. One explanation may be that as many as 38% of excluded patients died during follow-up. Excluded patients and especially those who were treated conservatively had a higher median age than randomized patients (Table I), thus the median age in the excluded patients who died was relatively high (84, range 38–100).

No GS-related deaths occurred in randomized patients. Even in excluded patients the GS mortality was low, especially when considering the deaths from other causes in this group. As noted earlier, out of 100 patients (randomized and excluded) treated conservatively, only two died (95% CI 0%–5%) in conjunction with AC. Others have reported a higher mortality (15).

The trial was initiated in the infancy of laparoscopic cholecystectomy, and a substantial proportion of patients had an open cholecystectomy (34 of 80 patients). Earlier reports have shown that the symptomatic outcome is independent of laparoscopic or open technique (16). Although no operative mortality was recorded, major complications occurred in 10%–12% of patients. One patient in the group randomized to surgery had a bile duct injury that warranted reconstructive surgery. The incidence of bile duct injuries is generally reported to occur in up to 1% (17). However, the numbers in our study are too small for a meaningful evaluation of this severe complication. Two excluded patients had to be re-operated, but the re-operations were indirectly related to the cholecystectomy.

The rate of complications corresponds with what others have reported (1, 4, 18), but was higher than observed in patients having a cholecystectomy for non-complicated GS disease (19) and may reflect a technically more challenging operation. The number of patients in each group was small, but there was no significant difference in rate of operative

complications between excluded patients or either group of randomized patients.

Most patients who eventually had a cholecystectomy had a delayed operation, as this was the standard treatment in the participating hospitals. We acknowledge the prevalent evidence suggesting that subacute cholecystectomy (within 72 h of admission) might be superior to delayed surgery, as it has been shown to lead to shorter overall hospital stay, lower costs, removes the risk of recurrent AC while waiting for operation and does not lead to higher complication or conversion rates (4). However, the focus of the present study was not the question of timing of cholecystectomy, but whether cholecystectomy was required.

A substantial number of patients (39%) were excluded by predefined criteria, the main reasons being old age and complications warranting operative treatment (as outlined in results). Secondly, cholecystectomy is considered, by both patients and physicians, as the established treatment of symptomatic GS disease. Accordingly, the primary cause of exclusion in 45 of 109 eligible patients (41%) assessed for participation was patient preferences or severity of GS-related pain attacks (Fig. 1).

Eventually, 59% of eligible patients were randomized. It was stipulated that a total of 200 randomized patients was sufficient. This goal was not achieved, because fewer than anticipated of the assessed patients met the inclusion criteria. To avoid selection bias, the inclusion period was not extended beyond 30 months. The difficulties of conducting such a study have been discussed previously (7).

We conclude that there is a certain risk of subsequent GS-related events following conservative treatment of AC, but this risk seems to subside over time. Mortality in the conservatively treated patients was low and only the very ill and frail died, whereas the risk of complications after cholecystectomy was not negligible. The majority of patients in the observation group opted not to have a cholecystectomy and cholecystectomy should not necessarily be compulsory after AC. Patients should receive balanced information and their preferences taken into account and our study may offer guidance when informing patients on possible treatment options for AC.

Acknowledgements

The study was initiated while two of the authors (K.S. and O.S.) were employed at the Dept. of Surgery, Haukeland University Hospital, Bergen, Norway. We acknowledge the supportive cooperation of the staff at the participating hospitals. The study was supported financially by the Research Council of Norway, the Research Committee of Rogaland Central Hospital, the University of Bergen, Helga

Semb's Foundation and Karla and Arne Oddmar's Foundation. Some of the data in this article were presented at the IHPBA 5th World Congress, Tokyo, May 2002, and published as an abstract in the *Journal of Hepato-Biliary-Pancreatic Surgery* 2002; 9 S1: 130, abstract F-249.

References

- Lai PB, Kwong KH, Leung KL, Kwok SP, Chan AC, Chung SC, et al. Randomized trial of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Br J Surg* 1998; 85: 764-7.
- Norrby S, Herlin P, Holmin T, Sjobahl R, Tagesson C. Early or delayed cholecystectomy in acute cholecystitis? A clinical trial. *Br J Surg* 1983; 70: 163-5.
- Lindahl F, Cederqvist CS. The treatment of acute cholecystitis. *Acta Chir Scand Suppl* 1969; 396: 9-15.
- Lo CM, Liu CL, Fan ST, Lai EC, Wong J. Prospective randomized study of early versus delayed laparoscopic cholecystectomy for acute cholecystitis. *Ann Surg* 1998; 227: 461-7.
- Lyndrup S, Kristensen K. Konservativ cholecystitis behandling. *Ugeskr Læger* 1957; 119: 743-54.
- Marton KI, Doubilet P. How to image the gallbladder in suspected cholecystitis. *Ann Intern Med* 1988; 109: 722-9.
- Sondenaa K, Nesvik I, Solhaug JH, Soreide O. Randomization to surgery or observation in patients with symptomatic gallbladder stone disease. The problem of evidence-based medicine in clinical practice. *Scand J Gastroenterol* 1997; 32: 611-6.
- Wenckert A, Robertson B. The natural course of gallstone disease: 11-year review of 781 nonoperated cases. *Gastroenterology* 1966; 50: 376-81.
- Lund J. Surgical indications in cholelithiasis. *Ann Surg* 1960; 151: 153-62.
- Jarvinen HJ, Hastbacka J. Early cholecystectomy for acute cholecystitis: a prospective randomized study. *Ann Surg* 1980; 191: 501-5.
- Lahtinen J, Alhava EM, Aukee S. Acute cholecystitis treated by early and delayed surgery. A controlled clinical trial. *Scand J Gastroenterol* 1978; 13: 673-8.
- Vetrhus M, Soreide O, Solhaug JH, Nesvik I, Sondenaa K. Symptomatic, non-complicated gallbladder stone disease. Operation or observation? A randomised clinical study. *Scand J Gastroenterol* 2002; 37: 834-9.
- Friedman GD, Raviola CA, Fireman B. Prognosis of gallstones with mild or no symptoms: 25 years of follow-up in a health maintenance organization. *J Clin Epidemiol* 1989; 42: 127-36.
- Telfer S, Fenyo G, Holt PR, de Dombal FT. Acute abdominal pain in patients over 50 years of age. *Scand J Gastroenterol Suppl* 1988; 144: 47-50.
- Van der Linden W, Edlund G. Early versus delayed cholecystectomy: the effect of a change in management. *Br J Surg* 1981; 68: 753-7.
- Peterli R, Schuppisser JP, Herzog U, Ackermann C, Tondelli PE. Prevalence of postcholecystectomy symptoms: long-term outcome after open versus laparoscopic cholecystectomy. *World J Surg* 2000; 24: 1232-5.
- Mjalund O, Adamsen S, Hjelmquist B, Ovaska J, Buanes T. Cholecystectomy rates, gallstone prevalence, and handling of bile duct injuries in Scandinavia. A comparative audit. *Surg Endosc* 1998; 12: 1386-9.
- Schafer M, Krahenbuhl L, Buchler MW. Predictive factors for the type of surgery in acute cholecystitis. *Am J Surg* 2001; 182: 291-7.
- Thiele H, Lang RD. Komplikationen nach 1000 laparoskopischen Cholezystektomien. *Chirurg* 1994; 65: 795-800.

Received 15 November 2002
Accepted 9 May 2003