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PATIENT BENEFIT AND EFFECTIVENESS OF CHOLECYSTECTOMIES

Mark P. Lamberts

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PROMOTOREN

Prof. dr. J.P.H. Drenth
Prof. dr. C.J.H.M. van Laarhoven
Prof. dr. G.P. Westert

COPROMOTOR

Dr. B.L. Den Oudsten (Tilburg University)

MANUSCRIPTCOMMISSIE

Prof. dr. A. van Kampen (voorzitter)
Prof. dr. G.J. van der Wilt
Prof. dr. M.A. Boermeester (Universiteit van Amsterdam)

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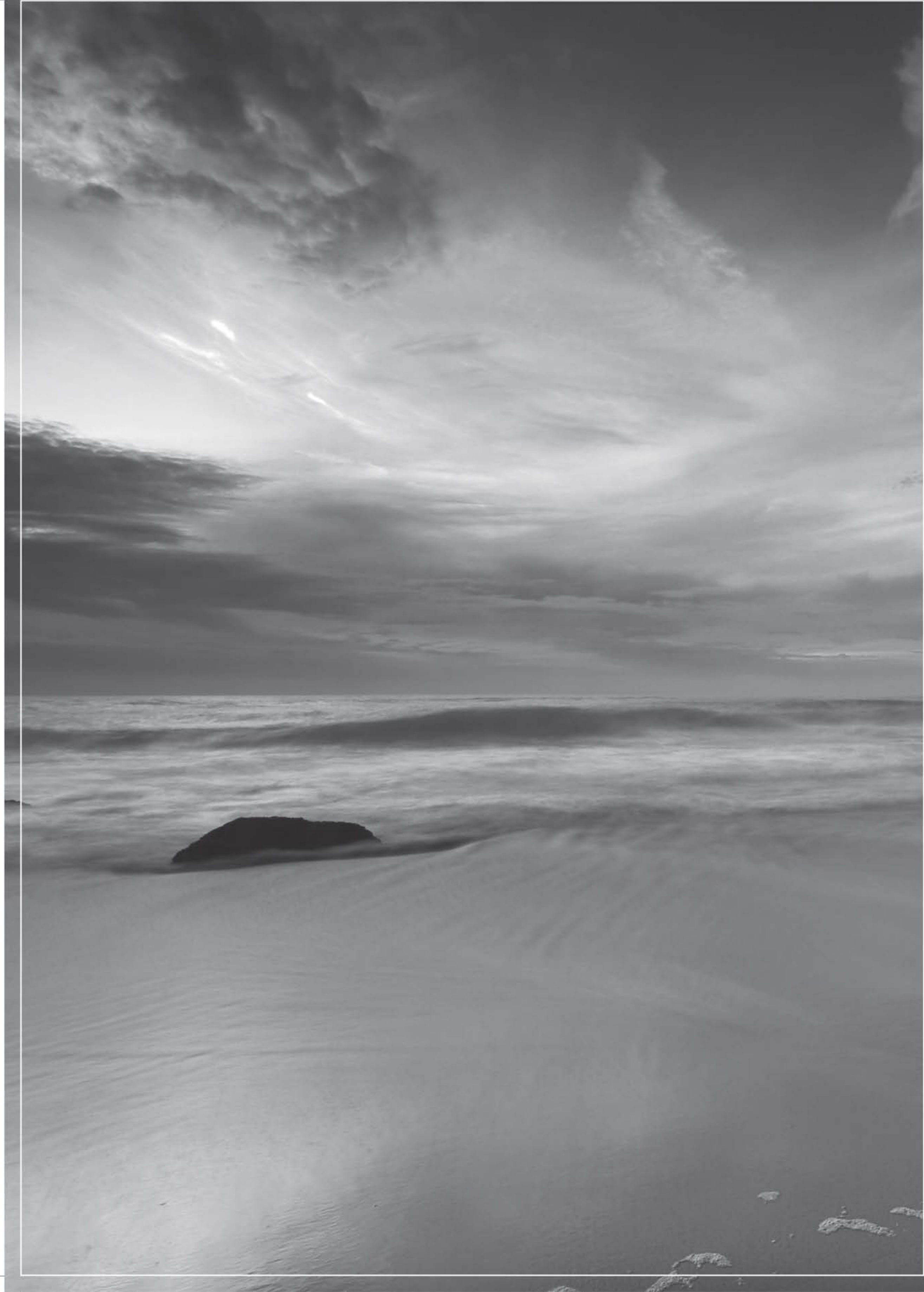
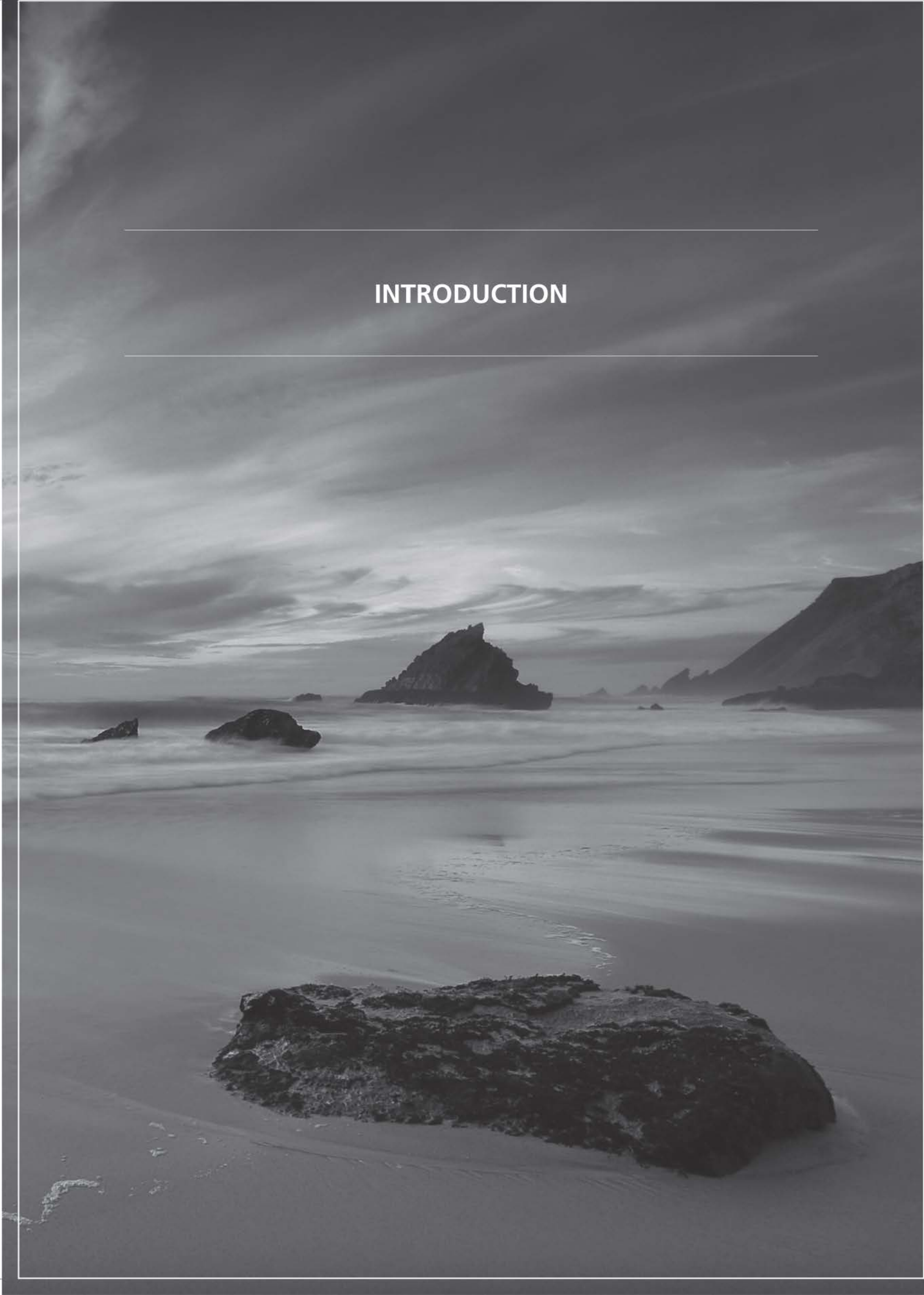




INTRODUCTION

CHAPTER 1

CHOLELITHIASIS AND VARIATIONS IN PRACTICE – AN INTRODUCTION

GALLSTONE DISEASE

Gallstone disease (cholelithiasis) is one of the most common gastroenterological disorders, associated with significant morbidity and expenses.[1] Gallstones are crystalline deposits and result from a misbalance in physical-chemical composition of bile. Approximately 37-86% of cholelithiasis patients have gallstones mainly consisting of cholesterol. Other types include pigment (2-27%) or mixed (4-16%) stones (a combination of cholesterol and pigmented stones).[2, 3] The types of gallstone vary by their cause. Risk factors for cholesterol stone formation include female gender, pregnancy, high dose estrogen treatment, increasing age, genetic susceptibility, obesity, high serum triglyceride levels, low levels of high density cholesterol, rapid weight cycling, high calorific diet, refined carbohydrate diet, lack of physical activity, cirrhosis, Crohn's disease, and ethnicity with higher prevalence in Caucasians and lower prevalence in Africans and Asians. Hemolysis and chronic bacterial or parasitic infections are considered the main risk factors for pigment stones.[4-6]

EPIDEMIOLOGY AND DIAGNOSIS

Depending on risk factors, the estimated prevalence of gallstones ranges between 5 and 22%.[6, 7] Approximately 80% of these patients remain asymptomatic during their lifetime. Annually, about 2-4% of patients with gallstones will develop symptoms.[8-10] This corresponds to 29,000 patients in the Netherlands a year, who are diagnosed with symptomatic cholelithiasis.[11] Cholelithiasis is complicated by acute calculous cholecystitis (0.3-0.4% annually),[5, 12-15] acute biliary pancreatitis (0.04-1.5% annually),[5, 15] common bile duct stones (0.1-0.4% annually),[5, 13-15] and cholangitis (0.3-1.6% annually).[16] Although the incidences are low, these complications can be serious and life threatening. Symptoms that suggest the presence of complications include fever, rigors, hypotension, dark urine, acholic stools, jaundice, or a positive Murphy's sign. Approximately 85% of patients with symptomatic gallstone disease have symptoms without signs of complications.[9] These patients mainly report biliary colicky pain, defined as severe steady pain, lasting 15-30 minutes or more, usually located in epigastrium and/or right upper quadrant,[17, 18] pain radiating to the back and a positive reaction to simple analgesics.[19] However, many patients report less specific abdominal symptoms ranging from dyspeptic symptoms to chronic abdominal pain that are often attributed to the coexisting gallstones.[20]

The diagnosis of uncomplicated symptomatic cholelithiasis is based on symptomatology and radiological detected gallstones.[20] Patients that present with symptoms suggestive of gallstones, who do not have features of complications, can be investigated with ultrasonography in an elective setting. Transabdominal ultrasonography is the first line method for detecting gallstones with a sensitivity of 84% and specificity of 99%.[21] After gallstones have been confirmed, patients can be referred to a surgeon for treatment.

TREATMENT

Conservative treatment is currently recommended for patients with asymptomatic gallstones. Only in patients with porcelain gallbladders or gallstones of > 3 cm

cholecystectomy may be considered, due to the association with gallbladder cancer.[22, 23] No evidence exists that lifestyle modifications such as decreasing fatty food intake or increasing exercise decreases or prevents the incidence of symptoms in people with asymptomatic gallstones. Surgical intervention for asymptomatic gallstones is not recommended because of potential surgery-related complications. These complications include bleeding, infection or bile duct injury.[24, 25] In addition, the majority of patients will never become symptomatic during their lifetime.[8-10] Therefore, treatment of patients with asymptomatic cholelithiasis is generally considered not to be appropriate.[26]

A treatment option for symptomatic cholelithiasis is extracorporeal shock wave lithotripsy. However, only 24% of carefully selected patients were free of stones after extracorporeal shock wave lithotripsy.[27] Another disadvantage is the high rate of recurrent gallstones: In more than 40% of patients gallstones recurred within four years.[28]

Bile acid dissolution therapy with ursodeoxycholic acid has also been suggested as treatment option for symptomatic cholelithiasis. However, only 38% of patients had dissolution of stones after treatment of ursodeoxycholic acid for more than 6 months.[29] Gallstones also often recurred and many patients remained symptomatic: Over three months, only 26% of patients remained colic free after treatment with ursodeoxycholic acid compared with 33% after placebo.[30] In addition, 2% of patients had gallstone complications after treatment with ursodeoxycholic acid, which is similar to the annual rate of complications in those not taking the drug.[31] These options are not recommended for the treatment of symptomatic cholelithiasis.[26]

A feasible option is to wait and see, especially in patients with cholelithiasis with more aspecific abdominal symptoms.[32, 33] Abdominal symptoms can be caused by a variety of alternative diseases, also in presence of ultrasound proven gallstones. Symptoms may be caused by functional dyspepsia, irritable bowel syndrome, peptic ulcer, chronic obstipation, or esophageal spasms. In these cases, the detected gallstones seem to be asymptomatic and just an incidental finding.[32-34]

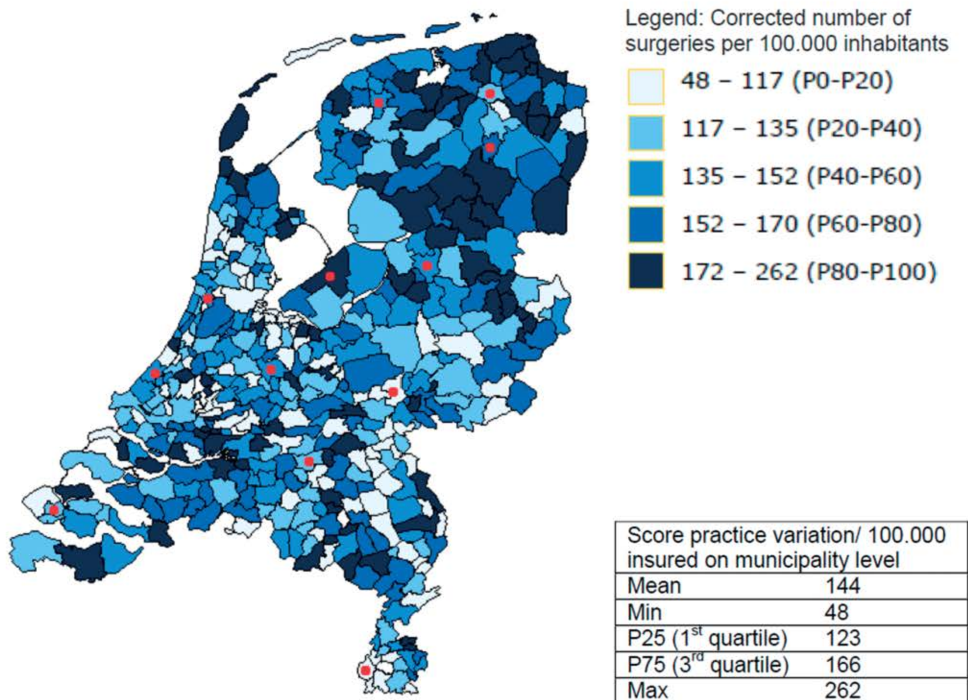
The first choice therapy for symptomatic cholelithiasis is cholecystectomy and is defined as the surgical removal of both gallbladder and gallstones. Cholecystectomy is generally performed by keyhole operation (laparoscopic cholecystectomy), because of the shorter length of hospital stay, decreased pain, earlier return to work, and better cosmesis as compared to open cholecystectomy.[24] Cholecystectomy is associated with 5.5% morbidity and 0.2% mortality.[35, 36] This surgical procedure is performed frequently with more than 22,000 cholecystectomies in the Netherlands a year.[11] The direct – hospital related – costs of cholecystectomy are approximately 55 million euro.[37] More than 60% of the total costs of employed patients are caused by indirect costs related to sick leave of employees.[38] In successful cholecystectomy, time before return to work ranges from 1 up to 10 weeks.[39] Consequently, the total costs related to cholelithiasis are many times higher than 55 million Euro.

In complicated symptomatic cholelithiasis the indication for cholecystectomy is strict, since the main aim of this procedure is to prevent recurrence of potential life-threatening complications. In uncomplicated symptomatic cholelithiasis cholecystectomy is also often

performed, mainly to cure abdominal symptoms. However, 10-40% of patients are not relieved from their symptoms, despite cholecystectomy.[40] These patients are considered to have had an unnecessary cholecystectomy with associated risks of complications and unnecessary healthcare expenses. In addition, Dutch insurance companies have noted a considerable practice variation in cholecystectomies in the Netherlands. In 2009, the number of cholecystectomies varied between 48 and 262 operations per 100,000 inhabitants among different areas, which is a fivefold difference. This remarkable discrepancy could not fully be explained by variations in patient characteristics as these data were corrected for age, gender, social economic status, and diabetes. This suggests similar patients with gallstones and abdominal symptoms receive cholecystectomy in one area, whereas treatment had been more conservative in another region. Consequently, these variations in practice are attributable to a lack of evidence and to preferences that differ by surgeon (Figure 1).[41]

PATIENT-REPORTED OUTCOME MEASURES

Patient-reported outcomes have been suggested as a tool to reduce variations in practice. Clinical outcome data that have been collected for a long time in health care have



Score practice variation/ 100.000 insured on municipality level	
Mean	144
Min	48
P25 (1st quartile)	123
P75 (3rd quartile)	166
Max	262

Figure 1. Practice variation in the number of cholecystectomies at the municipal level (number of operations per 100,000 insured) in the Netherlands in 2009. This is the municipality where the patient lives, not to municipality where the intervention took place.[41]

mainly centered on death. Other clinical indicators include infection rates, readmissions, re-operations, and adverse events. The aim of most health care services is to improve patients' health. However, routine measurement on the degree of improvement patients experience after treatment has not be initiated until quite recently. In fact, patients themselves are best able to judge how they feel. The patient's perspective of health is highly relevant for improving the quality and effectiveness of health care.[42]

Patients' viewpoints and priorities of patients may not be the same as the perspectives of their clinicians. Furthermore, there is often little correlation between symptom severity and disease severity.[43] This has led to increased interest in patient-reported outcome measures (PROMs). PROMs are important to clinicians as feedback on the care they have provided. PROMs are generally measured using generic and disease-specific standardized questionnaires, through which patients report on their symptoms, health-related quality of life, and satisfaction. The responses in addition to clinical outcome data can be used to predict which patient will benefit from a certain treatment and which patient will not.[43]

In case of patients diagnosed with symptomatic cholelithiasis PROMs can be applied to assess preoperative symptoms. Subsequently, PROMs can measure which patient has benefited from cholecystectomy and which patient did not. Eventually, these results may personalize healthcare by predicting which future type of patient with cholelithiasis will likely benefit from surgical treatment versus patients that will likely not.

MAIN AIM

Therefore, the main aim of this thesis is to assess which patients diagnosed with uncomplicated symptomatic cholelithiasis will benefit from cholecystectomy using PROMs. In addition, we aimed to evaluate a strategy to reduce the number of non-beneficial cholecystectomies and consequently unnecessary health care expenses.

THE APPROACH

In order to address the abovementioned issues we used three different study designs.

1. Systematic review with or without meta-analysis

We performed a systematic review of cohort studies to assess the effectiveness of cholecystectomy in patients with uncomplicated symptomatic cholelithiasis in terms of persistent and de novo symptoms. A systematic review with a similar aim had been performed previously. However, this review did not distinguish between persistent and de novo symptoms. Furthermore, this review was dated 2003, highlighting the need for an updated review.[44]

In addition, a systematic review with meta-analysis was performed to assess the value of esophagogastroduodenoscopy (EGD) in patients referred for cholecystectomy. Literature shows contradictory results about the value of routine EGD in patients referred for cholecystectomy highlighting the need for a systematic review and meta-analysis.[45] The advantage of this type of study method is the overview of evidence this model yields.

Furthermore, we consider this method as an ideal starting point for additional studies as reviews summarizes the available evidence.

2. Prospective cohort study

In order to assess characteristics that are associated with absence of pain after cholecystectomy, we performed a prospective cohort study with a short term follow-up as well as a cohort study with a long term follow-up. We used PROMs routinely to assess abdominal symptoms of patients that will undergo cholecystectomy. We chose to use the McGill Pain Questionnaire as disease specific PROM to measure pain characteristics,[46, 47] because the diagnosis of uncomplicated symptomatic cholelithiasis is based on abdominal pain in presence of ultrasound proven gallstones. As generic PROM we chose the Gastrointestinal Quality of life Index (GIQLI),[48, 49] because this questionnaire measures not only the broad spectrum of abdominal symptoms, but also emotional, physical and social well-being. These two questionnaires have been used separately in previous studies with cholelithiasis patients. We also used the Patient Experience of Surgery Questionnaire (PESQ) to ask patients if their abdominal symptoms had improved and how they rated the result of the cholecystectomy.[50, 51] Since the abdominal pain associated with gallstones frequently appears in episodes we also performed a cohort study with a long term follow-up. A short follow-up study may lead to beneficial cholecystectomies initially, but these may be not beneficial had the follow-up been longer. We asked patients to complete paper-based PROM questionnaires. The advantage of using paper-based questionnaires is that respondents can complete the questionnaire at a moment they prefer. Furthermore, both younger as well as older patients know how to complete such a questionnaire. The disadvantage is that respondents can skip questions or provide answers that are not readable, leading to incomplete questionnaires. Although these disadvantages are absent with internet based surveys, this type of questionnaire may be more prone to selection bias as a subset of the general population is unable to use the internet properly.[52, 53]

We have considered case-control as study model to assess our research question. However, this type of study has some disadvantages. First, selective reporting will bias the results. Second, this model would have been a challenge for logistical reasons to ascertain patients with postoperative pain. Therefore, we considered a prospective cohort study the best design for addressing our study aim.

3. Decision analytic modelling

A decision analytic model was performed to evaluate the cost-effectiveness of a strategy, based on predictors of postoperative absence of pain, to select patients for cholecystectomy versus the usual care strategy with variations in cholecystectomy indication. Decision analytic modeling compares the expected costs and consequences of decision options by synthesizing information from multiple sources and applying mathematical techniques with computer software. The aim of this type of study model is to provide decision makers with the best available evidence to reach a decision.[54] For our study this would indicate to

decide whether the strategy to select patients for cholecystectomy, based on predictors of postoperative absence of pain, should be adopted.

Economic evaluations can also be conducted alongside randomized controlled trials, providing researchers with individual patient data to estimate cost-effectiveness. However, randomized controlled trials do not always provide a sufficient basis for economic evaluations used to inform regulatory and reimbursement decisions. A single trial might not compare all the available options, provide evidence on all relevant input, or be conducted over sufficient time to capture differences in economic outcomes. Furthermore, reliance on a single trial may indicate ignoring evidence from other trials, meta-analysis and observational studies. Finally, an initial trial might be challenging to conduct randomizing patients between strategies. Under these circumstances, decision analytic modeling provides an alternative framework for economic evaluation.[54]

OUTLINE

The background and framework for the thesis is described in **Chapter 1**. In **Chapter 2** we systematically reviewed the effectiveness of elective cholecystectomy for patients with cholecystolithiasis in terms of persistent and de novo symptoms. **Chapter 3** describes a perspective on how to reduce variation in clinical practice using outcomes reported by patients. In **Chapter 4** we used PROMs to assess the association of preoperative pain characteristics with absence of pain after cholecystectomy in a Dutch multicenter prospective cohort study. Since abdominal symptoms associated with gallstones often occur in episodes, we also assessed which characteristics were associated with absence of pain and patient-reported success of surgery after at least 5 years of follow-up in **Chapter 5**. The easy access to ultrasonography and the overlap between symptomatology of cholelithiasis with other upper gastrointestinal diseases may be the reason for the low threshold towards cholecystectomy. Gastritis, esophagitis, or peptic ulcer might be alternative diagnoses for these abdominal complaints and these diseases can be easily diagnosed with EGD. In addition, literature on the value of routine EGD in patients referred for cholecystectomy is conflicting, highlighting the need for a systematic review and meta-analysis. We present these results in **Chapter 6**. In **Chapter 7** we used decision analytic modelling to evaluate the cost-effectiveness of a new diagnostic strategy to reduce the number of non-beneficial cholecystectomies. Research should not only further explore which patients will benefit from cholecystectomy, but also which patients will benefit most. In **Chapter 8** we aimed to assess the associations of frequency, maximum duration and intensity of abdominal pain episodes with improvement of health status in order to define the population with uncomplicated symptomatic cholecystolithiasis that benefit most from cholecystectomy. In addition to these studies we assessed the best evidence for management of cholelithiasis. The last Dutch guideline on management of cholelithiasis stems from 2007. **Chapter 9** describes the most recent developments on diagnosis and treatment of cholelithiasis of the 2007 revised Dutch guideline. Finally, we completed the thesis by a general discussion and future perspectives in **Chapter 10**. This chapter summarizes the results and offers suggestions for further reducing practice variations in management of cholelithiasis.

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CHAPTER 2

PERSISTENT AND DE NOVO SYMPTOMS AFTER CHOLECYSTECTOMY: A SYSTEMATIC REVIEW OF CHOLECYSTECTOMY EFFECTIVENESS

Mark P. Lamberts[1,2,5],
Marjolein Lugtenberg[2],
Maroeska M. Rovers[3],
Jan A. Roukema[4],
Joost P. H. Drenth[1],
Gert P. Westert[2],
Cornelis J. H. M. van Laarhoven[5]

[1]Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, the Netherlands
[2]Scientific Institute for Quality of Healthcare (IQ healthcare), Radboud University Medical Centre, Nijmegen, the Netherlands
[3]Department of Operating rooms and Epidemiology, biostatistics and HTA, Radboud University Medical Centre, Nijmegen, The Netherlands
[4]Department of Surgery, St. Elisabeth Hospital, Tilburg, The Netherlands
[5]Department of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands

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ABSTRACT

Background

Cholecystectomy is the preferred treatment option for symptomatic gallstones, but the exact relationship between cholecystectomies and symptoms still is unclear. This study aimed to assess the effectiveness of elective cholecystectomy for patients with cholecystolithiasis in terms of both persistent and de novo symptoms.

Methods

A systematic literature search was conducted in Pubmed and Embase. The search included studies comprising patients 18 years of age or older undergoing elective cholecystectomy for symptomatic cholecystolithiasis. The proportions of symptoms after cholecystectomy were calculated and then subdivided into persistent and de novo symptoms.

Results

A total of 38 studies reported the presence of postcholecystectomy symptoms. The results showed that upper abdominal pain, the main indication for cholecystectomy in the majority of the patients, mostly disappeared after surgery. However, it persisted in up to 33% of the patients and arose de novo in up to 14%. Diarrhea (85%) and constipation (76%) were the persistent symptoms most often reported, whereas upper abdominal pain and vomiting were the least often reported. Flatulence (62%) was the most often reported new symptom. However, we found large variations in symptoms between studies.

Conclusions

The review indicates that cholecystectomy often is ineffective with regard to persistent and de novo symptoms. The finding that the types and proportions of persistent symptoms differ from those that arise de novo suggests that this distinction may be useful in predicting which patients would and which would not benefit from a cholecystectomy.

BACKGROUND

About 5-22% of the adult Western population have gallstones.[1, 2] Only 13-22% of these patients with gallstones become symptomatic during their lifetime.[3, 4] Cholecystectomy currently is the preferred treatment option for symptomatic cholecystolithiasis.[5] Annually, more than 800,000 cholecystectomies are performed in the United States, and the associated costs are estimated to be more than $6 billion.[1, 6]

Despite the high number of cholecystectomies performed worldwide, this approach appears to be ineffective in up to 50% of patients.[7] Symptoms may persist or arise de novo after cholecystectomy.[8, 9]

The first challenge in evaluating patients with upper abdominal symptoms found to have gallstones is to determine whether the stones are the cause of the symptoms or merely an incidental finding.[10, 11] The second challenge is to identify symptoms after cholecystectomy that may have arisen de novo. Regardless whether the preoperative symptoms have disappeared, new symptoms may arise as a result of the surgical procedure.[12] To reduce the number of patients with persistent or new symptoms, more evidence of the exact relationship between cholecystectomies and symptoms is needed.

The effect of elective cholecystectomy on abdominal symptoms has been evaluated in a previously conducted review in this journal.[13] However, this review did not distinguish between persistent and de novo symptoms. Moreover, because this review was dated 2003, new evidence may be available, highlighting the need for an updated review.

This study therefore aimed to systematically assess the effectiveness of elective cholecystectomy for patients with symptomatic cholecystolithiasis in terms of both persistent and de novo symptoms.

MATERIALS AND METHODS

Literature search

A systematic literature search was conducted in the electronic databases Pubmed (January 1968-November 2011) and Embase (1980-November 2011) using several combinations of keywords, as shown in Table 1. The preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist was followed for all the steps reported in this review.[14]

Selection of studies

Two reviewers (M.P.L. and M.L.) independently screened the titles and abstracts of the articles and selected potentially relevant articles. They included studies assessing the effectiveness of elective cholecystectomy for patients 18 years of age or older with symptomatic cholecystolithiasis. Studies that contained patients subjected to acute cholecystectomy and patients with symptomatic gallstone disease undergoing elective cholecystectectomy also were included. Symptomatic gallstone disease was defined as the presence of one or more stones in the gallbladder confirmed by transabdominal ultrasonography and symptoms attributable to them.

Table 1. The search strategy

Search (7 Nov 2011)	Hits Pubmed (1968-2011)	Hits Embase (1980-2011)
No. Request		
Cholelithiasis	32,846	25,290
Cholelithiases	32,848	10
Stone	75,938	62,452
Stones	20,637	24,400
Gallstone	18,161	16,381
Gallstones	34,781	8,272
Cholecystolithiasis	9,092	830
Calculi	47,762	14,361
#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	104,206	104,648
Cholecystectomy	28,065	33,831
Cholecystectomies	28,304	2,036
#10 OR #12	28,304	33,998
Persistent[a]	282,968	315,050
Improved[a]	1,139,701	1,346,906
Reduced[a]	1,910,761	2,271,662
Remaining[a]	918,230	1,025,979
Relieved[a]	35,807	41,680
Relief	59,457	68,418
#13 OR #14 OR #15 OR #16 OR #17 OR #18	3,705,623	4,273,680
#9 AND #12 AND #19	2,574	3,151

[a] To include all conjugations the search terms (Persist*), (Improv*), (Reduc*), (remain*), and (Reliev*) were used
1-20: Subparts of the search strategy including different (combinations of) keywords

The two reviewers further selected the articles according to the following exclusion criteria. They excluded all studies other than (retrospective and prospective) cohorts or randomized controlled trials; studies that comprised only patients with systemic chronic diseases such as AIDS, liver cirrhosis, cystic fibrosis, sickle cell disease because the postoperative symptoms in these patients may be significant as a cause of the underlying systemic disease; and studies in which the results precluded a comparison between pre- and post-operative symptoms.

In addition, the reviewers consulted the reference lists of all articles retrieved for more detailed information. Discrepancies were resolved by discussion and consensus. If disagreement persisted, a third reviewer (M.M.R.) was available to make the final decision.

Data extraction

Data from each article regarding characteristics of the studies, participants, intervention, and symptoms were extracted by one reviewer (M.P.L.) and verified by a second reviewer (M.L.).The study characteristics included the authors, year of publication, country, study design, number of centers, length of the follow-up period, and method used to measure

the symptoms postoperatively. The intervention characteristics comprised the type and kind of intervention, intraoperative cholangiography, complications, and number of conversions. The patient characteristics included the inclusion and exclusion criteria used, the number of patients followed up and the losses to follow-up evaluation, mean age, and proportion of women. Symptoms comprised pre- and postoperative symptoms (upper abdominal pain, vomiting, nausea, dyspepsia, food intolerance, fat intolerance, heartburn, bloating, flatulence, constipation, diarrhea, belching, loss of appetite and, acid regurgitation), subdivided whenever possible into persistent and de novo symptoms. Discrepancies were resolved by discussion and consensus.

Methodologic quality

The methodologic quality of the eligible studies was assessed by one reviewer (M.P.L.) and checked by a second reviewer (M.L.) using the strengthening the reporting of observational studies in epidemiology (STROBE) checklist.[15] Four items considered the most relevant for assessing the methodologic quality of the studies included in this review were selected:

The design of the study preferably had to consist of a prospective cohort.

The eligibility criteria and methods used for participant selection had to be described.

The methods of assessment of pre- and postoperative symptoms had to be described and validated or based on validated measurements.

The numbers and reasons for loss to follow-up evaluation had to be addressed. If no dropouts occurred, this had to be described as well.

Data synthesis and analysis

The proportions of total postoperative symptoms and the proportion of persistent and de novo symptoms were calculated, separately. The proportion of symptoms after cholecystectomy was defined as the proportion of patients exhibiting the symptom postoperatively divided by the proportion of patients with the symptom preoperatively. The proportion of persistent symptoms was defined as the proportion of patients exhibiting the symptom before and after surgery divided by the proportion of patients with the symptom preoperatively. The proportion of symptoms de novo was defined as the proportion of patients exhibiting the symptom after but not before surgery divided by the proportion of patients with the symptom preoperatively.

A sensitivity analysis of the following quality criteria was performed:

- Retrospective cohort studies were compared with studies that had a prospective design.

- Studies using a nonvalidated measurement tool were compared with studies that used a validated instrument.

In addition, we performed the following subgroup analysis regarding the type of surgery:

- Studies that included only patients with an elective cholecystectomy were compared with studies that evaluated both patients who had emergency surgery and those who underwent elective cholecystectomy.

- Studies that included patients with a laparoscopic intervention were compared with studies that evaluated patients with an open cholecystectomy.

RESULTS

Selected studies

The initial search yielded 5,725 articles. After removal of duplicates and studies in other languages than English or Dutch, and after applying the first eligibility screening, the full texts of 83 articles were screened. After application of the exclusion criteria, 51 of the 83 studies were excluded. An additional nine publications were identified from the reference lists. If the study results were described in more than one article, they were considered as one study. This was the case with two articles describing the long-term results of three conducted trials.[16-20] Thus, 38 studies (described in 41 articles) were included in this review, as shown in Fig. 1.

Characteristics of the studies

The main characteristics of the included studies, participants, and interventions are shown in Table 2. The length of follow-up was at least 6 months for 32 and at least 1 year for 24 studies. In 26 studies, self-administered questionnaires were used postoperatively. Two studies included more than 1,000 patients. Laparoscopic cholecystectomy was performed in 23 studies.

Quality assessment

Nine (24%) of the included cohort studies had a retrospective study design.[21-29] The methods of participant selection were poorly or not reported in 11 studies (29%).[7, 9, 23, 30-37] One study (3%) lacked an assessment description of pre- and post-operative symptom measurement,[34] and in four studies (11%), the measurement was validated or based on validated measurements.[8, 25, 30, 38] The number of patients lost to follow-up evaluation and the reasons for these losses were not reported in 13 studies (34%).[21, 24, 26, 32, 34, 35, 37-43] All four methodologic quality criteria were fulfilled in 1 (3%) of the 38 studies.[8]

Proportion of symptoms after cholecystectomy

As shown in Fig. 2, the proportions of symptoms after cholecystectomy varied greatly across symptoms and across studies. The most reported postoperative symptom was

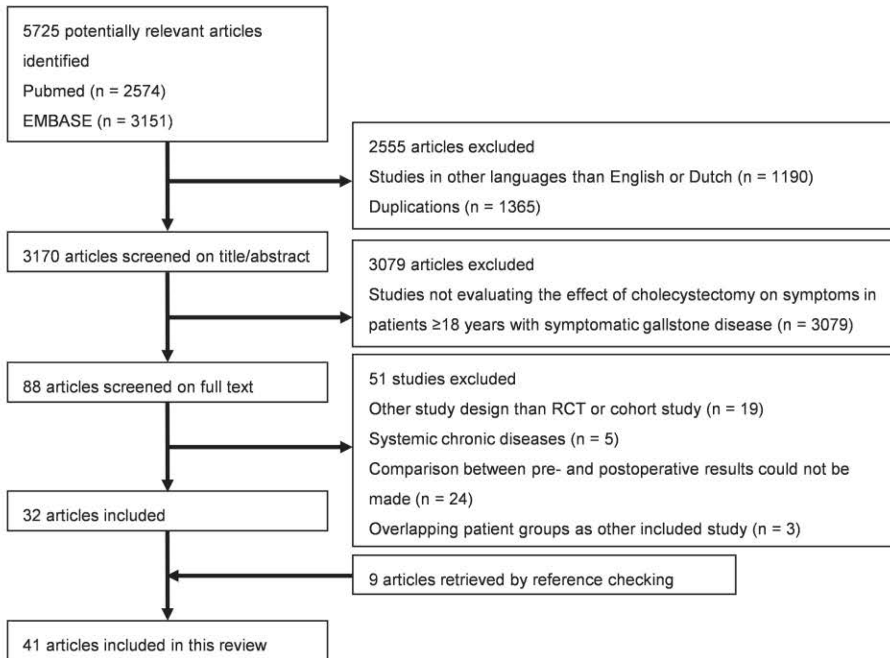

Figure 1. Selection of the studies.

Table 2. Main characteristics of the included studies

Reference	Year	Study design	Included patients (n)	Measurement postoperative	Follow-up (months)[a]	Intervention
Southam[37]	1968	Pros	12	Nonstructured interview	NR	Open
Bouchier et al.[32]	1968	Pros	17	Nonstructured interview	(6-24)	Open
Rhind & Watson[27]	1968	Retro	66	Interview	12	Open
Johnson[24]	1971	Retro	108	Interview or postal questionnaire	Mean 14.6 (3-42)	Open
Gunn & Keddie[58]	1972	Pros	107	Interview	(12-24)	Open
Kingston & Windsor[35]	1975	Pros	100	Interview	Mean 13 (3-36)	Open
Feretis et al.[34]	1983	Pros	47	NR	(3-6)	Open
Ros & Zambon[7]	1987	Pros	93	Questionnaire & interview	24	Open
Gillil& & Traverso[22]	1990	Retro	525	Medical records, questionnaire, long-term follow-up study was obtained by mail or telephone	Mean 45 (15-79)	Open

Table 2. (continued)

Reference	Year	Study design	Included patients (n)	Measurement postoperative	Follow-up (months)[a]	Intervention
Bates et al.[51]	1991	Pros	274	SCQ	12 & 24	Open
Jørgensen et al.[59]	1991	Pros	115	Interview	(6-12)	Open
Vander Velpen et al.[28]	1993	Retro	56 open; 68 LC	SCQ	Open: Median 14 (6-29); LC 9 (6-30)	Open & LC
Scriven et al.[36]	1993	Pros	75	SCQ	12	Open
Qureshi et al.[26]	1993	Retro	100	SCQ	Median 12 (10-19)	LC
Plaisier et al.[60]	1993	Pros	26	Pain diaries, SCQ	(0-3) & (3-6) & (6-12) & (12-18)	Open & LC
Black et al.[31]	1994	Pros	486	SCQ	1.5	Open
Ure et al.[61]	1995	Pros	468	SCQ	Mean 19 (350-988 days)	LC 4-trocar
Abu Farsakh et al.[39]	1995	Pros	30	Interview	(3-9)	NR
Fenster et al.[33]	1995	Pros	188	Physician-derived questionnaire, patient-derived questionnaire	3	LC
Luman et al.[44]	1996	Pros	97	St&ard questionnaire, outpatient review, or telephone interview	Median 7 (6-10)	LC
Gui et al.[23]	1998	Retro	92	Structured interview	Mean 31.1 (12-83)	Open & LC
Victorzon et al.[29]	1999	Retro	261	SCQ	Median 24 (6-NR)	LC 4-trocar
Borly et al.[62]	1999	Pros	80	SCQ	12	LC, SIC & CO
Weinert et al.[9]	2000	Pros	2,481	SCQ	6	Open & LC
Traverso et al.[63]	2000	Pros	691	Patient- & physician-derived questionnaires	Mean 3	LC & CO
Ahmed et al.[16,17]	2000	Pros	57	Questionnaire	Mean 60	Open
Niranjan et al.[45]	2000	Pros	111	Interview	1.5 & 3 & 12	LC 4-trocar
Mjaland et al.[42]	2000	Pros	487	Interview & questionnaire	3 & 36	LC & CO
Burney & Jones[40]	2002	Pros	140	SCQ	2 & 6	LC
Lublin et al.[25]	2004	Retro	573	Validated SCQ	Mean 48 (6-86)	LC
Vetrhus et al.[18-20]	2005	Pros	124	Structured interview	Mean 61	LC & CO
Finan et al.[8]	2006	Pros	55	Validated SCQ	Mean 17.1 (2-32)	LC & CO
Vignolo et al.[43]	2008	Pros	29	SCQ	6	LC
Bitzer et al.[30]	2008	Pros	130	Validated SCQ	0.5 & 6	LC & CO

Table 2. (continued)

Reference	Year	Study design	Included patients (n)	Measurement postoperative	Follow-up (months)[a]	Intervention
Halldestam et al.[41]	2008	Pros	200	SCQ	3 & 12	LC & CO
Mertens et al.[64]	2009	Pros	126	SCQ	(1.5-2.5)	LC 3-trocar & CO
Amir[21]	2009	Retro	200	Interview using predesigned performa	1 & 3 & 6	LC & SIC
Thistle et al.[38]	2011	Pros	1,008	Validated SCQ	3 & 12	Open, LC & SIC

Pros prospective, *NR* not reported, *Retro* retrospective, *SCQ* self-completed questionnaire, *LC* laparoscopic cholecystectomy, *SIC* small-incision cholecystectomy, *CO* converted open cholecystectomy,
[a] Values in parentheses are ranges.

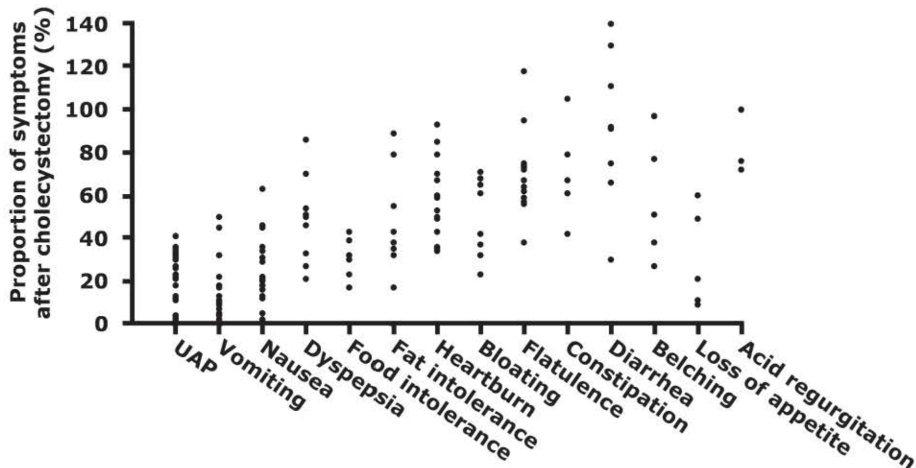

Figure 2. Proportion of symptoms after cholecystectomy as reported in the studies. Each dot represents the estimate of the symptom proportion as reported in one article. A proportion of more than 100% means that more patients exhibit the symptom postoperatively than preoperatively. References of the included studies: Upper abdominal pain, UAP [7, 8, 16, 18, 21-23, 26, 27, 29-34, 36, 38, 39, 41, 42, 44, 45, 51, 58-64]; vomiting [8, 9, 21, 23, 25, 26, 28, 29, 31, 39-41, 44, 45, 51, 61, 64]; nausea [8, 9, 21, 23, 25, 26, 28-31, 36, 39-41, 44, 45, 51, 60, 61, 64]; dyspepsia [7, 21, 23, 24, 26, 27, 35, 39, 43]; food intolerance [9, 25, 26, 29, 40, 41, 44, 61]; fat intolerance [8, 21, 23, 25, 28, 30, 36, 39, 60]; heartburn [9, 21, 23, 25, 28, 29, 37, 39-41, 44, 45, 58, 64]; bloating [8, 23, 26, 30, 36, 41, 44, 51, 60]; flatulence [8, 9, 21, 23, 26, 28, 30, 31, 40, 41, 45, 51, 61, 64]; constipation [8, 23, 29, 41, 44]; diarrhea [8, 23, 25, 29, 40, 41, 44, 64]; belching [8, 9, 36, 40, 45]; loss of appetite [8, 30, 36, 44, 61]; acid regurgitation [8, 41, 45]

diarrhea. The postcholecystectomy proportions of diarrhea, constipation, and flatulence exceeded 100%,[8, 25, 44] indicating that more patients experienced these symptoms postoperatively than preoperatively. One study[45] demonstrated that cholecystectomy did not resolve acid regurgitation as the proportion of patients reporting this symptom did

not change with surgery. Upper abdominal pain, vomiting, nausea, food intolerance, and loss of appetite showed the lowest postoperative proportions.

Diarrhea showed the largest variation between studies (30-140%), whereas food intolerance varied the least (17-43%). Upper abdominal pain, the most prevalent symptom of patients preoperatively (data not shown), demonstrated postcholecystectomy proportions ranging from 0 to 41%.

Proportion of persistent and de novo symptoms

For 11 of the 38 studies, a distinction was made between persistent and de novo symptoms. The proportions of persistent and de novo symptoms are presented in Fig. 3. The proportion of de novo symptoms was lower than that of persistent symptoms.

Diarrhea and constipation were the persistent symptoms most often reported, whereas upper abdominal pain and vomiting were the least often reported. Diarrhea

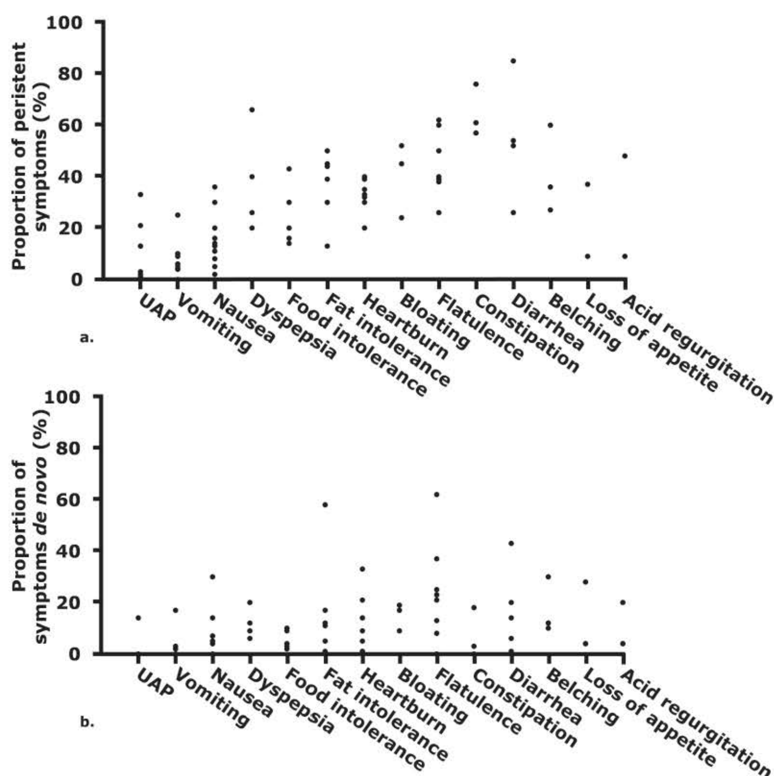

Figure 3. Persistent (**A**) and *de novo* (**B**) symptom proportions reported in 11 studies. Each dot represents the estimate of the symptom proportion reported in one article. References of the included studies: Upper abdominal pain, UAP [8, 21, 23, 26, 29, 39, 45]; vomiting [8, 9, 21, 23, 26, 28, 29, 39, 45, 61]; nausea [8, 9, 21, 23, 26, 28, 29, 39, 45, 61]; dyspepsia [21, 23, 26, 39]; food intolerance [9, 25, 26, 29, 61]; fat intolerance [8, 21, 23, 25, 28, 39]; heartburn [9, 21, 23, 25, 28, 29, 39, 45]; bloating [8, 23, 26]; flatulence [8, 9, 21, 23, 26, 28, 45, 61]; constipation [8, 23, 29]; diarrhea [8, 23, 25, 29]; belching [8, 9, 45]; loss of appetite [8, 61]; acid regurgitation [8, 45]

demonstrated the largest variation across studies (26-85%). whereas constipation varied the least (57-76%). Upper abdominal pain showed proportions ranging from 0 to 33%.

The most common de novo symptom after surgery was flatulence, whereas upper abdominal pain and vomiting only rarely ensued after cholecystectomy. There was a wide range in the proportion of patients reporting flatulence (0-62%), whereas food intolerance showed the least variation (2-10%). Upper abdominal pain demonstrated proportions ranging from 0 to 14%.

The effects of the sensitivity and subgroup analysis

The effects of the sensitivity analysis on the quality criteria and subgroup analysis regarding the type of surgery were assessed for upper abdominal pain because it is the main indication for cholecystectomy in the majority of patients. Prospective studies showed postoperative upper abdominal pain proportions ranging from 0 to 41%, whereas retrospective studies demonstrated figures varying between 2 and 38%. Studies using nonvalidated measurement tools showed proportions ranging from 0 to 41% compared with 4 to 35% in studies using validated instruments.

In addition, the proportions of upper abdominal pain in the studies that included only patients with an elective cholecystectomy ranged from 0 to 38%, whereas these proportions varied between 4 and 27% for studies that also included emergency cholecystectomies. Studies comprising either laparoscopic or open cholecystectomy showed upper abdominal pain proportions varying from 1 to 35%, and from 0 to 41%, respectively.

DISCUSSION

The review findings indicated that cholecystectomy often is ineffective with regard to persistent and de novo symptoms. Although upper abdominal pain disappeared after surgery for a large proportion of the patients, it persisted for up to 33% and arose de novo in up to 14% of the patients. The types of persistent symptoms also differed from those that arise de novo. Diarrhea (85%) and constipation (76%) were the most often reported as persistent symptoms, whereas upper abdominal pain and vomiting were described the least often. Flatulence (62%) was the de novo symptom most often reported. However, we found large variations in symptoms between studies.

The results regarding postoperative upper abdominal pain and other symptoms are consistent with those of a previous review.[13] Among the persistent symptoms, upper abdominal pain, vomiting, nausea, and food intolerance were the least likely to persist according to a large prospective cohort study,[9] which is in line with our results. These four symptoms also are the only symptoms related to gallstones according to a meta-analysis.[46]

Among the de novo symptoms, upper abdominal pain and flatulence were shown to be significantly more prevalent in surgically treated compared with non-surgically treated patients with gallstones and upper gastrointestinal symptoms in a cohort study.[47] Heartburn, regurgitation, bloating, and belching did not occur significantly more often.[47]

These results, in addition to our results of high new flatulence proportions and upper abdominal pain proportions up to 14%, indicate that surgery to cure non-pain symptoms seems improper.

Some potential limitations of our review also should be discussed. First, despite our broad search, nine of the 41 included articles were retrieved by searching reference lists. However, the majority of these articles were published in Pubmed without an abstract.

Second, most of the studies included in our review had low methodologic quality, with only one study fulfilling all four quality criteria. Our sensitivity analysis of quality criteria, however, did not show significant effects.

Third, the heterogeneity of the studies precluded a formal meta-analysis. Instead, we reported scatter plots showing the proportions of symptoms. The large variation of symptoms between studies found in our review could not be explained by the subgroup analysis regarding the type of performed surgery. However, the scattered results may have been due to large variations in regional practice.[48] These variations suggest a different diagnostic workup, a quicker referral, and a faster operative intervention in one study region and a more conservative treatment in another region. Fourth, by studying only the before and after effects, bias might have been introduced via the natural course of symptoms,[31] a placebo effect of surgery,[49] or expectancy of patients.[20, 50] However, this could not be changed due to ethical reasons.

The major strength of our review was that we differentiated between persistent and de novo postoperative symptoms. To our knowledge, we are the first making this distinction. The finding that the types and proportions of persistent symptoms differ from those that arise de novo suggests that these two entities may have different causes. Irritable bowel syndrome or gastroesophageal diseases such as peptic ulcers or gastritis can cause abdominal symptoms. These symptoms often are attributed to the presence of gallstones.[42, 51-54] On the other hand, de novo symptoms may be caused by postoperative changes in the intestinal environment.[12, 55, 56] By making this distinction, we believe we render this group of patients with postoperative symptoms less heterogeneous. This way of measuring yields significant valuable information to allow differentiation of patients with symptoms after cholecystectomy.

Future research should further explore the two aforementioned entities using patient-reported outcomes measured with standardized validated questionnaires. The use of patient-reported outcomes measures can be threefold. First, the use of standardized validated questionnaires reduces the variations in measurement and definitions of symptoms.

Second, symptom relief, as investigated in this review, is considered a patient-reported outcome critical for decision making.[57] The systematic use of patient-reported cholecystectomy outcomes in terms of quality improvement initiatives has been advocated by a previous study in this journal.[30] An accurate report of patient-reported outcomes may be important to clinicians and hospitals as feedback on the care they have provided, decreasing variations in practice.

Third, a systematic registration of patient-reported outcomes combined with demographic and clinical variables may be associated with patterns of persistent or de novo symptoms and could be useful in differentiating patients who would and would not benefit from an operation. Surgeons may use this information to inform patients about the prognosis of their symptoms and thereby create realistic expectations before a potential operation. Consequently, this could reduce the proportion of unnecessarily performed cholecystectomies as a result of better diagnostics or indications.

In conclusion, our results indicate that cholecystectomy often is ineffective because some symptoms persist and others occur de novo. This review gives a first indication that the types and proportions of persistent symptoms differ from those that arise de novo, suggesting that this distinction may be useful in predicting which patients would and would not benefit from a cholecystectomy. Future research should further explore these two entities using patient-reported outcome measures.

DISCLOSURES

Mark P. Lamberts, Marjolein Lugtenberg, Maroeska M. Rovers, Jan A. Roukema, Joost P. H. Drenth, Gert P. Westert and Cornelis J. H. M. van Laarhoven have no conflicts of interest or financial ties to disclose.

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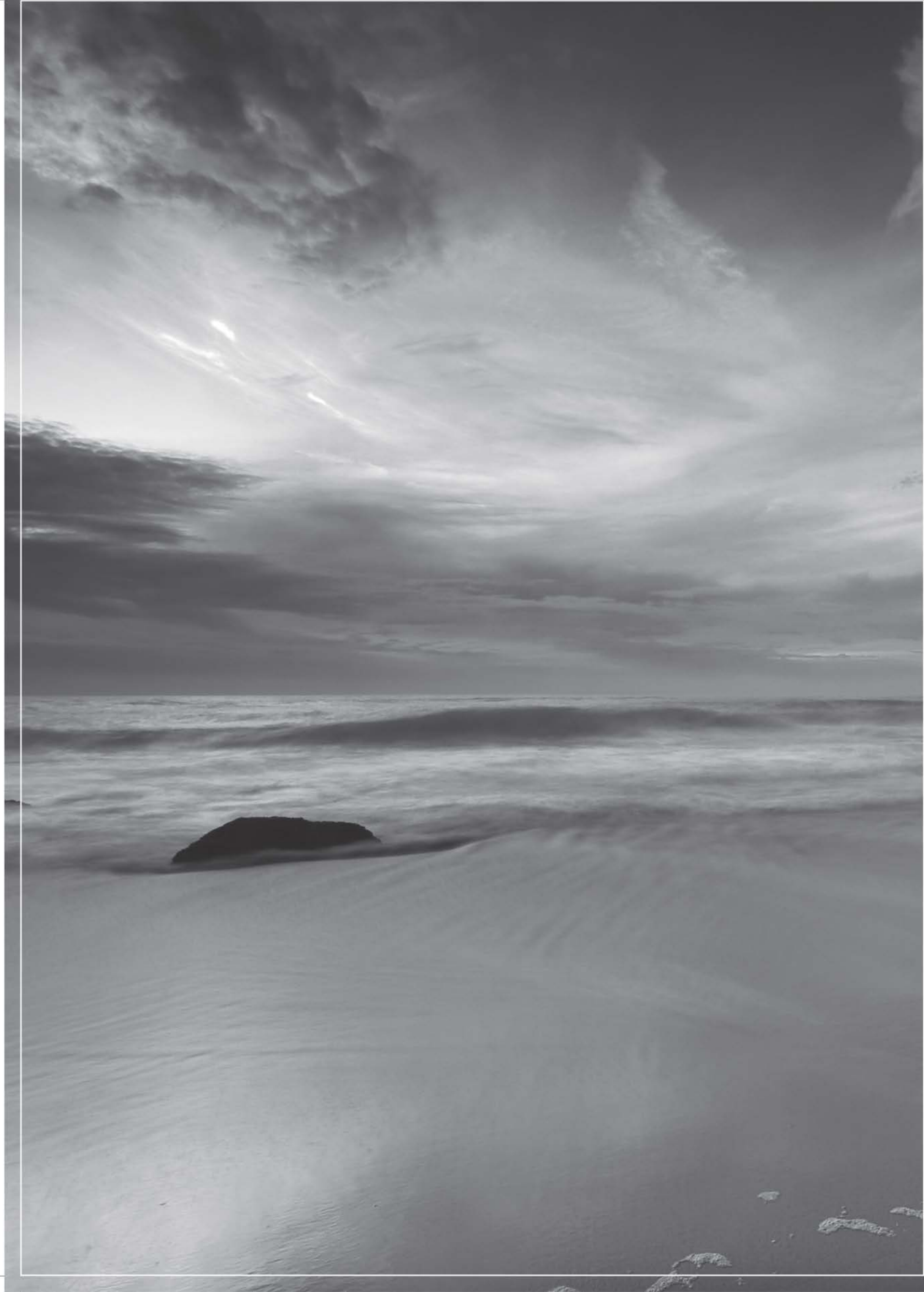

METHODS

CHAPTER 3

OUTCOME OF TREATMENT REPORTED BY PATIENTS: AN INSTRUMENT TO REDUCE VARIATIONS IN CLINICAL PRACTICE

Mark P. Lamberts[1,2,3],
Joost P.H. Drenth[1],
Cornelis J.H.M. van Laarhoven[2],
Gert P. Westert[3]

[1]Department of Gastroenterology and Hepatology, Radboud University Medical centre, Nijmegen, The Netherlands
[2]Department of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands
[3]Scientific Institute for Quality of Healthcare (IQ healthcare), Radboud University Medical Centre, Nijmegen, The Netherlands

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ABSTRACT

Medical treatment and its results varies between countries, but also between regions within countries. Because of these variations in clinical practice the quality of healthcare is suboptimal, unnecessary expenses are made and patients are at risk of complications caused by unnecessary interventions. Patient Reported Outcome Measures (PROMs) can help clarify whether patients have benefited from a certain treatment. Systematic measurement of PROMs is necessary to accurately determine therapy effects. By evaluating therapy effects and regional variations in practice, important insights will emerge of where too many and where to few patients are treated. We expect that systematic measurement of PROMs will be a valuable tool to improve the quality of Dutch healthcare.

It is relevant where you as a patient will be treated. The frequency of medical interventions and their results vary significantly between countries, but also between regions within a country. Surgery for spinal compression, secondary caesarean sections, and the prescription behavior of general practitioners are some interventions with a significant geographical practice variation.[1] Data from our country show that procedures for common diseases are sometimes conducted 2 to 5.5 more frequently in one region than in others.[2] Figure 1 shows how frequently 8 surgical procedures are performed in each region of The Netherlands when compared to the national average. In some regions these 8 procedures are performed four times less frequently than in others even when adjusted for age, gender, and socioeconomic status. Despite the differences between these 8 types of surgery a clear regional pattern can be distinguished.

Variations in practice partly exist because we as clinicians are evaluated and paid for delivering care and not, as you would expect, for the result of that care: improvement of health. Consequently, healthcare is driven by what we supply and less by what we demand: results for our patients.[3]

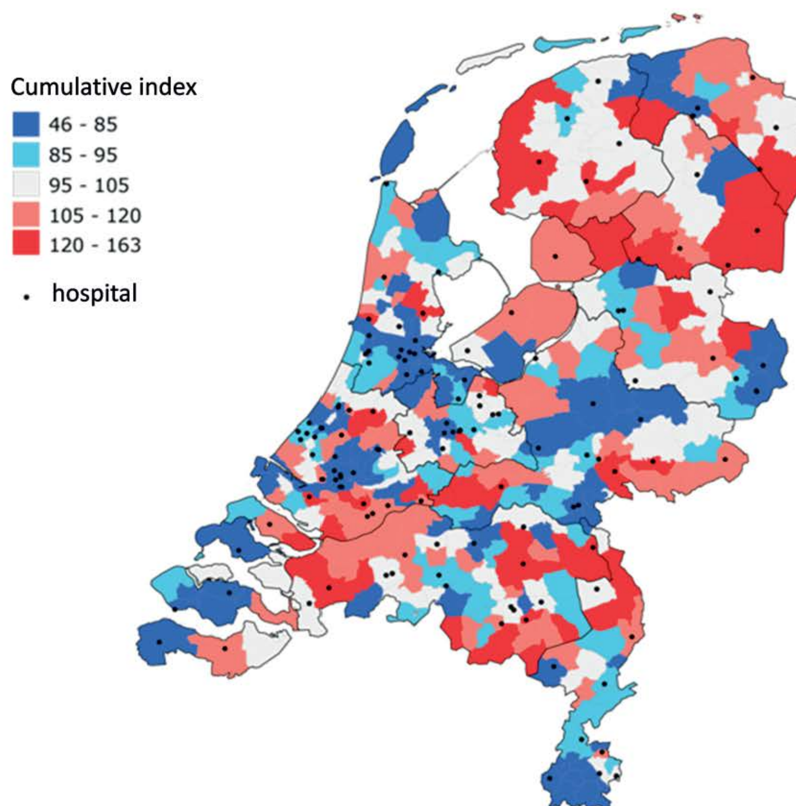

Figure 1. Regional differences in the performance of 8 common operations. Each region is represented by a cumulative index how often these 8 operations in total are performed annually per region and compared to the national average. The data are from Zorgverzekeraars Nederland and edited by PraktijkIndex and IQ healthcare.

Variation seems widest when there is limited evidence for the effectiveness of a certain treatment.[4] The question remains how to reduce these differences in our modern healthcare system. The quality of healthcare is suboptimal, unnecessary expenses are made, and patients risk complications due to unnecessary procedures, because of these variations.[5,6]

Outcomes reported by patients can help clarify whether they may benefit from a certain treatment. Internationally, patient-reported outcome measures are known as PROMs. Using PROMs we actually ask our patients to aid us in determining the result of a procedure. When it is found, for instance that few patients report significant improvement after a certain procedure, clinicians may use this information to refine the indication for this procedure.

In this contribution we argue that routine measurement of PROMs is necessary to show relevant differences in treatment effects. The combined use of differences in treatment effects and regional variations in practice, may clarify where too many and where too few surgeries are being performed. Without these outcome measurements, it is not possible answer this important question.

WHAT ARE PROMS?

The outcome of treatment is traditionally based on history, physical examination, and objective criteria, such as laboratory or radiological results. However, the perspective of patients is crucial to assess the result of a given treatment. Patients are best suited to evaluate whether their symptoms have improved and thus whether their quality of life has changed after treatment. This patient' perspective often strongly differs from the clinician's perspective. A patient may not feel effectively treated, even if the clinician deems the therapy a success.[7]

PROMs are a tool for patients to evaluate systematically whether they have benefited from a certain treatment. For this purpose, patients complete a questionnaire both before and after the intervention at fixed timepoints. The difference between the pretest and posttest shows if and how much benefit a patient has had from treatment. It is also possible to assess factors that predict outcomes for certain patients. For example, when using PROMs in combination with clinical data, it is possible to select certain subgroups in whom treatment is more effective. In short, PROMs in combination with clinical data can be used both to evaluate therapies as well as to predict outcomes.

GENERIC VERSUS CONDITION-SPECIFIC

PROMs are basically subdivided into generic and condition-specific outcome measures. Since this may sound somewhat abstract, we will give an example. Generic PROMs measure health aspects irrespective of the specific disease. For example, the generic EQ-5D questionnaire that measures quality of life can be used to compare the health of patients with arthritis of the hip and those with inguinal hernia. The disadvantage of these generic outcome measures is that questionnaires may include items that are not particularly relevant, or vice versa, lack items that are very important. A question

on the EQ-5D-questionnaire about mobility is far more relevant for patients with hip problems than for those with inguinal hernia. Generic outcome measures are therefore often combined with condition-specific PROMs. Currently, suitable questionnaires are not available for all diseases that can be evaluated using condition-specific PROMs. The development and validation of these questionnaires requires a significant effort of both clinicians and patients, as previously reported in the NTvG.[8]

REDUCTION OF INAPPROPRIATE VARIATIONS IN PRACTICE

PROMs provide the possibility to compare outcomes between healthcare facilities so that inappropriate variations in practice may be reduced. How can this be achieved? The initial step is to have patients fill out questionnaires regarding treatment. Subsequently, one must correct for patient characteristics, such as age, gender, socioeconomic status, and level of care. Finally, one can show which facilities have the best outcomes reported by patients for a certain procedure. The healthcare process can be improved and treatment policy adjusted accordingly.

PROMs can be useful to reduce inappropriate variations in practice on an international level as well. The universal nature of PROMs provide the possibility to compare outcomes of conditions not only within countries, but also between countries. The National Health Service (NHS) in Great-Brittain and the 'Patient reported outcome measurements information system' (PROMIS), initiated by the National Institutes of Health in the United States, develop and test measurement applications of PROMs in different patient groups.[9,10] Dutch healthcare should not lag behind. IQ healthcare in Nijmegen has initiated an international collaboration with NHS and PROMIS to accelerate this process by sharing international experiences and expertise.

In addition, comparisons of PROMs obtained before initial treatment provide a starting point for additional studies of decision making in healthcare facilities. For example, variations in decision making of general practitioners may impact patient referral to secondary care or patient treatment at different moments in the chain of care. Such variations have consequences for the equal access of patients to secondary care and also for the effective use of limited healthcare capacity.

PROMs should therefore be used in the context of health care expenses to achieve effective use of limited healthcare capacity. In this way, differences in cost-effectiveness between regions can be shown. For example, the results of treatment can be good, but achieved at high costs, or results may be poor and achieved at low costs. Regional cost-effectiveness can be shown this way. Additionally, these data may provide insight into the cost-effectiveness of different therapies. Clinicians, policy makers, and insurers can thus focus on quality and cost-effectiveness, and reduce variations in practice simultaneously.

THE LIMITATIONS OF PROMS

Although routine measurements of PROMs seem promising, this method does have limitations. Environmental factors bias outcome measures reported by patients. These factors partially determine how and what a patient will report. For example, a depressed patient will complete a questionnaire about spinal compression differently than patients without a depression. This can only be partially corrected.

In addition, outcomes are measured at only a limited number of time points. However, we know that the timing of outcome measurement is very important. Patients can be positive shortly after surgery, because they may be unconsciously relieved and satisfied that they survived surgery unharmed, even though symptoms may have remained. More frequent and long term measurements could limit this effect.[11]

Finally, the outcome of watchful waiting remains unknown. For example, in patients with gallstones and abdominal pain watchful waiting may be non-inferior or even better than surgery. PROMs may be used, to compare a strategy of watchful waiting with adequate analgesia to cholecystectomy.[12-14]

Currently, it is a significant challenge to improve and refine systematic measurement of patient-reported outcomes. Ideally, this should be conducted in interdisciplinary teams of statisticians, clinicians and patients. Development of questionnaires cannot succeed without the latter. Consequently, the development and application of PROMs are still a fertile research topic.

CONCLUSIONS

'Patient reported outcome measures' (PROMs) are a promising addition to existing objective indicators for quality of healthcare. A far better insight into outcomes of healthcare may be achieved by systematic measurement of the degree of health. Thus, it may become possible to choose the optimal care process, and reduce variations in clinical practice. Although PROMs do have limitations, they may provide a better insight of the patients' perspective on therapy results. We believe PROMs will be a valuable tool to improve the quality of Dutch healthcare.

DISCLOSURES

Conflicts of interest and financial support: a form with the authors' conflicts of interest has been attached to this article at www.ntvg.nl

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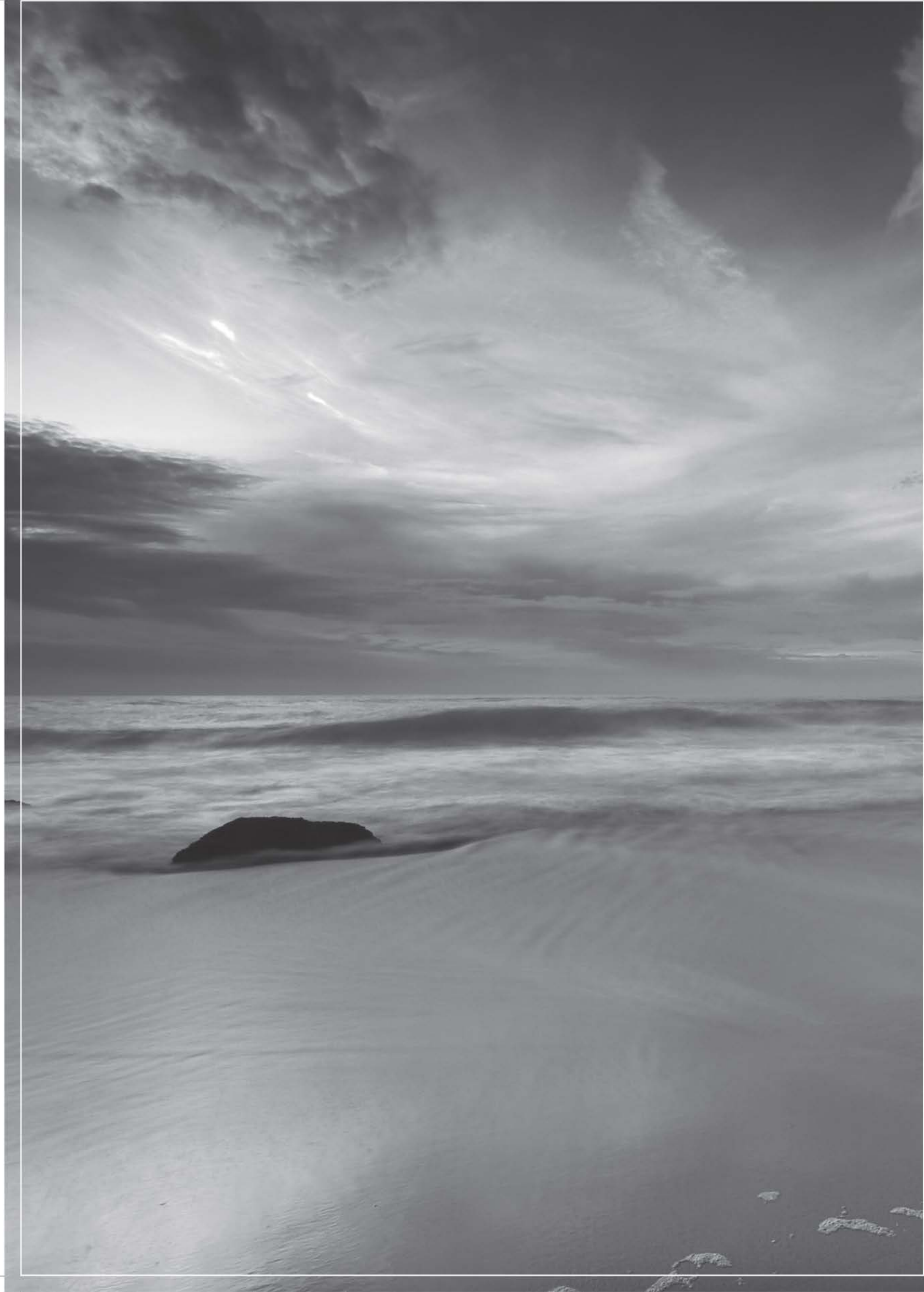

RESULTS

CHAPTER 4

A PROSPECTIVE MULTICENTRE COHORT STUDY OF PATIENT-REPORTED OUTCOMES AFTER CHOLECYSTECTOMY FOR UNCOMPLICATED SYMPTOMATIC CHOLECYSTOLITHIASIS

Mark P. Lamberts[1,2,3],
Brenda L. Den Oudsten[4],
Jos J. G. M. Gerritsen[5],
Jan A. Roukema[6],
Gert P. Westert[1],
Joost P. H. Drenth[2],
Cornelis J. H. M. van Laarhoven[3]

[1]Scientific Institute for Quality of Healthcare (IQ healthcare), Radboud University Medical Centre, Nijmegen, The Netherlands
[2]Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands
[3]Department of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands
[4]Department of Medical and Clinical Psychology, CoRPS, Tilburg University, Tilburg, The Netherlands
[5]Department of Surgery, Medisch Spectrum Twente, Enschede, The Netherlands
[6]Department of Surgery, St. Elisabeth Hospital, Tilburg, The Netherlands

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ABSTRACT

Background

Up to 33% of patients with uncomplicated symptomatic cholecystolithiasis report persistent pain after cholecystectomy. The aim of this study was to determine characteristics associated with patient-reported absence of abdominal pain after cholecystectomy, improved abdominal symptoms, and patient-reported positive cholecystectomy results in a prospective cohort multicentre study.

Methods

Patients aged 18 years or more with symptomatic cholecystolithiasis who had a cholecystectomy between June 2012 and June 2014 in one of three hospitals were included. Before surgery all patients were sent the Gastrointestinal Quality of Life Index (GIQLI) questionnaire and the McGill Pain Questionnaire (MPQ). At 12 weeks after surgery, patients were invited to complete the GIQLI and Patients' Experience of Surgery Questionnaire (PESQ). Logistic regression analyses were performed to determine associations.

Results

Questionnaires were sent to 552 patients and returned by 342 before and after surgery. Postoperative absence of abdominal pain was reported by 60.5% of patients. A high preoperative GIQLI score, episodic pain, and duration of pain of 1 year or less were associated with postoperative absence of pain. These factors showed no association with improved abdominal symptoms (reported by 91.5% of patients) or a positive surgery result (reported by 92.4%).

Conclusions

Preoperative characteristics determine the odds for relief of abdominal pain after cholecystectomy. However, these factors were not associated with patient-reported improvement of abdominal symptoms or patient-reported positive cholecystectomy results, highlighting the variation of internal standards and expectations of patients before cholecystectomy.

BACKGROUND

Cholecystectomy is the treatment of choice for patients with symptomatic cholecystolithiasis. Cholecystectomy is performed about 60,000 times a year in the UK alone, with significant costs.[1] Other Western countries have fairly similar patterns of care.[2-4] Patients with a history of complicated symptomatic cholecystolithiasis are offered cholecystectomy to prevent recurrent complications.[5] The main purpose of a cholecystectomy for uncomplicated symptomatic cholecystolithiasis is to relieve abdominal pain, as the diagnosis is based on abdominal pain combined with ultrasound-confirmed gallstones.[6-9] Despite the high number of cholecystectomies in the Western world, up to 33% of patients still report abdominal pain after cholecystectomy.[10]

The large proportion of patients with persistent postoperative pain is caused by a variation in the indication for, and timing of, cholecystectomy resulting from the lack of evidence and differing opinions among surgeons.[11-13] This variation may lead to unnecessary cholecystectomies, risk of complications and healthcare costs. Several characteristics have been shown to be associated with a good outcome following cholecystectomy, including sex,[14-16] age at surgery,[14, 16] preoperative absence of pain in the previous 2 weeks,[14, 16] centre where treated,[16] American Society of Anesthesiologists (ASA) classification,[17, 18] baseline Gastrointestinal Quality of Life Index (GIQLI) score,[15, 19] duration of pain of 1 year or less,[16] pain occurring during episodes[16] and pain-induced awakening at night.[16] However, study results are often inconsistent and the generalizability of these associations may be limited because of the heterogeneity of patient characteristics, settings, and patient-reported outcome questionnaires used.[16]

The present study aimed to assess the association between preoperative characteristics with absence of pain after cholecystectomy in a Dutch prospective multicentre cohort study. The association of these characteristics with patient-reported improved abdominal symptoms and with patient-reported positive cholecystectomy results was also determined.

METHODS

Study sites and subject selection

All patients aged 18 years or more with symptomatic cholelithiasis, who visited the surgical outpatient clinic at a tertiary referral centre (Radboud University Medical Centre, Nijmegen) or one of two non-academic teaching hospitals (St Elisabeth Hospital, Tilburg and Medisch Spectrum Twente Hospital, Enschede) between June 2012 and June 2014, and were scheduled for elective cholecystectomy were eligible for participation in the study. Cholelithiasis was defined as abdominal pain associated with gallstones, confirmed by ultrasound imaging.

Patients with a history of complicated symptomatic cholelithiasis (acute cholecystitis, cholangitis, biliary pancreatitis, choledocholithiasis requiring endoscopic retrograde cholangiopancreatography)[20, 21] were excluded. Other exclusion criteria were ASA fitness grade III or IV, insufficient knowledge of the Dutch language, non-Dutch residency, blindness, pregnancy, cirrhosis, cancer treatment, schizophrenia, or any other disorder

that might predispose the patient to unreliable responses. Eligible patients were asked to complete a questionnaire before and 12 weeks after cholecystectomy. Patients who did not return the questionnaire before and after surgery were excluded from the analyses.

The preoperative questionnaires included the GIQLI and the McGill Pain Questionnaire, as generic and disease-specific patient-reported outcome questionnaires respectively, in line with the taxonomy.[22] In addition, the GIQLI and Patients' Experiences of Surgery Questionnaire (PESQ) were completed after surgery.

The GIQLI, which was developed in Germany,[23] has been translated and validated in the Dutch language.[24] It contains 36 questions on gastrointestinal symptoms for both the upper and lower digestive tracts, and on general, physical, emotional and social functioning in the previous 2 weeks. Each question consists of five response categories. Questions are scored using a response scale ranging from 0 (worst appraisal) to 4 (best appraisal) points for each question, giving an overall score of 0-144 points. The higher the score, the better the health status. The characteristics of abdominal pain were measured using the MPQ.[25, 26] This questionnaire consists of four sections: a section of general questions regarding pain; a section on the effect of pain on quality of life; a section on visual analogue scales for pain; and a section that includes a list of adjectives describing pain. In the present study, the first two sections were used to assess the duration of pain, its episodic nature, and pain-induced awakening at night. The PESQ includes questions on complications of surgery, abdominal symptoms in relation to cholecystectomy, and patient-reported results of surgery.[27, 28] The latter two questions consisted of five response categories.

The study was approved by the medical ethics committees of three hospitals (Radboud University Medical Centre, Medisch Spectrum Twente Hospital and St Elisabeth Hospital) and conducted in accordance with the recommendations in the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[29]

Outcomes and variables of interest

The primary outcome was defined as absence of abdominal pain, as reported on the GIQLI 12 weeks after cholecystectomy. The results were dichotomized as absence of pain versus presence of pain.

Secondary outcomes included improvement of abdominal symptoms, and outcome of the operation as reported by patients. Responses were dichotomized as positive (successful) versus negative (not successful) ratings. Positive rating of current abdominal symptoms consisted of the combined response categories 'slightly better' and 'much better.' Positive rating of surgery results included the combined response categories 'excellent,' 'very good' and 'good.' Postoperative absence of abdominal pain was added to the selected independent variables to confirm the association with patient-reported success of the procedure.

Based on previous publications, the independent variables included sex,[14-16] age at operation,[14, 16] preoperative absence of pain in the previous 2 weeks,[14, 16] centre,[16] ASA fitness grade,[17, 18] baseline GIQLI score,[15, 19] duration of symptoms of 1 year or less,[16] episodic pain[16] and pain-induced awakening at night.[16]

Power analysis

An appropriate sample size was calculated for the proportion of patients with postoperative pain. Assumptions were based on the findings of a systematic review.[10] The proportion of patients with persistent pain was estimated at 33% with an error rate of 5% and a 95% CI, resulting in a sample size of 340 patients. In anticipation of an incomplete response rate of 40%, at least 476 patients were invited to participate in the study. Given the sample size in the smaller of the two response groups (approximately 112 patients without relief of abdominal pain), there were sufficient observations to accommodate the development of a model with up to 11 variables.

Statistical analysis

Differences between responders and non-responders were examined using χ^2 tests or Fisher's exact tests for categorical data and the Student t test for continuous data. For responders, logistic regression analyses were applied to determine which variables were associated with absence of pain after cholecystectomy. Variables with a P-value < 0.100 in univariable analyses were included in multivariable logistic regression analyses. Backward elimination was used as the variable selection method, retaining age, sex, centre and preoperative abdominal pain as reported on the GIQLI as co-variables. Postoperative absence of abdominal pain in relation to an increasing number of significantly associated preoperative pain characteristics was also assessed. The results of the analyses were reported as adjusted odds ratios (ORs) and 95% CI P < 0.050 was considered statistically significant. Similar methods were used to determine which variables were associated with the patient-reported improvement of abdominal symptoms and with the results of surgery. All missing values were considered to be completely at random and excluded from analyses. All statistical analyses were done with SPSS® statistical software version 20.0 (IBM, Armonk, New York, USA).

RESULTS

A total of 870 patients were considered for participation. After exclusion of 318 patients, questionnaires were sent to 552 patients. Some 423 (76.6%) returned the questionnaires before surgery, and 342 (62.0%) did so both before and after surgery (Fig. 1). Baseline characteristics both of these 342 study patients and the 210 non-reponders are shown in Table 1. Statistically significant differences were found between responders versus non-responders for mean ± SD age at surgery 49.7 ± 14.3 versus 43.5 ± 15.1 years; P < 0.001) and ASA fitness grade (53.2% of responders were classified as ASA II compared with 44.3% of non-responders; P = 0.042).

Associations with absence of pain after cholecystectomy

A total of 207 patients (60.5%) reported absence of pain at 12 weeks after cholecystectomy. Univariable analysis showed preoperative GIQLI score, episodic pain, and duration of pain of 1 year or less to be associated with absence of pain (Table 2). Preoperative GIQLI score (OR 1.02, 95% CI 1.01-1.03; P = 0.004), episodic pain (OR 2.13, 95% CI

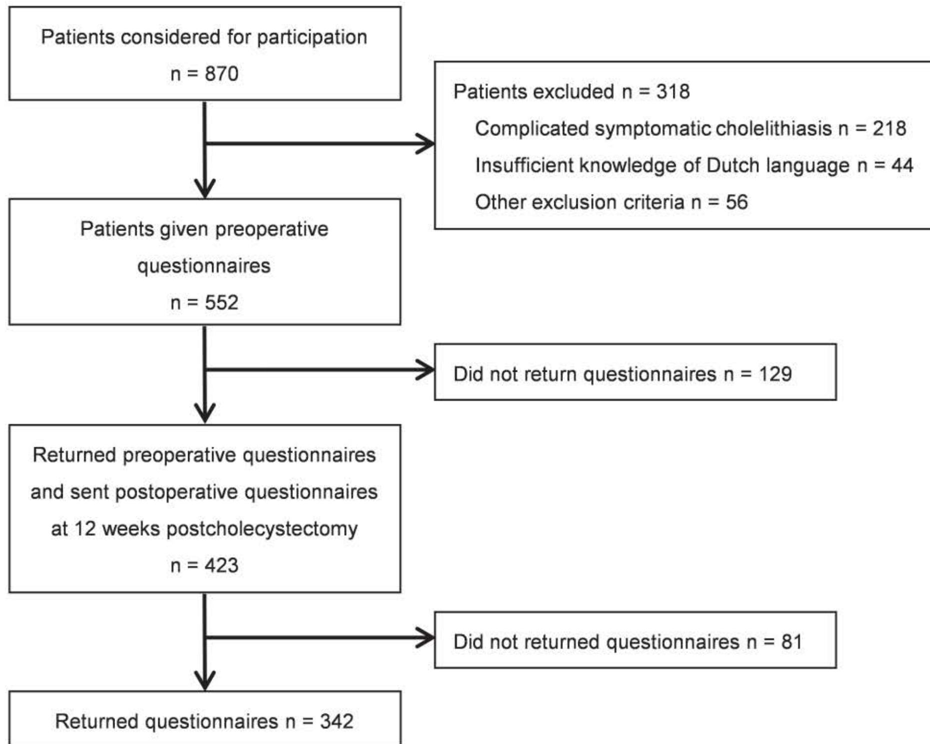

Figure 1. Flow chart showing inclusion of patients in the study

Table 1. Characteristics of responders and non-responders to the questionnnaires

	Responders (n = 342)	Non-responders (n=210)	P-value†
Age (years)*	49.7 ± 14.3	43.5 ± 15.1	<0.001‡
Sex ratio (M : F)	74 : 268	50 : 160	0.553
ASA fitness grade			0.042
I	160 (46.8)	117 (55.7)	
II	182 (53.2)	93 (44.3)	
Centre			
Radboud UMC	67 (19.6)	46 (21.9)	n.a.
MST	155 (45.3)	99 (47.1)	n.a.
St Elisabeth	120 (35.1)	65 (31.0)	n.a.

Values in parentheses are percentages unless indicated otherwise; *values are mean ± SD. ASA, American Society of Anesthesiologists; UMC, University Medical Centre; n.a. not applicable; MST, Medisch Spectrum Twente Hospital.
†χ2 test, except ‡independent *t* test.

Table 2. Univariable and multivariable analysis of factors associated with patient-reported absence of pain after cholecystectomy

	Abdominal pain		Univariable analysis		Multivariable analysis	
	Absent (n = 207)	Present (n = 135)	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age (years)*	50.0 ± 14.1	49.3 ± 14.6	1.00 (0.99-1.02)	0.670	1.00 (0.99-1.02)	0.725
Sex				0.029		0.129
F	154	114	0.54 (0.31-0.94)		0.60 (0.32-1.16)	
M	53	21	1.00 (reference)		1.00 (reference)	
Hospital type				0.206		0.041
Tertiary referral centre	36	31	0.71 (0.41-1.21)		0.52 (0.28-0.97)	
Non-academic	171	104	1.00 (reference)		1.00 (reference)	
Preop. pain in the last 2 weeks				0.002		0.420
No	39	9	3.25 (1.52-6.95)		1.46 (0.58-3.66)	
Yes	168	126	1.00 (reference)		1.00 (reference)	
ASA fitness grade				0.113		
II	103	79	0.70 (0.45-1.09)			
I	104	56	1.00 (reference)			
Baseline GIQLI score*	106.6 ± 20.2	95.2 ± 21.3	1.03 (1.02-1.04)	< 0.001	1.02 (1.01-1.03)	0.004
Duration of pain (years)‡				0.011		0.006
≤ 1	163	91	1.93 (1.16-3.20)		2.22 (1.25-3.94)	
> 1	39	42	1.00 (reference)		1.00 (reference)	
Type of pain‡				< 0.001		0.003
Episodic	132	58	2.31 (1.47-3.61)		2.13 (1.29-3.52)	
Non-episodic	72	73	1.00 (reference)		1.00 (reference)	
Awakened because of pain				0.465		
Yes	105	74	0.85 (0.55-1.32)			
No	97	58	1.00 (reference)			

Values are *mean(s.d.); ‡A few patients did not complete all questions for this factor. ASA, American Association of Anesthesiologists; GIQLI, Gastrointestinal Quality of Life Index.

1.29-3.52; P = 0.003) and duration of pain of 1 year or less (OR 2.22, 95% CI 1.25-3.94; P = 0.006) remained associated with postoperative absence of pain in multivariable analysis. Absence of abdominal pain was also assessed in relation to an increasing number of significantly associated pain characteristics (episodic pain, duration of pain of 1 year or less). The odds of pain relief increased progressively as the number of pain characteristics increased (Table 3).

Table 3. Multivariable logistic regression analysis of the association of increasing number of preoperative pain characteristics with postoperative absence of abdominal pain

No. of characteristics†	Absence of abdominal pain	Odds ratio (95% CI)	P-value
2	100 of 138 (72.5)	6.23 (2.37-16.38)	< 0.001
1	195 of 306 (63.7)	3.57 (1.49-8.54)	0.004
0	9 of 31 (29)	1.00 (reference)	

Values in parentheses are percentages unless indicated otherwise; †Episodic pain, and duration of pain of 1 year or less.

Associations with improved abdominal symptoms and with positive surgery results

A total of 313 patients (91.5%) rated their abdominal symptoms after cholecystectomy to be 'much better' or 'slightly better' compared with their preoperative experience. Univariable analysis revealed postoperative absence of abdominal pain to be associated with patient-reported improved abdominal symptoms, and this remained associated in multivariable analysis (OR 4.52, 95% CI 1.81-11.29; P = 0.001) (Table 4).

The postoperative result was rated as 'good,' 'very good' or 'excellent' by 316 patients (92.4%). In univariable analysis, baseline GIQLI score and postoperative absence of pain were associated with a patient-reported positive rating of the cholecystectomy result. Postoperative absence of pain remained associated in multivariable analysis (OR 19.01, 95% CI 4.20-85.93; P < 0.001) (Table 5).

DISCUSSION

In this prospective multicentre cohort study, only 60.5% of patients reported complete relief of pain at 12 weeks after cholecystectomy. However, most of the patients reported improved abdominal symptoms and a successful outcome after surgery. A higher preoperative GIQLI score, duration of pain of 1 year or less, and episodic pain were significantly associated with postoperative absence of pain, but not with improved abdominal symptoms or positive surgery results.

The proportion of patients with complete pain relief after cholecystectomy, with improved abdominal symptoms and a positive cholecystectomy result in the present study is consistent with other published literature. A systematic review[10] showed that 59-100% of patients experienced complete pain relief. In addition, 90 to 97% of patients reported improved abdominal symptoms and 88-97% rated the cholecystectomy result as positive.[30-32] A large cohort study[16] reported a 2% difference between the proportion of patients with postoperative pain at 12 weeks and 1 year after cholecystectomy. In addition, a long-term follow-up study[17] showed no significant differences in the proportion of patients reporting pain at 12 weeks and 10 years after cholecystectomy. These results suggest that pain relief at 12 weeks of follow-up persists for 10 years after cholecystectomy. This study also reported similar proportions of patient-reported improved symptoms and positive surgery results, indicating consistency of these outcomes as well.[17]

The association of episodic pain and duration of pain of 1 year or less with postoperative absence of pain was confirmed by the present study, increasing the generalizability of these predictors.[16] Pain associated with gallstones is most typically characterized by its episodic nature and relief following cholecystectomy.[6, 7, 9] Non-episodic abdominal pain is often caused by functional gastrointestinal disorders,[33, 34] which are chronic conditions and may have a significant impact on patients' health status.[35] Patients with functional disorders are likely to continue to report abdominal pain after surgery. This was confirmed by the finding that patients with a duration of pain of 1 year or less and a higher preoperative health status score were more likely to report complete pain relief after cholecystectomy compared with patients with a longer duration of pain and a lower health status.

Remarkably, factors that were associated with absence of abdominal pain after cholecystectomy did not show an association with improved abdominal symptoms or a positive surgery result, despite the association of postoperative absence of pain with the latter two outcomes. The placebo effect of surgery or natural decline of symptoms may account for this discrepancy.[36-38] In addition, these findings suggest a difference in internal standards and variable expectations from cholecystectomy.[39, 40] Many patients may not expect all types of abdominal pain to be relieved completely following cholecystectomy. It is therefore important to explore and set realistic expectations before the operation. This discrepancy also raises doubt regarding which patient-reported outcome to use for effective patient selection for cholecystectomy. Cholecystectomy appears to be far less successful when absence of abdominal pain is used as the benchmark compared with improved abdominal symptoms or positive surgery results as standard.

There are limitations of this study. First, selection bias may have occurred as a result of the limited response rate. The response rate of younger patients and those with ASA grade I might have been improved if both paper-based and web-based questionnaires had been used.[41] Second, the study was performed in a national setting with strict inclusion and exclusion criteria to limit recall bias. This may limit the generalizability of the results, although widely available patient-reported outcome questionnaires were employed. Third, multiple measurements might have added additional information, but could also have introduced additional bias as co-morbidities unrelated to gallstone disease or surgery may manifest themselves and cause abdominal pain. Finally, ORs in this study may overestimate risk ratios, and thus should not be interpreted as risk ratios.

Strengths of the study include the prospective multicentre design, limiting potential information bias and increasing external validity. Additional strengths are use of the MPQ, GIQLI and PESQ. Abdominal pain is the characteristic feature of uncomplicated symptomatic cholecystolithiasis and the main predictor of an unsuccessful outcome.[6-9, 18] Other abdominal symptoms may co-exist.[42] Finally, transient episodes of abdominal symptoms could easily be undetected if measured at short intervals. This emphasizes the importance of MPQ as pain-specific, the GIQLI as generic for abdominal symptoms and the PESQ as sequential follow-up questionnaires. Consequently, the authors believe that use of this combination of questionnaires will address all aspects of uncomplicated symptomatic cholelithiasis.

Table 4. Univariable and multivariable analysis of patient and clinical variables with patient-reported abdominal symptoms

	Abdominal symptoms	
	Much or slightly better (n = 313)	About the same, slightly worse or much worse (n = 26)
Age (years)*	50.1 ± 14.3	46.2 ± 14.0
Sex		
F	244	21
M	69	5
Hospital type		
Tertiary referral centre	61	6
Non-academic	252	20
Preop. pain in last 2 weeks		
No	42	5
Yes	271	20
ASA fitness grade		
ASA II	164	17
ASA I	149	9
Baseline GIQLI score*	102.2 ± 21.5	103.8 ± 19.8
Duration of pain (years)‡		
≤ 1	232	21
> 1	74	5
Type of pain‡		
Episodic	172	16
Non-episodic	135	10
Awakened because of pain		
Yes	168	9
No	137	16
Postop. pain in last 2 weeks		
No	198	8
Yes	115	18

Values are *mean ± SD; unless indicated otherwise; ‡A few patients did not complete all questions for this factor. ASA, American Society of Anesthesiologists; GIQLI, Gastrointestinal Quality of Life Index.

Future research should explore further not only which patients will respond favourably to cholecystectomy, but also which will benefit the most. Patients with uncomplicated symptomatic cholelithiasis may wonder whether a cholecystectomy is really necessary after one or few episodes of pain, or whether surgery can be delayed. A watchful waiting strategy[43] was shown to be a feasible option in 31% of patients with uncomplicated symptomatic cholelithiasis during 14 years of follow-up. At the same time, patients with uncomplicated symptomatic gallstone disease at risk of complicated symptomatic cholelithiasis should be considered for earlier surgery.[44] Selection for earlier cholecystectomy of those patients who are most likely to benefit from it will further increase the cost-effectiveness of this common surgical procedure.

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
	1.02 (0.99-1.05)	0.192	1.02 (0.99-1.05)	0.185
		0.739		0.837
	0.84 (0.31-2.32)		1.12 (0.38-3.28)	
	1.00 (reference)		1.00 (reference)	
		0.659		0.907
	0.81 (0.31-2.10)		1.06 (0.39-2.88)	
	1.00 (reference)		1.00 (reference)	
		0.413		0.112
	0.65 (0.23-1.82)		0.41 (0.13-1.23)	
	1.00 (reference)		1.00 (reference)	
	0.58 (0.25-1.35)	0.206		
	1.00 (reference)			
	1.00 (0.98-1.02)	0.731		
		0.570		
	0.75 (0.27-2.05)			
	1.00 (reference)			
		0.587		
	1.26 (0.55-2.86)			
	1.00 (reference)			
		0.108		
	1.96 (0.86-4.46)			
	1.00 (reference)			
		0.002		0.001
	3.87 (1.63-9.19)		4.52 (1.81-11.29)	
	1.00 (reference)		1.00 (reference)	

This study highlights the variation in internal standards and patient expectations. Doctors should explore and help create realistic expectations before admitting patients for cholecystectomy. Strict selection by the treating surgeon based on preoperative pain characteristics, whilst advocating the merits of a watchful waiting approach, is, for the present, the best way to avoid unnecessary surgery in patients with uncomplicated cholecystolithiasis.

Table 5. Univariable and multivariable analysis of patient and clinical variables associated with patient-reported results of surgery

	Surgery results	
	Good, very good or excellent (n = 316)	**Moderate or bad (n = 22)**
Age (years)*	49.9 ± 14.3	48.6 ± 14.7
Sex		
F	246	18
M	70	4
Hospital type		
Tertiary referral centre	59	8
Non-academic	257	14
Preoperative abdominal pain in last 2 weeks		
No	45	2
Yes	271	20
ASA fitness grade		
ASA II	166	14
ASA I	150	8
Baseline GIQLI score*	103.2 ± 21.2	91.9 ± 19.1
Duration of pain (years)‡		
≤1	238	14
>1	71	8
Type of pain‡		
Episodic	174	13
Non-episodic	136	9
Awakend because of pain‡		
Yes	164	13
No	144	9
Postop. pain in last 2 weeks		
No	204	2
Yes	112	20

Values are *mean ± SD; ‡A few patients did not complete all questions for this factor. ASA, American Society of Anesthesiologists; GIQLI, Gastrointestinal Quality of Life Index.

	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
	1.01 (0.98-1.04)	0.668	1.01 (0.97-1.04)	0.773
		0.664		0.694
	0.78 (0.26-2.38)		1.20 (0.35-4.09)	
	1.00 (reference)		1.00 (reference)	
		0.050		0.128
	0.40 (0.16-1.00)		0.46 (0.17-1.25)	
	1.00 (reference)		1.00 (reference)	
		0.504		0.774
	1.66 (0.38-7.35)		0.79 (0.16-3.99)	
			1.00 (reference)	
		0.316		
	0.63 (0.26-1.55)			
	1.00 (reference)			
	1.02 (1.00-1.05)	0.020		
		0.161		
	1.92 (0.77-4.75)			
	1.00 (reference)			
		0.787		
	1.13 (0.47-2.72)			
	1.00 (reference)			
		0.596		
	0.79 (0.33-1.90)			
	1.00 (reference)			
		< 0.001		< 0.001
	18.21 (4.18-79.35)		19.01 (4.20-85.93)	
	1.00 (reference)		1.00 (reference)	

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CHAPTER 5

PATIENT-REPORTED OUTCOMES OF SYMPTOMATIC CHOLELITHIASIS PATIENTS FOLLOWING CHOLECYSTECTOMY AFTER AT LEAST 5 YEARS OF FOLLOW-UP
A LONG-TERM PROSPECTIVE COHORT STUDY

Mark P. Lamberts[1,5,6],
Brenda L. Den Oudsten[2],
Frederik Keus[3],
Jolanda De Vries[2,4],
Cornelis J.H.M. van Laarhoven[5],
Gert P. Westert[6],
Joost P.H. Drenth[1],
Jan A. Roukema[7]

[1]Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands
[2]Department of Medical and Clinical Psychology, CoRPS, Tilburg University, Tilburg, The Netherlands
[3]Department of Critical Care, University Medical Centre Groningen, Groningen, The Netherlands
[4]Department of Medical Psychology, St. Elisabeth Hospital, Tilburg, The Netherlands
[5]Department of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands
[6]Scientific Institute for Quality of Healthcare (IQ healthcare), Radboud University Medical Centre, Nijmegen, The Netherlands
[7]Department of Surgery, St. Elisabeth Hospital, Tilburg, The Netherlands

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ABSTRACT

Background

Up to 41% of patients report pain after cholecystectomy and in most studies follow-up for these symptoms did not exceed 5 years. The episodic nature of abdominal pain associated with symptomatic cholelithiasis warrants long-term follow-up studies. We assessed which patient and surgical factors were associated with absence of pain and patient-reported success of surgery after ≥ 5 years of follow-up.

Methods

Patients of ≥ 18 years of age with symptomatic cholelithiasis, classified as ASA I or II, who had previously returned a preoperative questionnaire were sent a questionnaire consisting of the Gastrointestinal Quality of Life Index (GIQLI) and patient ratings of current versus presurgical abdominal symptoms and of surgery result. Logistic regression analysis was performed to determine associations.

Results

Questionnaires were sent to 197 patients and returned by 126 (64.0%) patients (73.8% female, mean age at surgery 47.5 ± 12.2 years) at a mean of 10.0 ± 1.0 years after cholecystectomy. Absence of abdominal pain was reported by 60.3% of the patients. Patients classified as ASA II as opposed to ASA I were less likely to report absence of pain (OR 0.41, 95% CI 0.17-0.99). A positive rating of long-term postsurgical versus presurgical abdominal symptoms was given by 89.7% of the patients and 90.5% considered the cholecystectomy result to be good. No variables were significantly associated with these latter two outcome measures.

Conclusions

We found a high patient-reported surgery success rate after > 5 years of follow-up after cholecystectomy despite residual abdominal pain in some of these patients. None of the patient and surgery-related characteristics were consistently associated with all three outcome measures. This discrepancy between patient' outcomes highlights the need for realistic expectations prior to cholecystectomy.

BACKGROUND

About 5-22% of the adult Western population have gallstones and approximately 13-22% of these patients become symptomatic.[1, 2] Symptomatic patients mainly report episodic abdominal pain.[3, 4] Cholecystectomy is often performed to relieve this pain.[5] Annually, this corresponds to more than 800,000 cholecystectomies in the United States alone and the associated costs are estimated to be approximately $6 billion.[1, 6] Other developed countries show similar trends.[7, 8]

Despite the high volume of cholecystectomies in the Western world, up to 41% of the patients report postoperative abdominal pain. These figures are mainly based on studies with a follow-up of less than 5 years after cholecystectomy.[9] However, the episodic nature of abdominal pain associated with symptomatic cholelithiasis warrants longer term follow-up studies.[10] To our knowledge only five studies followed patients for 5 years or more after cholecystectomy.[11-15] These studies showed patient-reported absence of pain ranging between 78 and 81.5%,[11-15] while 88% was satisfied with the result of the procedure.[15] None of these studies assessed multivariable associations with patient-reported outcome measures. Since there are variations in regional practice, more long-term follow-up data are needed to optimize the indication of a cholecystectomy and to minimize unnecessary surgery.[16-18]

This study therefore aimed to assess the association of patient and surgery-related characteristics with absence of pain after at least 5 years of follow-up. We also determined the association of these characteristics with patient-reported success of cholecystectomy. Finally, we assessed the effect of surgery on pain at long-term follow-up compared to short term follow-up.

MATERIALS AND METHODS

Study site and subject selection

We used the database of a previous cohort study conducted at the St Elisabeth Hospital Tilburg, The Netherlands. Details of study design were reported previously in this journal.[19] In short, included patients had visited the department of surgery between January 2001 and March 2004. Patients had to be 18 years or older, without relevant allergies, classified as American Society of Anesthesiologists (ASA) I or II, and diagnosed with symptomatic cholelithiasis. Patients had been asked to complete the Gastrointestinal Quality of Life Index (GIQLI) questionnaire preoperatively, and at 1 day, 2, 6, and 12 weeks after cholecystectomy.[19]

Patients that had returned a preoperative questionnaire were considered for participation in the current study. Patients with a malignancy, those with a mental disorder, those who had emigrated, those who eventually did not receive a cholecystectomy, and those who passed away during follow-up were excluded. Subsequently, we mailed the GIQLI and Patients' Experiences of Surgery Questionnaire (PESQ) to the remaining patients in March 2013. The GIQLI has been developed in Germany, and has been translated and validated in Dutch.[20, 21] It includes 36 questions on general physical, emotional and social functioning

and on gastrointestinal symptoms, for both the upper and lower digestive tracts in the last 2 weeks. Each question consisted of five response categories. The questions can be answered using a response scale from 0 to 4 for each question (where 0 is the worst and 4 is the best appraisal). An overall score (ranging from 0 to 144 points) can be calculated: The higher the score, the higher the health-related quality of life. The PESQ was used to assess how patients rated their abdominal symptoms in relation to cholecystectomy and to measure the patient-reported result of the procedure.[22, 23] Both questions consisted of five response categories. If no questionnaire was returned within 4 weeks, patients were approached by telephone and asked for participation. The study was approved by the medical ethics committee.

Variables of interest

Clinical data were extracted from the database or patient records. Based on a previous publication[19] and on clinical sensibility, the independent variables included gender, age at surgery, body mass index (BMI), ASA classification, history of complicated gallstone disease, preoperative endoscopic retrograde cholangiopancreatography (ERCP), duration of symptoms ≤ 1 year, histological inflammation, type of surgery (laparoscopic or small-incision cholecystectomy), conversion, serious intraoperative and postoperative complications including the need for an ERCP, preoperative absence of abdominal pain in the last 2 weeks, and the baseline GIQLI score.

Outcomes

The primary outcome was absence of abdominal pain as reported on the GIQLI after at least 5 years of follow-up. We dichotomized results into absence of pain versus presence of pain.

Secondary outcomes defining success of cholecystectomy included patient ratings of both postsurgical abdominal symptoms versus presurgical symptoms and surgery result. We dichotomized the responses into positive versus negative ratings. The positive rating of current abdominal symptoms consisted of the combined response categories "slightly better" and "much better." The positive rating of the surgery results included the combined response categories "excellent", "very good" and "good." Absence of abdominal pain at long-term follow-up was added to the selected independent variables to confirm the association with patient-reported success of the procedure.

Finally, absence of abdominal pain after at least 5 years after cholecystectomy was compared to the short term follow-up time points. The extent to which patients with or without pain were similar at long-term follow-up and short term follow-up were described.

This study follows those as stipulated by the guideline "strengthening the reporting of observational studies in epidemiology" (STROBE).[24]

Statistical analysis

Chi square tests or Fisher's Exact Test for categorical data and Student's t test for continuous data were used to examine significant differences between responders versus non-responders and dropouts. Patient and surgery-related characteristics were compared.

The primary analysis focused on identifying associations of variables with absence of abdominal pain using logistic regression models. Variables with a p-value < 0.1 in univariable analyses were included in multivariable regression analysis. Backward elimination was used as the variable selection method retaining age, gender and preoperative abdominal pain as reported on the GIQLI as covariates. The results were reported as adjusted odds ratios (ORs) and 95% confidence intervals (CIs). Similar methods were used to assess which variables were associated with the patient-reported rating of abdominal symptoms compared to before cholecystectomy and with the surgery result. McNemar's test was used to determine whether absence of pain significantly differed between long-term follow-up and 1 day, 2, 6, and 12 weeks after cholecystectomy, respectively. A p-value of < 0.05 was considered statistically significant. All missing values were considered to be completely at random and were excluded from analyses. All statistical analyses were done with IBM SPSS statistics version 20.0.

RESULTS

Baseline data

A total of 225 patients were considered for participation. After exclusion of 28 patients, 197 patients were sent the long-term follow-up questionnaire. Questionnaires were returned by 126 (64.0%) patients (Fig. 1). Baseline characteristics of the responders are shown in Table 1. Mean age at surgery was 47.5 ± 12.2 years with a mean follow-up of 10.0 ± 1.0 years. The proportion of female patients was 73.8%. No statistically significant differences were shown between responders versus non-responders and drop-outs.

Associations with absence of abdominal pain after cholecystectomy and with success

A total of 76 (60.3%) patients reported absence of postoperative pain using the GIQLI. Univariable analysis revealed ASA classification and the baseline GIQLI score as factors with a p-value < 0.1 (Table 2). Multivariable analysis showed that patients with ASA II were less likely to report absence of pain at long-term follow-up (OR 0.41, 95% CI 0.17-0.99).

Abdominal symptoms after cholecystectomy were rated "much better" or "slightly better" by 113 (89.7%) patients. Absence of abdominal pain at baseline and absence of abdominal pain at long-term follow-up were univariably associated with patient-reported positive rating of abdominal symptoms compared to before cholecystectomy (Table 3). In multivariable analysis, absence of abdominal pain at long-term follow-up remained associated (OR 7.66, 95% CI 1.47-39.88). A total of 114 patients (90.5%) reported the result of the surgery as "good," "very good" or "excellent." Univariable analysis

revealed age, absence of abdominal pain at baseline, and absence of abdominal pain at long-term follow-up to be associated with a positive rating of the cholecystectomy result. No variables remained associated in multivariable analysis.

Figure 1. The recruitment of patients

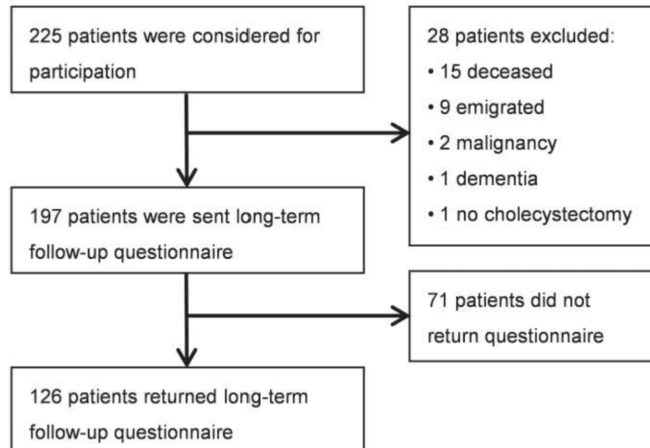

Table 1. Characteristics of the responders

	Responders	**P-value**
Gender, M/F (%F)	33/93 (73.8)	0.61
Age in years, mean ± SD	47.5 ± 12.2	0.34
BMI in kg/m^2, mean ± SD	27.8 ± 4.3	0.86
ASA, I/II (%II)	87/39 (31.0)	0.31
History of complicated gallstone disease, n (%)	12 (9.5)	0.39
Preoperative ERCP, n (%)	10 (7.9)	0.20
Duration of symptoms ≤1 year, n (%)	92 (73.0)	0.55
Inflammation, n (%)	26 (20.6)	0.39
Follow-up in years, mean ± SD (range)	10.0 ± 1.0 (8-12)	NA
Type of surgery, SIC/LC (%LC)	67/59 (46.8)	0.69
Conversion, n (%)	22 (17.5)	0.12
Serious complications, n (%)	15 (11.9)	0.85
Preoperative absence of abdominal pain in the last two weeks, n (%)	23 (18.3)	0.36
Baseline GIQLI score, mean ± SD	104.2 ± 15.8	0.71

SD Standard deviation *BMI* Body Mass Index *ASA* American Association of Anesthesiologists *ERCP* Endoscopic Retrograde Cholangiopancreatography *NA* Not applicable *SIC* Small-incision cholecystectomy *LC* Laparoscopic cholecystectomy *GIQLI* Gastrointestinal Quality of Life Index

Table 2. Univariable and multivariable association of patient and surgical variables with postcholecystectomy patient reported absence of pain

	Absence of abdominal pain	Presence of abdominal pain	Univariable analyses (p-value)	Odds ratio (95% CI)	P-value
Female gender, n (%)	55 (72.4)	38 (76.0)	0.65	1.00 (0.38-2.68)	0.99
Age in years, mean ± SD	48.5 ± 12.5	46.0 ± 11.7	0.25	0.99 (0.96-1.03)	0.71
BMI in kg/m^2	27.9 ± 4.5	27.6 ± 3.9	0.70		
ASA II, n (%)	19 (25.0)	20 (40.0)	0.08	0.41 (0.17-0.99)	0.049
History of complicated gallstone disease, n (%)	8 (10.5)	4 (8.0)	0.76		
Preoperative ERCP, n (%)	6 (7.9)	4 (8.0)	1.00		
Duration of symptoms ≤1 year, n (%)	53 (79.1)	39 (83.0)	0.61		
Inflammation, n (%)	19 (25.0)	7 (14.0)	0.14		
LC, n (%)	36 (47.4)	23 (46.0)	0.88		
Conversion, n (%)	16 (21.1)	6 (12.0)	0.19		
Serious complications, n (%)	9 (11.8)	6 (12.0)	0.98		
Preoperative absence of abdominal pain in the last two weeks, n (%)	17 (22.4)	6 (12.0)	0.14	2.38 (0.73-7.78)	0.15
Baseline GIQLI score, mean ± SD	106.3 ± 16.7	101.0 ± 13.9	0.08		

SD Standard deviation *BMI* Body Mass Index *ASA* American Society of Anesthesiologists *ERCP* Endoscopic Retrograde Cholangiopancreatography *LC* Laparoscopic cholecystectomy *GIQLI* Gastrointestinal Quality of Life Index

Effectiveness of cholecystectomy on pain after at least 5 years of follow-up compared to short-term follow-up

Absence of abdominal pain after cholecystectomy was not significantly more reported at long-term follow-up compared to 12 weeks of follow-up (p = 0.10). In contrast, absence of pain was significantly more reported at long-term follow-up compared to 1 day (p = < 0.001), 2 weeks (p = < 0.001) and 6 weeks (p = < 0.001) after cholecystectomy, respectively. The extent to which patients with or without pain were similar at long-term follow-up and 12 weeks of follow-up are shown in Fig. 2.

DISCUSSION

This study demonstrates that only 60.3% of the patients reported complete absence of pain at an average of 10 years after cholecystectomy, but that approximately 90% of the patients rated the abdominal symptoms and the surgery result as positive. We found that presence of ASA II was associated with abdominal pain after cholecystectomy. None of the variables of interest were associated with a positive rating of the abdominal symptoms compared to before surgery or with the positive rating of the cholecystectomy result. The proportion of patients reporting absence of pain at long-term follow-up versus 12 weeks of follow-up was not significantly different in contrast to prior timepoints.

Table 3a. Univariable and multivariable association of patient and surgical variables with patient-reported much or slightly better symptoms compared to before the cholecystectomy

	Much or slightly better abdominal symptoms	About the same, slightly worse or much worse abdominal symptoms	Univariable analyses (p-value)	Odds ratio (95% CI)	P-value
Female gender, n (%)	84 (74.3)	7 (63.6)	0.48	2.43 (0.57-10.40)	0.23
Age in years, mean ± SD	47.5 ± 12.2	46.0 ± 13.3	0.70	1.01 (0.95-1.06)	0.86
BMI in kg/m^2, mean ± SD	28.0 ± 4.3	26.7 ± 3.5	0.31		
ASA II, n (%)	33 (29.2)	5 (45.5)	0.31		
History of complicated gallstone disease, n (%)	11 (9.7)	1 (9.1)	1.00		
Preoperative ERCP, n (%)	9 (8.0)	1 (9.1)	1.00		
Duration of symptoms ≤1 year, n (%)	80 (79.2)	10 (90.9)	0.69		
Inflammation, n (%)	22 (19.5)	4 (36.4)	0.24		
LC, n (%)	54 (47.8)	4 (36.4)	0.47		
Conversion, n (%)	19 (16.8)	3 (27.3)	0.41		
Serious complications, n (%)	14 (12.4)	1 (9.1)	1.00		
Preoperative absence of abdominal pain in the last two weeks, n (%)	20 (17.7)	1 (9.1)	0.10	2.49 (0.25-24.82)	0.44
Baseline GIQLI score, mean ± SD	105.0 ± 15.9	96.8 ± 15.3	0.12		
Postoperative absence of abdominal pain in the last two weeks, n (%)	72 (63.7)	2 (18.2)	0.001<	7.96 (1.61-39.40)	0.01

SD Standard deviation *BMI* Body Mass Index *ASA* American Society of Anesthesiologists *ERCP* Endoscopic Retrograde Cholangiopancreatography *LC* Laparoscopic cholecystectomy *GIQLI* Gastrointestinal Quality of Life Index

The proportion of patients with abdominal pain after cholecystectomy in our study is consistent with literature. A systematic review indicated that up to 41% of patients report abdominal pain after cholecystectomy,[9] while studies with a follow-up ≥5 years showed lower figures (18.5-22%).[11-15] We did not find any relation with gender, age, nor complicated gallstone disease and abdominal pain in our study. This is in contrast with previous studies. In one study patients whose symptoms hardly improved 5 years after cholecystectomy were most likely to be women.[11] Another study concluded that persisting abdominal pain 5 years after cholecystectomy was mainly nonspecific, found mostly in younger women who had experienced uncomplicated gallstone disease.[15] The use of different patient-reported outcome measurement tools between studies or variations in the indication to perform a cholecystectomy may explain these different

Table 3b. Univariable and multivariable association of patient and surgical variables with patient-reported good, very good or excellent result of surgery

	Good, very good or excellent result of surgery	Moderate or bad result of surgery	Univariable analyses (p-value)	Odds ratio (95% CI)	P-value
Female gender, n (%)	85 (74.6)	7 (63.6)	0.48	1.66 (0.39-7.00)	0.49
Age in years, mean ± SD	46.9 ± 12.6	53.3 ± 5.7	0.006	0.95 (0.89-1.01)	0.08
BMI in kg/m^2, mean ± SD	27.9 ± 4.3	26.8 ± 3.8	0.40		
ASA II, n (%)	34 (29.8)	4 (36.4)	0.73		
History of complicated gallstone disease, n (%)	11 (9.6)	1 (9.1)	1.00		
Preoperative ERCP, n (%)	9 (7.9)	1 (9.1)	1.00		
Duration of symptoms ≤1 year, n (%)	82 (80.4)	9 (81.8)	1.00		
Inflammation, n (%)	22 (19.3)	4 (36.4)	0.24		
LC, n (%)	54 (47.4)	5 (45.5)	1.00		
Conversion, n (%)	19 (16.7)	3 (27.3)	0.41		
Serious complications, n (%)	13 (11.4)	2 (18.2)	0.62		
Preoperative absence of abdominal pain in the last two weeks, n (%)	20 (17.5)	2 (18.2)	0.06	0.83 (0.14-5.14)	0.84
Baseline GIQLI score, mean ± SD	104.8 ± 15.9	98.5 ± 15.4	0.24		
Postoperative absence of abdominal pain in the last two weeks, n (%)	71 (62.3)	4 (36.4)	0.001<	3.62 (0.93-14.06)	0.06

SD Standard deviation *BMI* Body Mass Index *ASA* American Society of Anesthesiologists *ERCP* Endoscopic Retrograde Cholangiopancreatography *LC* Laparoscopic cholecystectomy *GIQLI* Gastrointestinal Quality of Life Index

results.[25] Younger women with gallstones may have been treated more conservatively in our study, as suggested by variations in practice.[16, 17]

A large prospective cohort study detected an association of ASA classification with abdominal pain 6 months after cholecystectomy that was independent of the patient-reported success of the surgery.[26] Patients-reported success rates ranges between 82 and 93%.[15, 26-28] These findings are consistent with our results. Since ASA classification has no effect on patient ratings of surgery success, the association of ASA II classification with abdominal pain may be related to concurrent co morbidity. In addition, postoperative abdominal pain has been shown to be strongly associated with the patient-reported success of the operation.[26] The success of a procedure may depend on symptom relief, complications and cosmetic result.[27] By asking patients explicitly how they would rate

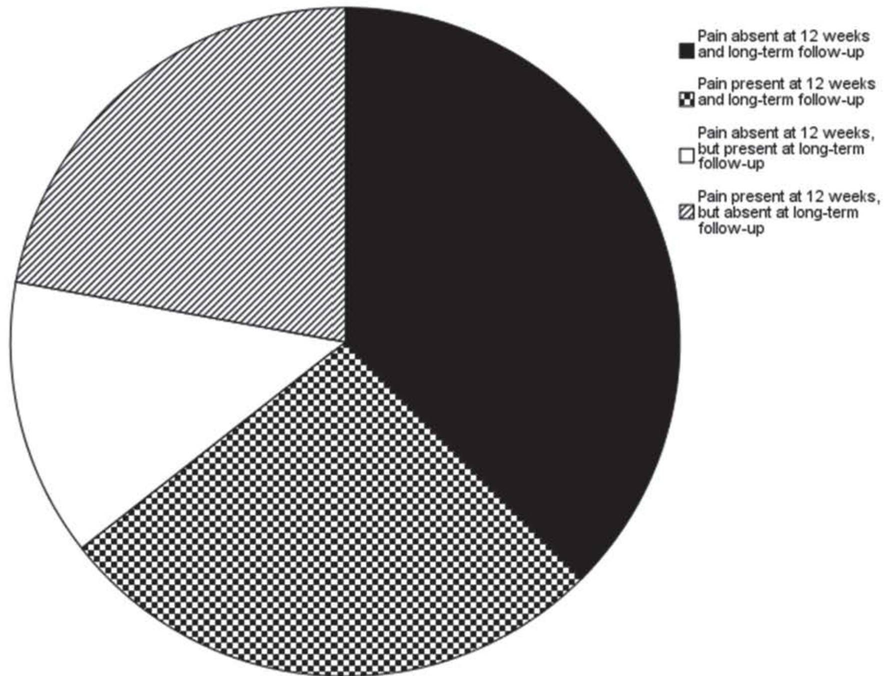

Figure 2. Comparison of patients with or without pain after cholecystectomy at 12 weeks and long-term follow-up. A total of 39 (37.5%) patients reported absence of pain at both timepoints, while pain remained present in 28 (26.9%) patients. Patients reporting absence of pain at 12 weeks after cholecystectomy showed presence of pain in 13 (13.5%) cases at long-term follow-up. Patients showing presence of pain at 12 weeks after cholecystectomy reported absence of pain at long-term follow-up in 24 (22.1%) cases. The remaining 22 patients had not returned the questionnaire at 12 weeks of follow-up.

their symptoms and how they would judge the surgery result, we aimed to elucidate which element was rated as successful.

Some limitations of our study should also be discussed. First, bias may have occurred due to the limited response rate of our population. However, a comparison between responders versus non-responders and drop-outs did not show any significant differences. Second, since this study was performed in a single-center the generalizability may be limited. It is documented that variations in regional practice and in postoperative pain management may depend on the diagnostic work-up, the time of referral, and the indication for an operative intervention.[16-18] Third, by only measuring the before and after results, bias might have been introduced.[14, 29] This study confirmed the natural episodic course of abdominal pain. Bias could be reduced by measuring symptoms at multiple follow-up moments. In order to curtail this possibility we conducted this long-term follow-up study.

Strengths of our study included the use of widely translated and validated standardized questionnaires. We measured absence of pain as primary outcome using the GIQLI and success using the PESQ in order to obtain valid patient responses. The systematic measurement of patient-centered cholecystectomy outcomes using validated

questionnaires in differentiating who would and would not have benefited from surgery has been advocated in previous studies in this journal.[9, 27] Moreover, our study included a prospective measurement of pain at 5 years or longer after cholecystectomy. Abdominal pain may come in episodes, sometimes with intervals of several years.[29] Pain may therefore be relieved after cholecystectomy at short term follow-up, but may re-emerge at long-term. Furthermore, we surmise that the placebo effect of cholecystectomy will have faded 5 years after cholecystectomy.[30]

The discrepancy between the proportion of patients with pain and proportion of patients rating the surgery as successful highlights the need for realistic expectations prior to a potential cholecystectomy. It seems that many patients will accept some degree of pain, since it may be caused by concurrent co morbidity. Future research should focus on further optimizing the indication and timing of cholecystectomy in large numbers of patients diagnosed with symptomatic cholelithiasis systematically using validated patient-reported outcome measures. The characteristics of pain pre- and postoperatively have to be the main scope. Persistence of abdominal pain should be measured after at least 12 weeks following cholecystectomy, as this predicts the persistence of this symptom until 10 years after the procedure. With this information physicians could inform patients based on evidence about the odds of pain relief and thereby create realistic expectations. Furthermore, patients that benefit the most from a cholecystectomy could be selected improving the cost-effectiveness of this common surgical procedure.[31] This would reduce the variations of cholecystectomy indications in patients diagnosed with symptomatic cholelithiasis and thereby decrease healthcare expenses.

In conclusion, we found a high patient-reported operative success rate of 90% at >5 years of follow-up after cholecystectomy despite residual abdominal pain in a substantial percentage of these patients. This discrepancy between outcome measures highlights the need for setting realistic expectations prior to cholecystectomy. Systematic measurement of validated patient-reported outcomes is needed to further optimize the indication and timing of cholecystectomy in patients diagnosed with symptomatic cholelithiasis.

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CHAPTER 6

VALUE OF EGD IN PATIENTS REFERRED FOR CHOLECYSTECTOMY: A SYSTEMATIC REVIEW AND META-ANALYSIS

Mark P. Lamberts[1,2,3],
Wietske Kievit[4],
Cihan Özdemir[4],
Gert P. Westert[1],
Cornelis J. H. M. van Laarhoven[2],
Joost P. H. Drenth[3]

[1]Scientific Institute for Quality of Healthcare (IQ healthcare), Radboud University Medical Centre, Nijmegen, The Netherlands
[2]Department of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands
[3]Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands
[4]Department for Health Evidence, Radboud University Medical Centre, Nijmegen, The Netherlands

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ABSTRACT

Background

As many as 33% of patients with symptomatic cholelithiasis report persisting abdominal pain after cholecystectomy, suggesting alternative causes for these symptoms. EGD may serve as a tool to identify additional symptomatic abdominal disorders beforehand to avoid unnecessary gallbladder surgery. There is controversy as to whether routine EGD before cholecystectomy is appropriate.

Objective

To perform a systematic review and meta-analysis to assess the value of EGD before cholecystectomy.

Design

A systematic literature search was conducted to identify studies that reported the proportion of patients who were referred for cholecystectomy, but in whom initial surgery could be avoided after treatment of abnormalities detected with EGD. Pooled estimates with 95% confidence intervals (CIs) were calculated by using random effects models.

Setting

Meta-analysis of 12 cohort studies.

Patients

A total of 6317 patients with cholelithiasis underwent EGD.

Results

The pooled estimate of abnormalities detected with EGD was 36.3% (95% CI, 28.0-45.0). In a total of 3.8% (95% CI, 1.4-7.6) of patients referred for cholecystectomy who underwent previous EGD, gallbladder surgery was avoided.

Limitations

Lack of information regarding characteristics of patients referred for cholecystectomy, criteria for performing EGD, algorithms for the treatment of identified pathologies, and response criteria for the decision to avoid cholecystectomy in included studies.

Conclusions

Our study indicates that, despite the high diagnostic yield of EGD, its value as a tool to prevent gallbladder surgery is limited. EGD should only be considered selectively in patients with cholelithiasis referred for cholecystectomy.

INTRODUCTION

In as many as 22% of patients with gallstones, symptoms will develop eventually.[1] Treatment of first choice is a cholecystectomy. This strategy results in more than 800,000 cholecystectomies in the United States annually, with associated costs that are estimated to exceed $6 billion.[2, 3] Data from other countries are no different.[4, 5] However, as many as 33% of patients continue to have abdominal pain despite cholecystectomy,[6] which sheds doubt on whether the initial diagnosis of symptomatic cholelithiasis was correct. Symptomatology of cholelithiasis may be confounded with symptoms related to other upper GI diseases. The easy access to US for detecting gallstones and the low threshold for performing a therapeutic procedure may contribute to the high number of cholecystectomies. There is a large variation in surgical treatment of patients with gallstones, giving rise to doubt about the diagnostic accuracy and concerns about the inappropriate use of health care resources.[7-9] Gastritis, esophagitis, and peptic ulcer might be alternative diagnoses for the abdominal symptoms, and these diseases can be easily diagnosed by EGD.[10, 11] The medical literature on the value of routine EGD in patients referred for cholecystectomy is conflicting,[12] highlighting the need for a systematic review and meta-analysis.

This study, therefore, aimed to systematically assess and analyze the value of EGD in patients diagnosed with symptomatic cholelithiasis who were referred for cholecystectomy. Value was defined as the proportion of avoided cholecystectomies after treatment of abnormalities detected by EGD.

METHODS

Medical literature search

We conducted a systematic literature search of the databases of Pubmed, Embase, Web of Science, ClinicalTrials.gov, and the Cochrane Library (March 2014) by using the combination of the following keywords: cholelithiasis, cholecystolithiasis, biliary, gallstone, gall stone, calculi, AND cholecystectomy AND gastroscopy, gastroduodenoscopy, oesophagogastroduodenoscopy, esophagogastroduodenoscopy, oesophagoduodenoscopy, esophagoduodenoscopy. We followed the Meta-analysis of Observational Studies in Epidemiology checklist for all steps reported in this systematic review and meta-analysis.[13]

Selection of the studies

Two reviewers (M.P.L. and C.O.) independently screened the titles and abstracts of the studies and selected potentially relevant articles, irrespective of the language. We included studies assessing the proportion of patients in whom a cholecystectomy was avoided because of EGD findings in patients diagnosed with symptomatic cholelithiasis. Letters, books, conference abstracts, and double publications were excluded.

In addition, we checked the reference lists of all articles that were retrieved for additional studies. Discrepancies were resolved by discussion and consensus. If disagreement persisted, a third reviewer (W.K.) was available to make the final decision.

Data extraction

Data from each study regarding characteristics of the studies and EGD were extracted by 2 reviewers (M.P.L. and C.O.) independently. The study characteristics included the authors, year of publication, country, number of patients referred for cholecystectomy, sex, mean age, type of cholecystectomy, and duration of follow-up. The EGD characteristics comprised the number of patients undergoing EGD; the number of patients having abnormal findings on EGD; the different EGD findings including gastric ulcer, duodenal ulcer, gastritis, esophagitis, hiatal hernia, and malignancy; and the number of patients in whom initial cholecystectomy was avoided after treatment of the EGD findings. Discrepancies were resolved by discussion and consensus.

Methodological quality

The methodological quality of the eligible studies was assessed by the 2 reviewers (M.P.L. and C.O.) independently, by using the Newcastle-Ottawa Scale for assessing the risk of bias of nonrandomised studies.[14] The items included the representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not present at start of study, and comparability of cohorts on the basis of the design or analysis, assessment of outcome, and duration and adequacy of follow-up. Each item of high quality was given 1 star, except for comparability, which was given 2 stars. A total of 9 stars could be given. Appropriate selection criteria of cohorts were considered to be consecutive series of patients with controls from the same or similar population. A star was given for matching on age and sex and a star for matching on pre-endoscopic additional diagnostics or treatment, when assessing comparability. The follow-up had to be at least 3 months, and adequacy of follow-up had to be more than 80% of the original cohort to be allocated a star each. The overall risk of bias rating that was given was based on the number of stars assigned. A rating of low risk of bias required 7 to 9 stars, moderate risk cohort studies required 4 to 6 stars, and high risk required 3 or fewer stars. Disagreements between the 2 reviewers were resolved by consensus.

Data analysis

Pooled estimates of proportions with 95% confidence intervals (CIs) were calculated according to the random effects model of DerSimonian and Laird.[15] Heterogeneity among studies was estimated by using the I^2 statistic. We performed a subgroup analysis regarding study characteristics to assess the influence on outcomes: (1) studies conducted in the same country because these patients may be more homogeneous; (2) studies reporting laparoscopic cholecystectomy (LC) as the type of surgery because the indication to perform gallbladder surgery has broadened with LC,[16] and (3) the 50% most recent

studies versus the 50% least recent studies because the diagnostic properties of EGD may have improved in time.

All calculations were performed with StatsDirect statistical software V.2.8.0 (StatsDirect Ltd, Cheshire, United Kingdom).

RESULTS

Selected studies

The initial search yielded 2561 articles. After removal of duplicates and after applying the initial step of eligibility screening, 22 articles remained for full-text screening. After application of the exclusion criteria, 11 of 22 studies were excluded. An additional publication was identified through citation snowballing, leaving 12 studies to be included in this review (Fig. 1).

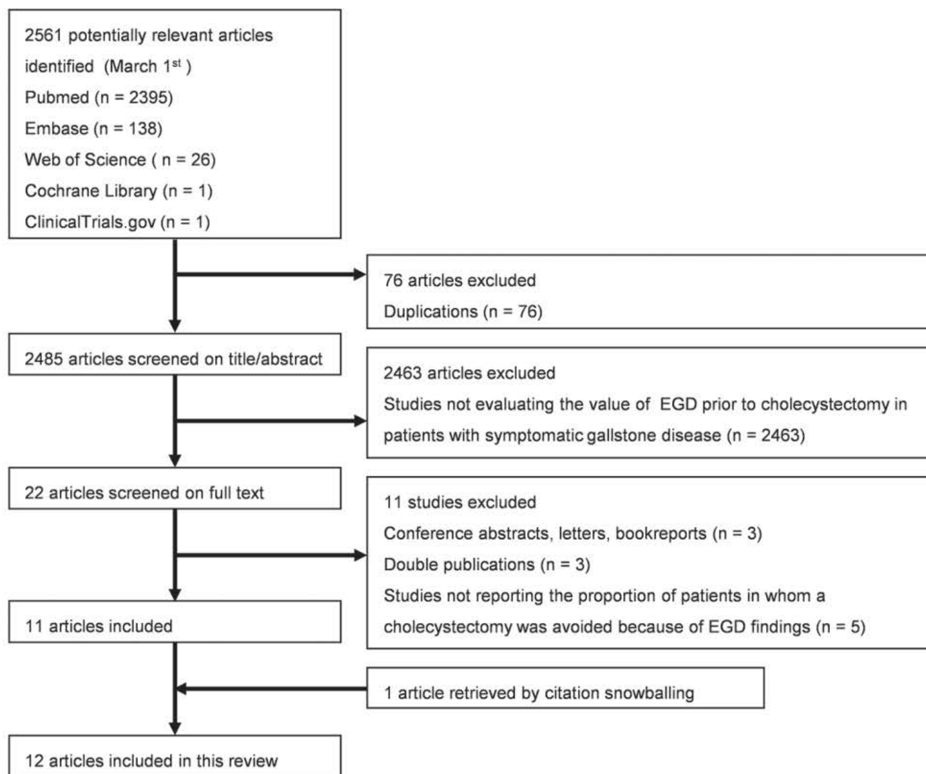

Figure 1. Flow diagram of the studies identified in the systematic review.

Characteristics of the studies and EGD

The characteristics of the included studies are shown in Table 1. A total of 8 studies were performed in Germany.[12, 17-23] In 4 studies cholecystectomy was performed laparoscopically.[19, 23-25] The number of patients having a prior EGD ranged from 57 up

Table 1. Characteristics of the included studies

Study and setting	No. of patients referred for cholecystectomy	Sex, M/F	Mean age, y
Dimitriou et al,[12] Germany, 2012	766	NR	NR
Al-Azawi et al,[24] Ireland, 2006	400	47/171	49.8 (16-79)
Sosada et al,[25] Poland, 2005	2800	475/2325	51 (14-87)
Fahlke et al,[19] Germany, 2001	700	141/559	42
Thybusch et al,[22] Germany, 1996	338	110/228	51 (14-87)
Lankisch et al,[20] Germany, 1996	100	27/73	58 (38-86)
Niv and Fraser[27] Israel, 1995	57	20/37	59.2±15.2 (10-90)
Beyermann et al,[17] Germany, 1992	670	206/464	55 (15-93)†
Ure et al,[23] Germany, 1992	376	94/282	51 (18-87)†
Diettrich et al,[18] Germany, 1990	100	32/68	58.3
Rassek et al,[21] Germany, 1988	960	1:3	NR
Coleman et al,[26] Australia, 1981	100	25/75	NR

M/F, Male/female; *NR,* not reported; *C,* cholecystectomy; *LC,* laparoscopic cholecystectomy.
*Gastric and duodenal ulcers combined.
†median age.

to 2,800 patients. The number of abnormalities detected varied between 22 and 1187, and the number of avoided cholecystectomies ranged between 0 and 125. GI ulcer was the most common diagnosis that led to avoidance of cholecystectomy.

Quality assessment

Table 2 describes the methodological quality of the included studies. All studies drew their cohort from the referred general population and were from single centers which may have resulted in selection bias. All studies ascertained EGD using health care records. One study reported to have excluded patients having had an EGD within 3 months of admission that was reported to have normal findings.[23] None of the studies showed comparability of cohorts on the basis of the design or analysis. In all studies, the outcome was adequately assessed by using record linkage. Three studies reported a follow-up duration of at least 3 months.[24, 26, 27] The length of follow-up of the cohorts was adequate in 7 studies.[18, 20, 22, 23, 25-27] The overall risk of bias was high to moderate, with scores ranging from 2 to 4 out of 9.

Outcomes and subgroup analysis

The pooled proportion of detectable GI abnormalities was 36.3% (95% confidence interval [CI] 28.0-45.1%) of a total of 6317 patients with cholelithiasis who underwent EGD (Table 3). In 11.0% of patients with abnormalities (95% CI 3.9-21.1%), the initial cholecystectomy was avoided leading to 3.8% (95% CI 1.3%-7.6%) of waived gallbladder surgery in all patients previously undergoing an EGD EGD (Fig. 2).

Type of surgery	Follow-up, mo (range)	No. of patients undergoing EGD	No. of patients with abnormal EGD findings, (%)
C	NR	766	330 (43.1)
LC	374 days (150-613)	218	120 (55.0)
LC	NR	2800	1187 (42.4)
LC	NR	487	40 (8.2)
C	NR	338	160 (47.3)
C	NR	100	45 (45.0)
C	12	57	30 (52.6)
C	NR	386	159 (41.2)
LC	NR	376	60 (16.0)
C	NR	100	31 (31.0)
C	NR	589	259 (44.0)
C	11 (5-21)	100	22 (22.0)

The effects of the subgroup analyses are shown in Table 3. The proportions of abnormalities in German studies, in LC studies, and in the 50% least recent studies were lower compared with the proportion of abnormalities of the total group. The pooled proportion of the 50% most recent studies showed a higher percentage. The proportion of avoided cholecystectomies was lower in German, LC only, and 50% most recent studies. The pooled results of the 50% least recent studies showed a higher proportion compared with the proportion of avoided cholecystectomies of the total group.

DISCUSSION

Our study indicates that the value of EGD as a strategy to prevent cholecystectomies is limited. Although a total pooled proportion of 36.3% of abnormalities was detected with EGD, cholecystectomy was prevented in only 3.8% of patients. The finding of a GI ulcer was the most common reason that led to avoidance of a cholecystectomy.

The routine or selective use of EGD needs to be considered in light of its expense. A total of 100 / 3.8% = 26 (95% CI 13-77) EGDs are needed to avoid 1 cholecystectomy. In our hospital, a cholecystectomy without overnight stay costs $4,533 (€3,238), whereas EGD expenses are $2,744 (€1960). To be cost-effective, only up to 1.7 (4,533 ÷ 2,744) EGDs need to be performed to avoid 1 cholecystectomy. Therefore, routine EGD in patients referred for cholecystectomy cannot be recommended.

The value of EGD before cholecystectomy is limited compared with its effectiveness in patients with persistent symptoms after cholecystectomy. In fact, EGD appears to be more useful in patients with persistent symptoms after cholecystectomy because studies reported between 14% and 31% of patients with abnormalities at endoscopy, explaining

Table 2. Quality assessment of the studies by using the Newcastle-Ottawa scale14

Study	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Outcome not present at start of study
Dimitriou et al[12]			★	
Al-Azawi et al[24]			★	
Sosada et al[25]			★	
Fahlke et al[19]			★	
Thybusch et al[22]			★	
Lankisch et al[20]			★	
Niv and Fraser[27]			★	
Beyermann et al[17]			★	
Ure et al[23]			★	★
Dietrrich et al[18]			★	
Rassek et al[21]			★	
Coleman et al[26]			★	

★ Symbol indicates that quality measure was met.

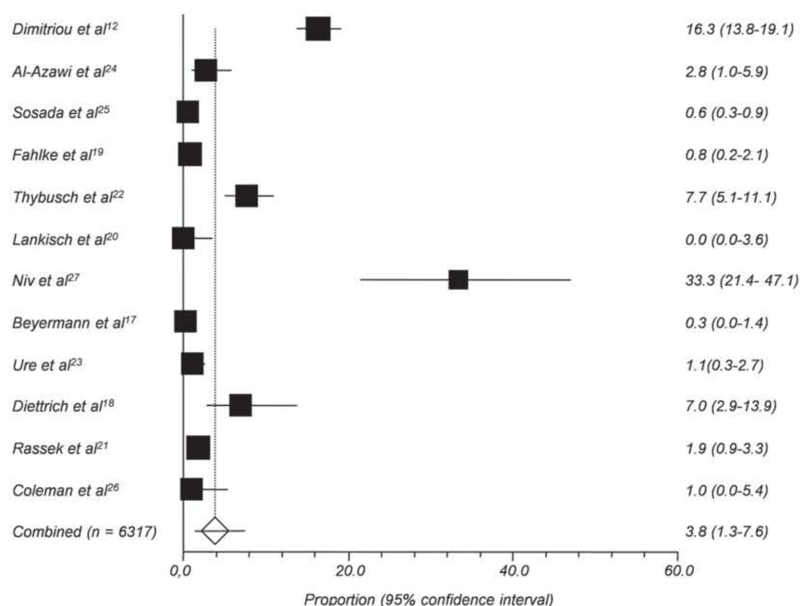

Figure 2. Forest plot of avoided cholecystectomies in all cholelithiasis patients previously undergoing an EGD.

the persistent symptoms.[10, 11, 28] At this point, however, patients have already experienced an unnecessary, more-invasive surgical procedure. The challenge ahead, therefore, will

	Comparability	Assessment of outcome	Follow-up length	Follow-up adequacy
		★		
		★	★	
		★		★
		★		
		★		★
		★		★
		★	★	★
		★		
		★		★
		★		★
		★		
		★	★	★

be to identify patients who will benefit from additional diagnostic assessments before a potential cholecystectomy from patients who will not.

The number of abnormalities found with EGD in patients diagnosed with symptomatic cholelithiasis is lower compared with the general population with abdominal symptoms (36.3% vs 58.5%).[3] This discrepancy is due to a difference in indication to perform EGD. The indication for EGD in the majority of the general population was reflux symptoms,[3] whereas abdominal pain is the main feature of symptomatic cholelithiasis.[29, 30] According to several guidelines, one of which one has been published in this journal, EGD is appropriate in case of alarm symptoms such as dysphagia or odynophagia, unintentional weight loss, or persistent vomiting of unknown cause. In addition, EGD may be considered in patients of 50 years of age and older with persistent or recurrent abdominal symptoms despite using antacids who tested negative for Helicobacter pylori.[31, 32] Therefore, we believe that EGD should only be considered in this select group of patients to prevent unnecessary, burdensome, and costly endoscopic procedures in patients with US-proven cholelithiasis with abdominal symptoms of uncertain cause.

Our review also has some potential limitations. First, all studies included in our review had an inherent high to moderate risk of bias, and in fact none fulfilled all quality criteria. Second, disease incidence, such as incidence of gastroesophageal malignancies, varies between countries and regions.[33] As a consequence, the diagnostic yield and value of EGD differ among populations. Third, there is variation in referral behavior, and diagnostic work-up may vary among studies.[34] Essential information such as characteristics of patients referred for cholecystectomy, criteria for performing EGD, algorithms for treatment of

Table 3. Pooled results of the included studies

	Abnormalities, % (95% CI)	Heterogeneity, I^2 (95% CI)	Avoided cholecystectomies in patients with abnormalities, % (95% CI)
Total	36.3 (28.0-45.1)	97.6 (97.1-98.0)	11.0 (3.9-21.1)
German	33.3 (21.8-46.1)	98.1 (97.6-98.4)	10.1 (2.3-22.5)
LC only	28.4 (10.3-51.1)	99.3 (99.1-99.4)	5.0 (1.4-10.6)
Most recent 50%	38.9 (25.9-52.7)	98.5 (98.1-98.8)	9.2 (0.7-26.1)
Least recent 50%	33.7 (22.4-46.0)	95.7 (93.5-96.9)	12.8 (3.3-27.4)

CI, Confidence interval; *LC*, laparoscopic cholecystectomy

identified pathologies, and response criteria for the decision to avoid cholecystectomy is not or is to a limited extent reported in the included studies. Consequently, the strategic effectiveness of EGD varies significantly. A trial randomizing referred patients to EGD and no EGD would curtail bias, but we surmise that the strategic yield would be limited.

The strengths of our study included the systematic assessment of the value of EGD in patients referred for cholecystectomy. We think we increase the reliability of the EGD findings by pooling results from individual studies. The analyses of pooled subgroups increases the generalizability of the findings. Physicians can use these numbers for clinical decision making in patients referred for cholecystectomy.

Future research in this area should focus on the process of clinical decision making. The effectiveness of diagnostics and therapeutics can be increased by critically evaluating its necessity at each step in treating patients. For patients with abdominal symptoms this indicates physicians should consider ultrasonography, EGD, initiate pharmacological symptomatic treatment or conduct a cholecystectomy. A critical assessment of patient characteristics and symptoms at each step should be part of this research to predict the effectiveness of clinical decision making.

In conclusion, our results indicate that, although many abnormalities are found with EGD in patients with cholelithiasis referred for gallbladder surgery, treatment of these findings rarely prevents cholecystectomy. Therefore, EGD should only be considered in a selective group of patients. Identification of this patient population should be subject of future research in order to increase the effectiveness of diagnostic and therapeutic modalities in the process of clinical decision making.

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Heterogeneity, I^2 (95% CI)	Total no. of cholecystectomies avoided, % (95% CI)	Heterogeneity, I^2 (95% CI)
97.3 (96.7-97.8)	3.8 (1.3-7.6)	97.1 (96.5-97.6)
96.7 (95.5-97.4)	3.2 (0.6-7.9)	97.0 (96.1-97.7)
82.7 (36.7-91.5)	1.1 (0.4-1.9)	64.9 (0.0-85.9)
98.5 (98.1-98.8)	3.3 (0.2-9.8)	98.4 (98.0-98.7)
93.8 (89.7-95.7)	4.2 (1.1-9.1)	93.0 (88.1-95.3)

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CHAPTER 7

COST-EFFECTIVENESS OF A NEW STRATEGY TO IDENTIFY UNCOMPLICATED GALLSTONE DISEASE PATIENTS THAT WILL BENEFIT FROM A CHOLECYSTECTOMY

Mark P. Lamberts[1,2,3],
Cihan Özdemir[4],
Joost P.H. Drenth[1],
Cornelis J.H.M. van Laarhoven[2],
Gert P. Westert[3],
Wietske Kievit[4]

[1]Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands
[2]Department of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands
[3]Scientific Institute for Quality of Healthcare (IQ healthcare), Radboud University Medical Centre, Nijmegen, The Netherlands
[4]Department for Health Evidence, Radboud University Medical Centre, Nijmegen, The Netherlands

Submitted

ABSTRACT

Background

The aim of this study was to determine the cost-effectiveness of a new strategy for the preoperative detection of patients that will likely benefit from a cholecystectomy, using simple criteria that can be applied by surgeons. Criteria for a cholecystectomy indication are: (1) Having episodic pain; (2) onset of pain 1 year or less before the outpatient clinic visit.

Methods

The cost-effectiveness of the new strategy was evaluated against current practice using a decision analytic model. The incremental cost-effectiveness of applying criteria for a cholecystectomy for a patient with abdominal pain and gallstones were compared to applying no criteria. The incremental cost-effectiveness ratio (ICER) was expressed as extra costs to be invested to gain one more patient with absence of pain. Scenarios were analyzed to assess the influence of applying different criteria.

Results

The new strategy of applying 1 out of 2 criteria resulted in a 4% higher mean proportion of patients with absence of pain compared to current practice with similar costs. The 95% upper limit of the ICER was €4,114 ($4,633) per extra patient with relief of upper abdominal pain. Application of 2 out of 2 criteria resulted in a 3% lower mean proportion of patients with absence of pain with lower costs.

Conclusion

The new strategy of using one out of two strict selection criteria may be an effective but also a cost-effective method to reduce the proportion of patients with pain after cholecystectomy.

BACKGROUND

Gallstones constitute a significant health problem in developed societies, affecting 5 to 22% of the adult population, but only an estimated 13 to 22% of gallstone carriers will eventually become symptomatic.[1, 2] The diagnosis of uncomplicated symptomatic gallstone disease is based on the Rome III criteria consisting of a steady abdominal pain, usually located in epigastrium and/or right upper quadrant lasting 30 minutes or longer in the presence of radiological detected gallstones.[3, 4] However, the sensitivity of these criteria is limited and 40% of the patients with symptomatic gallstones report far less specific abdominal pain symptoms.[5, 6]

A cholecystectomy is the therapy of first choice for patients diagnosed with uncomplicated symptomatic cholecystolithiasis.[7] There are no international guidelines that indicate which patient to offer a cholecystectomy or conservative treatment. Therefore the indication to perform a cholecystectomy lies within the surgeons' preference leading to variations in practice and consequently unnecessary cholecystectomies.[8-11] A systematic review reported in this journal demonstrated that up to 33% of patients has persistent abdominal pain following cholecystectomy.[12]

A strategy that is effective in selecting patients with abdominal pain and gallstones for surgery most likely to benefit from a cholecystectomy was developed. This strategy uses fixed selection criteria based on pain characteristics that are easy to use in clinical practice. Patients with abdominal pain and gallstones are selected for cholecystectomy if they fulfill one of the following two selection criteria[13, 14]: (1) episodic pain; (2) pain onset of 1 year or less before the outpatient clinic visit. Preoperative identification of patients with abdominal pain and gallstones who will benefit from a cholecystectomy from patients who will not, will probably lead to more effective use of cholecystectomies, fewer surgery-related complications and fewer unnecessary healthcare expenses. We performed a model based economic evaluation to evaluate a strategy based on fixed criteria for selecting patients for a cholecystectomy against current practice.

MATERIALS AND METHODS

The incremental cost effectiveness of the new strategy, restrictive care, compared with the usual care strategy was analyzed, following a healthcare perspective for a time horizon of one year. A decision analytic model was used with effectiveness expressed as absence of abdominal pain and costs in Euros (indexed to 2014). Models were built and analyzed using the decision analysis program TreeAge Software, Inc Williamstown, MA, USA, 2014 version (Fig. 1.). The study was approved by the medical ethics committee and informed consent for this modelling study was not needed.

Cost effectiveness model and model input

Cholecystectomy or watchful waiting were the treatment possibilities in both strategies. In the usual care strategy, the indication for cholecystectomy was left to the preference of the treating surgeon, thus without fixed selection criteria. In the restrictive care

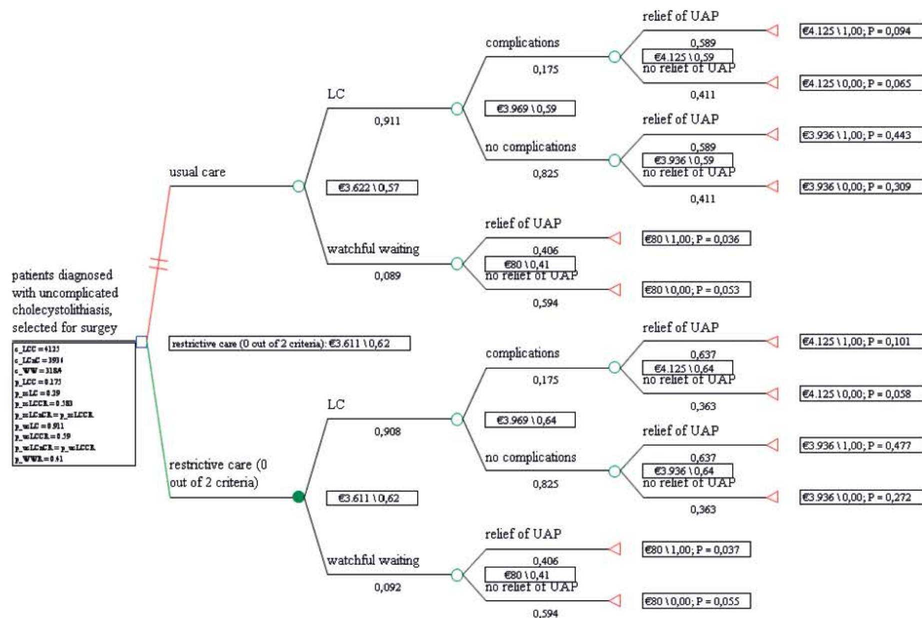

Figure 1. Decision model

strategy, the indication for cholecystectomy was only made after meeting criteria as described above.

Table 1 shows the variables used as input and the specific data sources. A database of a prospective multicentre cohort study was used for the probability of getting a cholecystectomy.[13] In this database, all patients with cholelithiasis referred for cholecystectomy that visited the departments of surgery of one tertiary referral centre and two non-academic teaching hospitals between June 2012 and June 2014 were recorded. The same prospective database was used for the probability of meeting the proposed criteria and the relief of upper abdominal pain afterwards. The relief of pain after cholecystectomy in usual care was based on a systematic review.[12] Following a healthcare perspective, we only used direct medical costs for analysis. A previous study and existing guideline prices for the Netherlands were used to value an outpatient clinic visit, a cholecystectomy including an overnight stay, and surgical complications.[15, 16] Application of the criteria itself for cholecystectomy in the restrictive care strategy did not lead to additional costs in itself.

For every modeling study assumptions need to be made, which were the following in this study: Watchful waiting included an extra outpatient clinic visit made in one year. Additional diagnostic work-up is patient-dependent and only rarely applied and is therefore not included in this model.[17]

Table 1. Basic input variables and sources used in the decision model (shown in Figure 1).

Input for the cost effectiveness model	Data source
Probability that a patient with abdominal symptoms and gallstones:	Prospective multicentre cohort study[13]
Satisfies one out of two criteria (thus receiving cholecystectomy)	(306/337=0.908)
Satisfies two out of two criteria (thus receiving cholecystectomy)	(138/337=0.409)
Probability of receiving cholecystectomy in usual care strategy	Prospective database of a multicentre cohort study[13] (0.911)
Probability of having a complication of the surgery	Randomized controlled trial[16] (0.175)
Probability of having absence of pain after watchful waiting	Prospective study[25] (0.41)
Probability of having absence of pain after cholecystectomy in usual care	Systematic review[12] (0.59)
Probability that a patient has absence of pain after cholecystectomy in restrictive care:	Prospective multicentre cohort study[13]
Satisfies one out of two criteria	(195/306=0.637)
Satisfies two out of two criteria	(100/138=0.725)
Costs of watchful waiting (=1 extra outpatient clinic visit)	Cost-effectiveness guidelines[15] €314 ($354)
Costs	Randomized controlled trial and cost-effectiveness guidelines[15, 16]
Cholecystectomy including overnight stay, with or without complications, outpatient clinic visit	€4,125 ($4,645) with complications €3,936 ($4,432) without complications

Analyses

The main outcome of both models were the incremental cost-effectiveness ratio expressed as the extra costs that need to be invested in order to get one more patient with relief of abdominal pain. Two analyses were performed. The first analysis focused on the incremental cost effectiveness of the new strategy in gallstone patients having a cholecystectomy if **one** of two criteria would be fulfilled compared with usual care. The second analysis focused on the incremental cost effectiveness of the new strategy in gallstone patients having a cholecystectomy if **two** out of two criteria would be fulfilled. Models were analyzed using a probabilistic sensitivity analysis. With this analysis the model is run a 1,000 times, each time picking another value from the distribution underlying the input parameters. Beta distributions for the probabilities of getting a cholecystectomy and relief of abdominal pain were used. For the cost parameters however no data were available to construct a distribution. Results from the 1,000 runs are graphically presented as scatterplots on cost-effectiveness planes and as means with 95% percentiles.

RESULTS

The results of the probabilistic sensitivity analysis of the first decision model with the new strategy of gallstone patients having a cholecystectomy if one of two criteria have been satisfied are shown in Figure 2. The new strategy was more effective compare with the usual care strategy and also less expensive. The mean percentage of patients with absence of pain in the new strategy was 62% (95% percentile 0.57-0.66), whereas with the usual care strategy this was 57% (95% percentile 0.55-0.60). The costs of the new strategy were €3,610 (95% percentile 3,487-3,722) ($4,065; 95% percentile 3,927-4,191), whereas the costs of the usual care strategy was €3,622 (95% percentile 3,536-3,706) ($4,078; 95% percentile 3,982-4,173). The mean cost difference was -€12 (95% percentile -134-105) (-$14; 95% percentile -151-118) with a mean effectiveness difference of 4.0 (95% percentile 0.2-8.0) for the new strategy compared with the usual care strategy. Fifty-three per cent of the simulations are located in the dominant quadrant, meaning a higher percentage of patient with relief of upper abdominal pain against lower costs. The 95% upper limit of the incremental cost-effectiveness ratio (ICER) is €4,114 ($4,633) per extra patient with relief of upper abdominal pain.

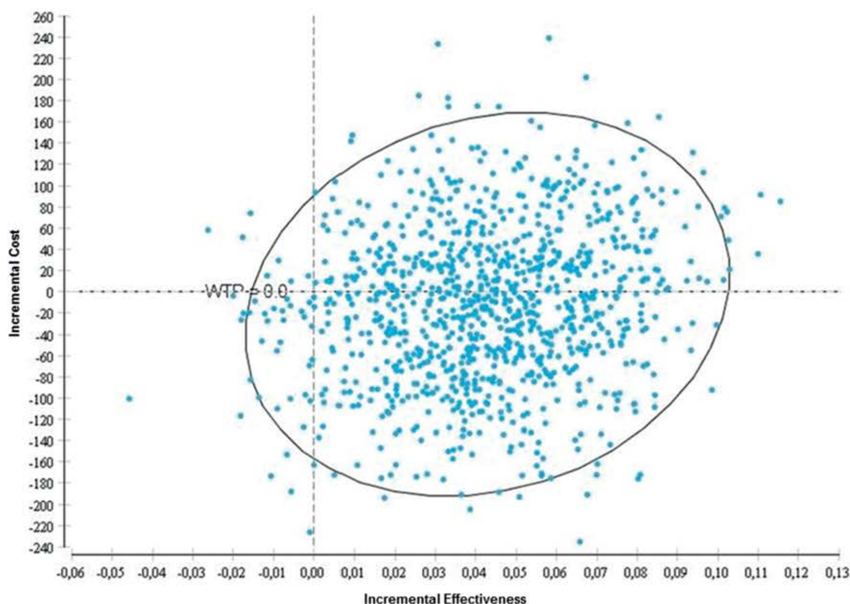

Figure 2. Probabilistic sensitivity analysis of the model with the new strategy of gallstone patients having cholecystectomy if one out of two criteria have been satisfied.

The results of the probabilistic sensitivity analysis of the second model with the new strategy of gallstone patients having a cholecystectomy if both criteria have been satisfied is shown in Figure 3. The mean percentage of patients with absence of pain in the new

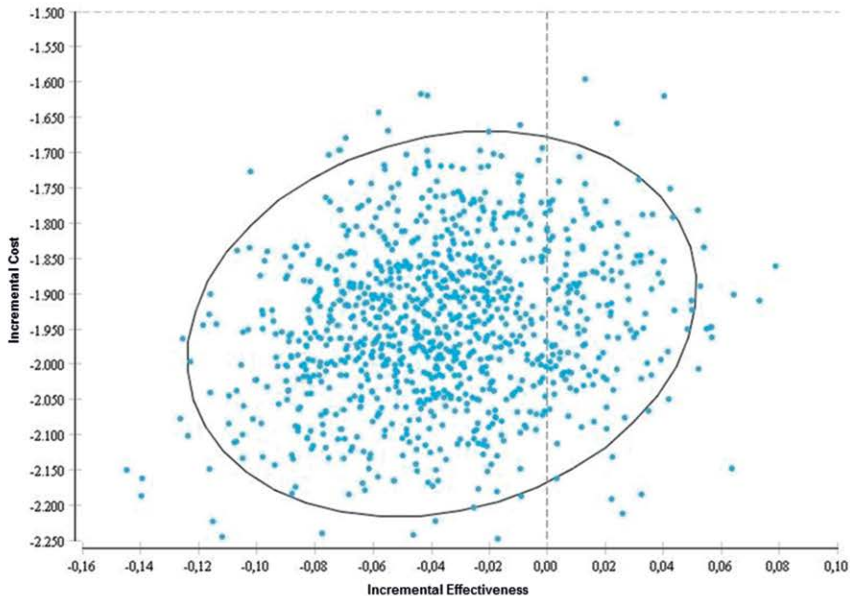

Figure 3. Probabilistic sensitivity analysis of the model with the new strategy of gallstone patients having cholecystectomy if both criteria have been satisfied

strategy was 54% (95% percentile 0.46-0.61), whereas with the usual care strategy this was 57% (95% percentile 0.55-0.60) and therefore more effective. The costs of the new strategy was €1,675 (95% percentile 1,471-1,886) ($1,886; 95% percentile 1,656-2,124), whereas the costs of the usual care strategy was €3,618 (95% percentile 3,527-3,700) ($4,074; 95% percentile 3,972-4,167). While in all simulations, the new strategy resulted in lower costs, only 16% of the simulations resulted in a higher percentage of patients with relief of upper abdominal pain.

DISCUSSION

This study showed that the strategy of using strict selection criteria may be a cost-effective method to reduce the proportion of patients with pain after cholecystectomy. The strategy of applying 1 out of 2 criteria resulted in a 4% higher mean proportion of patients with absence of pain compared to current practice with similar costs. The majority (54%) of the simulations resulted in the restricted care being dominant, meaning less expensive and more effective. In those simulations were the restrictive care strategy was more effective but also more expensive, there was a fair maximum to be paid per extra patient with relief of abdominal pain. Application of the more stringent 2 out of 2 criteria resulted in a 3% lower mean proportion of patients with absence of pain, but against lower costs.

In a previous study we showed that duration of pain of one year or less has a slightly higher odds ratio for absence of pain after cholecystectomy as compared to episodic abdominal pain (2.22 versus 2.13), although this difference is not significant.[13] Altogether

we would recommend to implement the strategy of applying 1 out of 2 criteria. Application of these criteria would offer surgeons less room for personal preferences which patient to offer a cholecystectomy and which patient to treat conservatively. This strategy would therefore provide a tool for better patient selection for each treatment arm. A recent cost-effectiveness study reported in this journal comparing cholecystectomy with observation for uncomplicated symptomatic cholecystolithiasis or acute cholecystitis reported that cholecystectomy is the preferred treatment for symptomatic gallstones. On average, surgery costs £1,236 (€1,448; $1,631) more per patient than conservative management, but was more effective. However, the study also reported that 55% of the patients randomized to the observation group did not require surgery indicating that it may be a valid alternative to surgery.[18] Application of fixed criteria for cholecystectomy may increase the cost-effectiveness of cholecystectomy and conservative treatment as shown in this study.

Effectiveness of an intervention is often reported in cost-effectiveness studies as quality adjusted life years (QALY).[18] However, abdominal pain is the most characteristic feature of uncomplicated symptomatic cholecystolithiasis and therefore relief of abdominal pain is the main aim of cholecystectomy in this patient group.[3-6] In addition, absence of pain after cholecystectomy is the main predictor of a patient-reported successful outcome of the operation.[19] The Gastrointestinal Quality of Life Index, a patient-reported outcome measure computing quality of life, may not be sufficiently disease specific.[20, 21] Abdominal pain, for example, is equally scored as flatulence in this questionnaire. Other patient-reported outcome measures computing quality of life are no different in weighing persistent abdominal pain.[22] Furthermore, a quality of life score is less applicable in surgical practice compared to presence or absence of abdominal pain. We therefore selected absence of postoperative abdominal pain as effectiveness outcome.

This study must be considered within the context of some limitations. First, the criteria for selection for cholecystectomy remain non-specific, although they are more specific than current practice entirely based on the surgeons' preference. Second, the criteria of the new strategy were not externally validated, although this may have been challenging to perform due to strong treatment preferences of patients and surgeons.[23-25] Third, we focused on uncomplicated symptomatic cholelithiasis patients. Patients with complicated symptomatic cholelithiasis were not considered. Exclusion of complicated symptomatic cholelithiasis may not have had a large impact as the patient group with uncomplicated symptomatic cholelithiasis only have an annual 1-3% risk on complications because of the stones.[26] Furthermore, the observation group of a randomized controlled trial of patients with uncomplicated symptomatic cholecystolithiasis did not suffer complications during 14 years of follow-up.[27] Forth, we excluded patients having a bile duct injury as this specific complication of cholecystectomy has a low incidence of 0.04-1.5%.[28, 29] Fifth, we did not consider additional diagnostic work-up because of lack of data, variability and patient-dependency.[17] Finally, the new strategy was evaluated from a healthcare perspective for a time horizon of 1 year. If a societal perspective would be taken into account, the restrictive care strategy of having one out of two criteria satisfied would

probably be even more cost-effective, because this strategy was more effective in terms of relief of abdominal pain and prevented cholecystectomies, probably preventing sick leave. Patients with ongoing abdominal pain would continue to seek medical help with additional diagnostic interventions.

This study should be considered a pilot study before assessing the cost-effectiveness of the application of these criteria in an actual trial. Apart from confirming these results in a prospective randomized multicentre study, future research should focus on further maximizing the cost-effectiveness of cholecystectomy. Determination of patients with cholelithiasis at risk for complications due to the gallstones may benefit from earlier cholecystectomy. Selection for earlier surgery of those patients who are most likely to benefit will further increase the cost-effectiveness of this common surgical procedure. In addition, not only should be assessed which patient will benefit from cholecystectomy, but also which patient will benefit most. Episodic abdominal pain due to gallstones may not significantly affect the health status of all patients to that extent that a cholecystectomy is required. The necessity may depend on frequency, duration, and intensity of the abdominal pain episodes.[30] Reliable prediction models combining clinical parameters with patient-reported outcome measures may facilitate efficient use of scarce healthcare resources.[31]

In conclusion, the new strategy was more effective, against similar costs, than current practice if one out of two criteria were applied. More stringent application of criteria resulted into loss of effectiveness. The new strategy of using strict selection criteria may be a cost-effective method to reduce to proportion of patients with pain after cholecystectomy.

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CHAPTER 8

EPISODIC ABDOMINAL PAIN CHARACTERISTICS ARE NOT ASSOCIATED WITH CLINICALLY RELEVANT IMPROVEMENT OF HEALTH STATUS AFTER CHOLECYSTECTOMY

Mark P. Lamberts[1,2,3],
Wietske Kievit[4],
Jos J. G. M. Gerritsen[5],
Jan A. Roukema[6],
Gert P. Westert[1],
Joost P. H. Drenth[2],
Cornelis J. H. M. van Laarhoven[3]

[1]Scientific Institute for Quality of Healthcare (IQ healthcare), Radboud University Medical Centre, Nijmegen, The Netherlands
[2]Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands
[3]Department of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands
[4]Department for Health Evidence, Radboud University Medical Centre, Nijmegen, The Netherlands
[5]Department of Surgery, Medisch Spectrum Twente, Enschede, The Netherlands
[6]Department of Surgery, St. Elisabeth Hospital, Tilburg, The Netherlands

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ABSTRACT

Background

Cholecystectomy is the therapy of first choice in patients with uncomplicated symptomatic cholecystolithiasis, but it remains unclear which patients truly benefit in terms of health status improvement. Patients generally present with episodic abdominal pain of varying frequency, duration and intensity. We assessed whether characteristics of abdominal pain episodes are determinants of clinically relevant improvement of health status after cholecystectomy.

Methods

In a post-hoc analysis of a prospective multicentre cohort study patients of ≥ 18 years of age with uncomplicated symptomatic cholecystolithiasis subjected to cholecystectomy were included. Preoperatively, patients received a structured interview and a questionnaire consisting of the visual analogue scale (VAS, range 0-100) and gastrointestinal quality of life index (GIQLI). At 12 weeks after cholecystectomy, the GIQLI was again administered. Logistic regression analyses were performed to determine significant associations.

Results

Questionnaires were sent to 261 and returned by 166 (63.6%) patients (128 females, mean age at surgery 49.5 ± 13.8). A total of 131 (78.9%) patients reported a clinically relevant improvement of health status. The median (interquartile range) frequency, duration and intensity of abdominal pain episodes were 0.38 (0.18-0.75) a week, 4.00 (2.00-8.00) hours and 92 (77-99), respectively. None of the characteristics was associated with a clinically relevant improvement of health status at 12 weeks after cholecystectomy.

Conclusions

Characteristics of abdominal pain episodes cannot be used to inform patients with symptomatic cholecystolithiasis who are skeptic about the timing of cholecystectomy for optimal benefit. Timing of cholecystectomy should therefore be based on other characteristics and preferences.

INTRODUCTION

Cholecystolithiasis represents a clinical spectrum that ranges from asymptomatic gallstone disease to uncomplicated symptomatic gallstone disease to acute cholecystitis. Likewise, therapeutic options may go from conservative treatment to cholecystectomy. Patients with asymptomatic cholecystolithiasis benefit least from cholecystectomy in terms of improvement of health status and should receive conservative care, whereas those with acute cholecystitis benefit most and should receive surgery.[1-4] The optimal timing that results in the highest benefit for patients with uncomplicated symptomatic cholecystolithiasis remains less clear.

Uncomplicated symptomatic cholecystolithiasis is frequently characterized by abdominal pain episodes of widely varying frequency. These episodes may last minutes or several hours, and their intensity is variable.[5] Previous studies have shown that patients with a higher frequency of episodic abdominal pain were less likely to obtain pain relief after cholecystectomy.[6-10] Conversely, those with a typical episode duration between 30 minutes and 24 hours were more likely to report absence of pain after surgery, whereas patients with a higher pain intensity were not more likely to report absence of pain.[10] Abdominal symptom characteristics may also indicate which patients are most likely to display clinically relevant improvement of patient-reported overall health status after cholecystectomy: a more comprehensive outcome measure that not only includes symptom evaluation, but also emotional, physical, and social functioning.[11]

We aimed to assess whether frequency, maximum duration, or intensity of abdominal pain episodes were associated with improvement of health status in order to define which patients with uncomplicated symptomatic cholecystolithiasis may benefit most from cholecystectomy. We also assessed the associations of these episode characteristics with different subscales of health status at 12 weeks after cholecystectomy.

METHODS

Study sites and patient selection

We performed a post-hoc analysis using the database established during a previous multicentre cohort study conducted in The Netherlands. Details of study design were reported previously.[12] In short, all individuals aged 18 years and over with symptomatic cholelithiasis, who visited the surgical outpatient clinic at a tertiary referral centre (Radboud University Medical Centre, Nijmegen) or one of two non-academic teaching hospitals (St. Elisabeth Hospital, Tilburg and the Medisch Spectrum Twente Hospital, Enschede) between June 2012 and June 2014, and were scheduled for elective cholecystectomy were eligible for participation in the study. Cholelithiasis was defined as abdominal pain associated with gallstones, confirmed with ultrasound imaging. Medical histories were obtained by a single physician (MPL) through a structured interview.

Patients were asked to recall the duration of symptoms, the number of episodes, and longest episode duration. Patients with a history of symptoms for more than 1 year or who reported to have experienced more than five episodes were excluded,

because most of these patients could not recall the frequency. Consequently, these data were only sporadically reported in the database. In addition, we excluded those with schizophrenia or other mental disorders that may impair recall. Other exclusion criteria were as follows: a history of complicated symptomatic cholelithiasis (acute cholecystitis, cholangitis, biliary pancreatitis, choledocholithiasis requiring endoscopic retrograde cholangiopancreatography (ERCP)),[13, 14] ASA fitness grade III and IV, insufficient knowledge of the Dutch language, non-Dutch residency, blindness, pregnancy, cirrhosis, or cancer treatment. Eligible patients were asked to complete a questionnaire before cholecystectomy and 12 weeks after cholecystectomy. Patients who failed to return or complete the questionnaire before and after surgery were excluded.

The questionnaire consisted of the Gastrointestinal Quality of Life Index (GIQLI). The GIQLI has been developed in Germany and has been translated and validated in Dutch.[15, 16] For an example of the questions and response categories of this questionnaire, we refer to a previous study.[15] The GIQLI addresses upper and lower gastrointestinal symptoms (19 questions), emotional (5 questions), physical (7 questions), social well-being (4 questions) and effect of medical treatment (1 question) in the previous 2 weeks. Each question contains five response categories. Questions can be scored using a response scale ranging from 0 (worst appraisal) to 4 points (best appraisal) for each question, giving an overall score of 0-144 points. The higher the score, the better overall health status is. A clinically relevant improvement after surgery was defined as an increase of 5 points or more in the overall score or in any of the subscales.[17] We also included a visual analogue score (VAS) providing a range of scores from 0 to 100 to quantify the maximum severity of pain preoperatively.

The study was approved by the medical ethics committee and reported in accordance with the recommendations in the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for reporting observational studies.[18]

Outcomes and Variables of Interest

The primary outcome was defined as a clinically relevant improvement of overall health status. Secondary outcomes included a clinically relevant improvement of upper and lower gastrointestinal symptoms, or on the emotional, physical, and social subscales, respectively. Based on previous publications, the independent variables included sex,[10, 19] age at operation,[10, 19] centre,[10] baseline GIQLI score,[19] ASA fitness grade, frequency, maximum duration and intensity of abdominal pain episodes.

Statistical Analysis

We examined whether baseline clinical and abdominal pain characteristics differed between responders and non-responders to the questionnaire, using χ^2 tests or Fisher's exact tests for categorical data, Student's t tests for continuous data, and Mann-Whitney U tests for ordinal data. We determined which variables were associated in univariable analysis with a clinically relevant improvement of health status after surgery using logistic regression analyses. Significant variables in univariable analysis ($P < 0.10$) were

introduced into a backward multivariable regression model to determine whether there were independent predictors of clinically relevant improvement of overall health status or any of the subscales after surgery. Age at operation, sex, centre, and baseline GIQLI score were the variables that were retained in the model as co-variables. Results were reported as adjusted odds ratios (ORs) with corresponding 95% confidence intervals. $P < 0.05$ was considered statistically significant. All missing values were considered to be completely at random and excluded from analyses. Statistical analyses were performed using SPSS statistical software version 20.0 (IBM, Armonk, New York, USA).

RESULTS

The database consisted of 870 potentially eligible patients. A total of 261 patients were included. Preoperative and postoperative questionnaires were returned and completed by 166 (63.6%) patients (Fig. 1). Baseline characteristics of the responding patients are shown in Table 1. One hundred and twenty-eight of the responding patients were females. Mean age at surgery was 49.5 ± 13.8 years. The median (interquartile range) frequency, duration and intensity of abdominal pain episodes were 0.38 (0.18-0.75) a week, 4.00 (2.00-8.00) hours and 92 (77-99), respectively. Baseline and abdominal pain characteristics did not differ between responders and non-responders.

One hundred and thirty-one (78.9%) patients reported an overall clinically relevant improvement after surgery. Univariable analysis showed maximum intensity of abdominal pain episodes to be associated with clinically relevant improvement of overall health status (OR 1.02, 95% CI 1.00-1.04; $P = 0.069$) (Table 2). Maximum intensity of abdominal pain episodes did not remain associated in multivariable analysis (OR 1.03, 95% CI 1.00-1.05; $P = 0.066$).

On the gastrointestinal symptoms subscale, 105 (63.3%) patients reported a clinically relevant improvement (Table 3). The emotional subscale showed a clinically relevant improvement in 37 (22.3%) patients. A clinically relevant improvement of the physical subscale was reported by 54 (32.5%) patients. Thirty-nine (23.5%) patients showed a clinically relevant improvement of the social subscale.

Duration was associated with clinically relevant improvement of the physical (OR 1.07, 95% CI 1.02-1.12; $P = 0.007$) and social subscales (OR 1.09, 95% CI 1.04-1.14; $P < 0.001$) in univariable analysis (Table 3). Univariable analysis showed frequency to be associated with clinically relevant improvement of the social subscale (OR 2.39, 95% CI 1.11-5.12; $P = 0.025$). In multivariable analysis, duration (OR 1.10, 95% CI, 1.03-1.17; $P = 0.003$) and frequency (OR 2.95, 95% CI 1.08-8.08; $P = 0.035$) of abdominal pain episodes with clinically relevant improvement of the social subscale remained associated.

DISCUSSION

This study showed a clinically relevant improvement of overall health status in 131 (78.9%) patients at 12 weeks after cholecystectomy. Episode characteristics of pain were not associated with an overall clinically relevant improvement of health status after

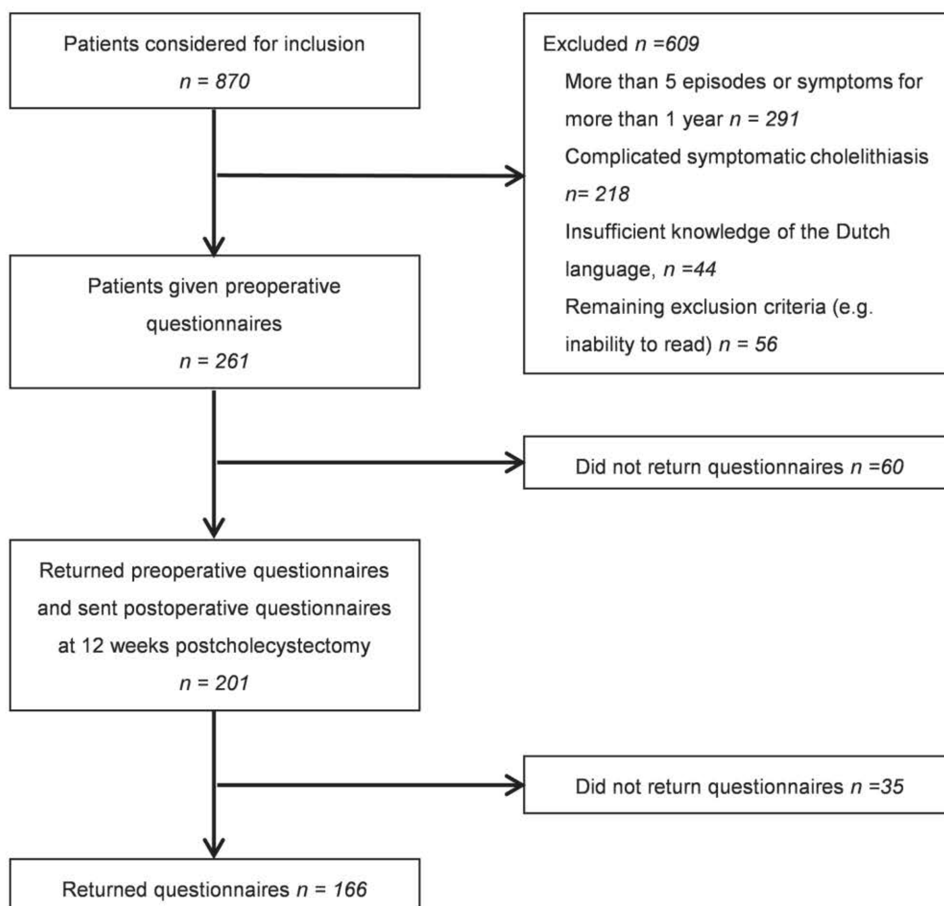

Figure 1. Flow chart showing inclusion of patients in the study.

surgery, but patients with a higher frequency and a longer duration of abdominal pain episodes were more likely to have a clinically relevant improvement of social functioning after surgery.

The preoperative health status score and improvement of health status were similar to studies using the same patient-reported outcomes.[1-4] We measured patient-reported outcomes at 12 weeks after cholecystectomy as studies suggest that the results at this time point persist at long term follow-up.[10, 20] In studies defining clinically relevant health outcome after surgery exclusively as pain or symptom relief, abdominal pain episode characteristics were associated with a better outcome.[6-10] We showed, however, that characteristics of abdominal pain episodes were not associated with overall health outcome when other factors such as emotional and social functioning are also taken into account. No associations were found between abdominal pain episode characteristics and all the subscales of health status, except for the social subscale. This study showed an association of increased pain episode frequency with the social subscale of health status

Table 1. Characteristics of the responding and non-responders to the questionnaires

Characteristic	Responders, n = 166	Non-responders, n = 95	P value
Age (years)	49.5 ± 13.8	46.3 ± 16.3	0.09
Sex			0.81
Male	38 (22.9)	23 (24.2)	
Female	128 (77.1)	72 (75.8)	
ASA fitness grade			0.46
I	83 (50.0)	52 (54.7)	
II	83 (50.0)	43 (45.3)	
Center			
Radboud UMC	36 (21.7)	19 (20.0)	NA
MST	69 (41.6)	47 (49.5)	NA
St Elisabeth Hospital	61 (36.7)	29 (32.2)	NA
Frequency of abdominal pain episodes a week	0.4 (0.2-0.8)	0.3 (0.2-0.7)	0.65
Duration of longest abdominal pain episode in hours	4.0 (2.0-8.0)	4.0 (2.0-6.3)	0.48
Maximum intensity of pain episode ranging 0-100	92 (77-99)		NA
Baseline GIQLI score	103.5 ± 22.1		NA
GIQLI score 12 weeks after cholecystectomy	124.4 ± 13.7		NA

Data are expressed as mean (standard deviation) or n (%) or median (interquartile range).
ASA, American Society of Anesthesiologists; GIQLI, Gastrointestinal Quality of Life Index;
UMC, University Medical Center; NA, not applicable; MST, Medisch Spectrum Twente hospital.

improvement. In addition, a longer duration of pain episodes has been associated with absence of pain,[10] whereas an association was found with clinically relevant improvement of social functioning in this study. The higher frequency and longer duration may have been caused by an undetected social disabling mild acute cholecystitis.[13] This suggestion may certainly fit with the spectrum of cholecystolithiasis.

The main explanation for the discrepant results with literature is the difference in patient-reported outcomes. The most comprehensive patient-reported outcome measure in patients with uncomplicated symptomatic cholecystolithiasis to determine appropriate and efficient utilization of cholecystectomy is still under debate. Postoperative absence of pain, satisfaction, and health status improvement all have been previously used as primary patient-reported outcome measures.[11] Argument for using patient-reported absence of postoperative pain as primary outcome is that the diagnosis of uncomplicated symptomatic cholecystolithiasis is based on abdominal pain.[21-23] In addition, postoperative pain after cholecystectomy is the main predictor of a patient-reported unsuccessful outcome.[24] Satisfaction as primary outcome has the advantage of providing information about the relationship between patient expectations and the treatment experience. Satisfaction incorporates the description of healthcare from the patient's viewpoint, measurement of the process of care, and evaluation of its outcome.[11] Finally, arguments for using health status improvement is that it measures various domains of health and on a continuous scale. This outcome allows us to determine which patient benefits most from therapy.[11]

Table 2. Univariable and multivariable association of pain episode characteristics with patient-reported minimal clinically important improvement of health status

	Clinically relevant improvement		**Univariable analysis**		**Multivariable analysis**	
	< 5 points on GIQLI, n = 35	**≥ 5 points on GIQLI, n = 131**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Age (years)	50.6 ± 13.6	49.2 ± 13.9	0.99 (0.97-1.02)	0.586	1.0 (0.96-1.04)	0.885
Sex				0.179		0.650
Female	24 (68.6)	104 (79.4)	1.77 (0.77-4.05)		0.76 (0.24-2.46)	
Male	11 (31.4)	27 (20.6)	1.00 (reference)			
Hospital type				0.850		0.812
Tertiary referral center	8 (22.9)	28 (21.4)	0.92 (0.38-2.24)		0.86 (0.24-3.06)	
Non-academic	27 (77.1)	103 (78.6)	1.00 (reference)			
Baseline GIQLI score	126.6 ± 11.8	97.3 ± 20.0	0.88 (0.84-0.92)	< 0.001	0.88 (0.84-0.92)	< 0.001
ASA fitness grade				0.568		
II	16 (45.7)	67 (51.1)	1.24 (0.59-2.63)			
I	19 (54.3)	64 (48.8)	1.00 (reference)			
Frequency of pain episodes a week	0.4 (0.2-0.5)	0.4 (0.2-1.0)	1.66 (0.65-4.26)	0.287		
Maximum duration of longest pain episode in hours	4.0 (2.5-9.0)	4.0 (2.0-8.0)	1.01 (0.96-1.07)	0.648		
Maximum intensity of pain episode ranging 0-100	88.5 (72.0-94.3)	93.5 (79.0-99.8)	1.02 (1.00-1.04)	0.069	1.03 (1.00-1.05)	0.066

Data are expressed as mean (standard deviation) or n (%) or median (interquartile range). *95% CI*, 95% confidence interval; *ASA*, American Society of Anesthesiologists; *GIQLI*, Gastrointestinal Quality of Life Index

Health status improvement was therefore chosen as primary patient-reported outcome in this study.

Our study has some limitations. First, we cannot fully rule out recall bias, although we limited this type of bias by excluding patients that could not recall abdominal pain frequency. The generalizability of the results may therefore be limited, although the patient characteristics are no different compared with the characteristics of other studies.[5-10] Second, the inclusion of referred patients and the limited response rate may have caused selection bias, although we did not find any significant differences between the responding and non-responding patients. Third, we performed a post-hoc analysis

Table 3. Univariable and multivariable association of pain episode characteristics with patient-reported improvement of health status subscales

	Clinically relevant improvement		Univariable analysis		Multivariable analysis	
Gastrointestinal symptoms subscale	**< 5 points on GIQLI, n = 61**	**≥ 5 points on GIQLI, n = 105**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Age (years)	47.1 ± 15.2	50.9 ± 12.7	1.02 (1.00-1.05)	0.087	1.03 (1.00-1.06)	0.048
Sex				0.056		0.230
Female	42 (68.9)	86 (81.9)	2.05 (0.98-4.27)		1.74 (0.71-4.32)	
Male	19 (31.1)	19 (18.1)	1.00 (reference)			
Hospital type				0.143		0.228
Tertiary referral center	17 (27.9)	19 (18.1)	0.57 (0.27-1.21)		0.56 (0.22-1.43)	
Non-academic	44 (72.1)	86 (81.9)	1.00 (reference)			
Baseline GIQLI score	117.9 ± 17.8	95.1 ± 19.9	0.94 (0.92-0.96)	< 0.001	0.94 (0.91-0.96)	< 0.001
ASA fitness grade				0.148		
II	26 (42.6)	57 (54.3)	1.60 (0.85-3.02)			
I	35 (57.4)	48 (45.7)	1.00 (reference)			
Frequency of pain episodes a week	0.4 (0.2-0.7)	0.4 (0.2-0.8)	1.21 (0.58-2.50)	0.613		
Duration of longest pain episode in hours	4.0 (2.0-8.0)	4.0 (2.0-8.0)	1.01 (0.96-1.05)	0.828		
Maximum intensity of pain episode ranging 0-100	89.0 (77.0-96.5)	94.0 (78.0-100.0)	1.01 (0.99-1.03)	0.329		

	Clinically relevant improvement		Univariable analysis		Multivariable analysis	
Emotional subscale	**< 5 points on GIQLI, n = 129**	**≥ 5 points on GIQLI, n = 37**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Age (years)	49.6 ± 13.8)	49.0 ± 13.7	1.00 (0.97-1.02)	0.790	0.99 (0.95-1.02)	0.389
Sex				0.277		0.568
Female	97 (75.2)	31 (83.8)	1.70 (0.65-4.46)		0.71 (0.22-2.32)	
Male	32 (24.8)	6 (16.2)	1.00 (reference)			
Hospital type				0.991		0.736
Tertiary referral center	28 (21.7)	8 (21.6)	1.00 (0.41-2.42)		1.20 (0.42-3.47)	

Table 3. (continued)

Emotional subscale	Clinically relevant improvement: < 5 points on GIQLI, n = 129	Clinically relevant improvement: ≥ 5 points on GIQLI, n = 37	Univariable analysis: Odds ratio (95% CI)	Univariable analysis: P-value	Multivariable analysis: Odds ratio (95% CI)	Multivariable analysis: P-value
Non-academic	101 (78.3)	29 (78.4)	1.00 (reference)			
Baseline GIQLI score	109.7 ± 18.5	81.9 ± 20.2	0.93 (0.91-0.95)	< 0.001	0.93 (0.90-0.95)	< 0.001
ASA fitness grade				0.852		
II	65 (50.4)	18 (48.6)	0.93 (0.45-1.94)			
I	64 (49.6)	19 (51.4)	1.00 (reference)			
Frequency of pain episodes a week	0.4 (0.2-0.7)	0.4 (0.2-1.0)	1.01 (0.44-2.31)	0.978		
Duration of longest pain episode in hours	4.0 (2.0-8.0)	5.0 (2.0-8.0)	1.02 (0.97-1.08)	0.362		
Maximum intensity of pain episode ranging 0-100	92.0 (77.0-99.0)	95.0 (79.0-99.3)	1.01 (0.99-1.03)	0.524		

Physical subscale	Clinically relevant improvement: < 5 points on GIQLI, n = 112	Clinically relevant improvement: ≥ 5 points on GIQLI, n = 54	Univariable analysis: Odds ratio (95% CI)	Univariable analysis: P-value	Multivariable analysis: Odds ratio (95% CI)	Multivariable analysis: P-value
Age (years)	49.6 ± 14.4	49.3 ± 12.5	0.99 (0.98-1.02)	0.916	0.99 (0.96-1.02)	0.524
Sex				0.353		0.584
Female	84 (75.0)	44 (81.5)	1.47 (0.65-3.29)		0.76 (0.28-2.03)	
Male	28 (25.0)	10 (18.5)	1.00 (reference)			
Hospital type				0.278		0.310
Tertiary referral center	27 (24.1)	9 (16.7)	0.63 (0.27-1.45)		0.61 (0.23-1.59)	
Non-academic	85 (75.9)	45 (83.3)	1.00 (reference)			
Baseline GIQLI score	111.2 ± 19.7)	87.5 ± 17.9	0.94 (0.92-0.96)	< 0.001	0.94 (0.92-0.96)	< 0.001
ASA fitness grade				1.000		
II	56 (50.0)	27 (50.0)	1.00 (0.52-1.91)			
I	56 (50.0)	27 (50.0)	1.00 (reference)			
Frequency of pain episodes a week	0.38 (0.19-0.67)	0.33 (0.18-1.00)	1.27 (0.62-2.62)	0.514		

Table 3. (continued)

	Clinically relevant improvement		Univariable analysis		Multivariable analysis	
Physical subscale	**< 5 points on GIQLI, n = 112**	**≥ 5 points on GIQLI, n = 54**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Duration of longest pain episode in hours	4.0 (2.0-6.0)	5.0 (2.4-13.5)	1.07 (1.02-1.12)	0.007		
Maximum intensity of pain episode ranging 0-100	91.0 (77.0-100.0)	94.0 (86.0-99.0)	1.01 (0.99-1.03)	0.316		

	Clinically relevant improvement		Univariable analysis		Multivariable analysis	
Social subscale	**< 5 points on GIQLI, n = 127**	**≥ 5 points on GIQLI, n = 39**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Age (years)	47.5 ± 12.6	50.1 ± 14.1	0.99 (0.96-1.01)	0.303	0.97 (0.94-1.01)	0.096
Sex				0.207		0.622
Female	95 (74.8)	33 (84.6)	1.85 (0.71-4.83)		1.40 (0.37-5.28)	
Male	32 (25.2)	6 (15.4)	1.00 (reference)			
Hospital type				0.132		0.069
Tertiary referral center	31 (24.4)	5 (12.8)	0.46 (0.16-1.27)		0.28 (0.07-1.10)	
Non-academic	96 (75.6)	34 (87.2)	1.00 (reference)			
Baseline GIQLI score	109.8 ± 19.7	82.7 ± 15.9	0.93 (0.91-0.96)	< 0.001	0.93 (0.91-0.96)	< 0.001
ASA fitness grade				0.855		
II	63 (49.6)	20 (51.3)	1.07 (0.52-2.19)			
I	64 (50.4)	19 (48.7)	1.00 (reference)			
Frequency of pain episodes a week	0.33 (0.17-0.63)	0.50 (0.21-1.00)	2.39 (1.11-5.12)	0.025	2.95 (1.08-8.08)	0.035
Duration of longest pain episode (hours)	4.0 (2.0-6.0)	6.0 (3.0-23.0)	1.09 (1.04-1.14)	< 0.001	1.10 (1.03-1.17)	0.003
Maximum intensity of pain episode ranging 0-100	91.5 (77.0-98.0)	95.0 (79.3-100.0)	1.01 (0.99-1.03)	0.546		

Data are expressed as mean (standard deviation) or n (%) or median (interquartile range). 95% CI, 95% confidence interval; ASA, American Society of Anesthesiologists; GIQLI, Gastrointestinal Quality of Life Index

using a database of a previous multicentre cohort study. A formal power analysis was therefore not conducted. Finally, the natural course of symptoms,[25, 26] placebo effect of surgery,[27] or expectancy of patients[28] may have biased the questionnaire answers. Concerning the wax and waning of abdominal pain episodes,[5] we corrected for preoperative health status. Unfortunately, randomized trials to limit biased questionnaire answers were prohibited due to ethical reasons.

This study included several strengths as well. First, the database of a prospective observational study was used limiting confounding bias. Second, we used a standardized and validated questionnaire allowing reliable comparisons with other studies using this widely translated and validated questionnaire.[15, 16] Third, using a single interviewer in all three centres excluded interobserver bias. Finally, patients were recruited from both tertiary and general hospitals increasing the generalizability.

Since patients that benefit most in terms of health status improvement cannot be predicted using abdominal pain episode characteristics, future studies should assess which uncomplicated symptomatic cholecystolithiasis patients are at increased risk for complicated cholecystolithiasis. Although the risk of complications because of gallstones in uncomplicated symptomatic cholecystolithiasis patients is estimated to be only 1-3% a year, these complications can be serious and life threatening as previously reported in this journal.[29, 30] Preventing uncomplicated symptomatic cholecystolithiasis patients to proceed to complicated symptomatic cholecystolithiasis by early cholecystectomy would increase the cost-effectiveness of this common surgical procedure.

In conclusion, frequency, maximum duration, and intensity of abdominal pain episodes are not associated with a patient-reported clinically relevant improvement of health status at 12 weeks after cholecystectomy. Characteristics of abdominal pain episodes cannot be used to inform patients with symptomatic cholecystolithiasis who are skeptic about the timing of cholecystectomy for optimal benefit. Timing of cholecystectomy for these patients should therefore be based on other characteristics and preferences.

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CHAPTER 9

THE DUTCH GUIDELINE FOR DIAGNOSIS AND TREATMENT OF CHOLELITHIASIS

Mark P. Lamberts[1, 2],
Jennifer M.J. Schreinemakers[2],
Djamila Boerma[3],
Erik A. Rauws[4],
Erwin de Boer[5],
Karel J. van Erpecum[6],
John J. Hermans[7],
Cornelis J.H.M. van Laarhoven[2]

[1]Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, The Netherlands
[2]Department of Surgery, Radboud University Medical Centre, Nijmegen, The Netherlands
[3]Department of Surgery, St Antonius Hospital, Nieuwegein, The Netherlands
[4]Department of Gastroenterology and Hepatology, Amsterdam Medical Centre, Amsterdam, The Netherlands
[5]Department of Radiology, Isala Klinieken, Zwolle, The Netherlands
[6]Department of Gastroenterology and Hepatology, University Medical Centre Utrecht, Utrecht, The Netherlands
[7]Department of Radiology, Radboud University Medical Centre, Nijmegen, The Netherlands

Submitted

ABSTRACT

In this updated Dutch guideline for diagnosis and treatment of gallstone disease we provide recommendations for management of cholelithiasis. The number of new cholecystectomy techniques, the development regarding the treatment of biliary pancreatitis, and many other recent studies on gallstone disease warranted an updated guideline. Recently, the Dutch health care insurance companies have noted considerable variations in practice of cholecystectomies in the Netherlands. Guidelines are eminently a tool to reduce practice variations by offering recommendations for diagnosis and treatment, and levels of evidence of the studies on which the guidelines are based. This guideline, formulated on behalf of The Dutch Association of Surgery, The Dutch Association of Gastroenterology and Hepatology and The Dutch Association of Radiology serves as an evidence-based manual for clinicians for diagnosis and treatment of gallstone disease.

INTRODUCTION

Gallstone disease is one of the most prevalent gastrointestinal diseases in Western countries.[1,2] Gallstones are most frequently diagnosed by ultrasonography. Most gallstones are asymptomatic and are treated conservatively. Treatment of symptomatic gallstone disease (symptomatic cholecystolithiasis) is customized. The traditional treatment of symptomatic cholecystolithiasis is a cholecystectomy.[3] Until the end of the '80's open cholecystectomy was considered the gold standard for treatment of cholecystolithiasis. By adopting minimal invasive techniques for cholecystectomies patients recovered more quickly and morbidity decreased.[4] The challenge to even further minimize incisions resulted in a number of new minimal invasive cholecystectomy techniques. In addition, there have been several exciting studies regarding the management of biliary pancreatitis. These and other recent innovations highlighted the need of an updated guideline on gallstone disease. The last Dutch guideline on management of gallstone disease stems from 2007. We provide the reader with a revised guideline with concise recommendations for the diagnosis and treatment of gallstone disease in order to guide the clinician through the updated therapeutic environment. For the complete guideline we refer to www.heelkunde.nl.

BACKGROUND

In Western countries, approximately 75% of gallstones are cholesterol stones and 25% are pigment stones.[5] Cholesterol stones can arise in case of cholesterol supersaturation due to increased cholesterol secretion and decreased bile salt and phospholipid secretion. Phospholipids and bile salts solubilize in mixed micelles. In case of excess cholesterol secretion or decreased bile salt or phospholipid secretion, cholesterol crystals may nucleate from the supersaturated bile (the earliest event in gallstone formation).[6,7] Impaired gallbladder emptying allows aggregation of the cholesterol crystals into macroscopic stones. Risk factors for cholesterol gallstones include increasing age, female gender, obesity, substantial weight loss, pregnancy, ethnicity, parenteral nutrition, consumption of estrogen or somatostatin analogues, and a positive family history. There is no evident association between dietary habits and the genesis of gallstones.[7]

Non-cholesterol gallstones can be divided into black and brown pigment stones. These stones mainly consist of bilirubin. Black pigment stones develop in the gallbladder and are associated with hemolytic disorders including thalassemia or sickle cells disease, whereas brown pigment stones occur in the bile ducts in general as a result of infection.[5,7] Brown pigment stones mainly occur in the far East and often lead to relentless cholangitis ("oriental cholangitis").

ASYMPTOMATIC CHOLECYSTOLITHIASIS

The number of patients with incidentally detected asymptomatic cholecystolithiasis has increased, due to the introduction of ultrasonography. The prevalence of asymptomatic cholecystolithiasis in people between the age of 20 to 69 years is 13% and rises to

22% in patients older than 70 years.[8, 9] The overall cumulative 10 years incidence is 6.6% in men and 8.1% in women.[10] In general, treatment of patients with asymptomatic cholecystolithiasis is considered to be inappropriate.

Children and adolescents

Asymptomatic cholecystolithiasis can also be detected in children and adolescents. Pregnant adolescents or patients with Down syndrome, with parenteral nutrition, or with hemolytic diseases including sickle cells disease or hereditary spherocytosis, have an increased risk of cholecystolithiasis.[11, 12] In addition, obesity as a risk factor for cholecystolithiasis will become more important in children and adolescents, because the incidence of obesity is rising.[13] Similar to adult patients, children and adolescents with asymptomatic cholecystolithiasis do not need prophylactic cholecystectomy.

Diabetes

Asymptomatic cholecystolithiasis in healthy adult patients without diabetes should be distinguished from asymptomatic patients with diabetes. Asymptomatic cholecystolithiasis is more prevalent in diabetic patients compared to the non-diabetic population.[14] No causal relationship exists between diabetes and cholecystolithiasis. Both diseases including cardiovascular disease and obesity, known as the metabolic syndrome, are the result of a changed Western lifestyle and diet.[15] Despite a higher prevalence of cholecystolithiasis no indication exists requiring a different management in diabetic patients.

Obesity / weight reduction

The number of obese patients is increasing, particularly in Western countries. Besides dietary measures and medication, bariatric surgery offers the final solution to achieve weight reduction in a selected group of patients. However, weight loss of more than 1.5 kilograms / week in combination with a fat intake of less than 7-10 grams a day leads to a significantly increased incidence of gallstone formation of up to 3% a week.[16]

The risk of gallstone formation appears to depend on the type of bariatric surgery. Gastric banding does not lead to an increased risk of gallstone formation because weight loss is more gradual, whereas laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy are associated with increased gallstone prevalence. Patients treated with Roux-en-Y gastric bypass did not show a significant difference regarding symptomatic gallstones compared to patients treated with laparoscopic sleeve gastrectomy.[17, 18] It is not necessary to perform a prophylactic cholecystectomy in patients with asymptomatic cholecystolithiasis who will have bariatric surgery, despite the higher incidence of gallstone formation after bariatric surgery.[19] Ursodeoxycholic acid of median 750 (500-1200) milligrams a day prevents formation of gallstones and should therefore be considered during the period of weight loss.[20]

Transplantation

The incidence of asymptomatic cholecystolithiasis increases in cardiac, pulmonary, renal and pancreas transplantation patients the first two years after transplantation with an

increased incidence of complications. However, prophylactic cholecystectomy does not appear to be justified in these patients.[21] In symptomatic cholecystolithiasis patients who underwent heart or lung transplation cholecystectomy should be performed at least five months after transplantation, because mortality of cholecystectomy is significantly increased in the first months after transplantation.[22] In contrast, risks of treatment of cholecystolithiasis in patients with a history of a solid organ transplantation is comparable to the general population.[21]

Uncomplicated symptomatic cholecystolithiasis

Twenty-two percent of patients with asymptomatic cholecystolithiasis will become symptomatic within 9 years.[23] Symptomatic cholecystolithiasis is characterized by colicky pain as formulated by the ROME criteria. These criteria include pain, usually localized in the epigastric region or right upper quadrant of the abdomen, lasting for at least 30 minutes.[24, 25] In addition to biliary colicky pain (OR 2.6, 95%CI 2.4-2.6), radiation to the back (OR 2.8, 95%CI 2.2-3.7) and a positive reaction to simple analgesics (OR 2.0, 95%CI 1.6-2.5) are weakly associated with gallstones.[26] If all three symptoms are present, the positive likelihood ratio for the clinical suspicion of symptomatic gallstones is 1.34 (95%CI 1.05-1.71).[27] Blood examination does not contribute to the diagnosis of uncomplicated symptomatic cholecystolithiasis, but can aid in exclusion of bile duct stones or pancreatitis in selected cases. Ultrasonography with a sensitivity of 0.84 (95%CI 0.76-0.92) and a specificity of 0.99 (0.97-1.00) is the most appropriate diagnostic modality to detect gallstones.[28] The diagnosis of uncomplicated symptomatic cholecystolithiasis is therefore based on patients' history and ultrasound confirmed gallstones.

For these patients cholecystectomy is the treatment of choice[3] and can be performed in daycare setting.[29] However, the indication of performing cholecystectomy is not evidence-based and we therefore recommend to use the ROME criteria. Due to this lack of evidence variations in practice exist. In some areas in the Netherlands more cholecystectomies are performed compared to other areas which cannot be explained by demographic differences between patients.[30] In addition, symptoms may persist after cholecystectomy.[31] We therefore recommend to discuss the risk of persistent symptoms with patients to create realistic expectations prior to a potential cholecystectomy.

Both laparoscopic (LC) and small-incision cholecystectomy (SIC) have shown to be superior to open cholecystectomy.[32, 33] Recently, many innovations in cholecystectomy techniques have been developed. The goal of these innovations is to increase the minimal invasive aspect of removing the gallbladder. In mini-laparoscopic cholecystectomy (mini-LC) smaller trocars (two of 5 mm and two of 3 mm) are used compared to the trocars used in conventional laparoscopic cholecystectomy (two of 10 mm and two 5 mm). Despite smaller trocars, mini-LC has not shown to be superior to conventional laparoscopic cholecystectomy. The duration of surgery is significantly longer and safety of this cholecystectomy technique is yet to be determined.[34] Another recent cholecystectomy technique is the single-incision laparoscopic cholecystectomy (SILC) in which an incision is made through the umbilicus. SILC is associated with better cosmetics on short-term follow-up. However, SILC is associated with incisional hernia more often.[35]

In women, the gallbladder can also be excised through the vaginal orifice. Transvaginal cholecystectomy (TVC) is generally performed as part of a hybrid technique with an additional transabdominal laparoscopic entrance. TVC is not superior compared to conventional laparoscopic cholecystectomy. The duration of TVC is significantly longer.[36] Since none of the techniques have shown to be superior, we still recommend LC or SIC as first choice of treatment.

COMPLICATED SYMPTOMATIC CHOLECYSTOLITHIASIS

Symptomatic choledocholithiasis

Choledocholithiasis is defined as the presence of gallstones in the common bile duct. Although bile duct stones may cause complications such as jaundice, cholangitis and pancreatitis, biliary pain alone caused by bile duct stones may be difficult to differentiate from biliary pain caused by gallbladder stones. Bile duct stones can be localized in intrahepatic as well as extrahepatic bile ducts. Common bile duct stones are frequently coexistent with gallbladder stones. The prevalence of choledocholithiasis during cholecystectomy varies between 3.4% and 16.3%.[37-45] This variation is probably caused by demographic differences and variations in use of additional diagnostic modalities. Transabdominal ultrasonography is the diagnostic modality of first choice with high specificity (1.00, 95% CI 0.99-1.00) and limited sensitivity 0.38 (95% CI 0.27-0.49) for choledocholithiasis. Sensitivity and specificity for diagnosing a dilated common bile duct are 0.42 (95% CI 0.27-0.49) and 0.96 (95% CI 0.94-0.98), respectively.[46] The most important predictors of choledocholithiasis are shown in Table 1. Based on these predictors a risk assessment of choledocholithiasis can be determined. Additional diagnostics are recommended preoperatively in case choledocholithiasis is clinically suspected. The aim is to prevent a second operative intervention. It is not recommended to routinely screen for choledocholithiasis, because its prevalence is low and screening is therefore not cost-effective. One can determine the indication for further screening based on predictive indicators. No additional diagnostic modalities are necessary, if the risk of choledocholithiasis is low (positive likelihood ratio < 3). If the risk of choledocholithiasis is moderate (positive likelihood ratio 4-7) additional magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) are recommended. MRCP has a sensitivity of 92% (95%CI 80-99%) and specificity of 94% (95%CI 83-99%) for choledocholithiasis.[47] EUS shows comparable results, but may be preferable in case of small (<5 mm) bile duct stones which are often missed by MRCP.[48] Direct endoscopic retrograde cholangiopancreatography (ERCP) is only indicated in patients with a high risk (positive likelihood ratio > 10) of choledocholithiasis (i.e. cholangitis, jaundice, ultrasonographic detection of common bile duct stones). ERCP has the advantage that it allows a simultaneous therapeutic intervention, but may cause serious complications. Intraoperatively performed ERCP is associated with less ERCP related complications and a shorter hospital stay compared to preoperative ERCP. Scheduling intraoperative ERCP is however challenging for logistic reasons.[49, 50] Intraoperative cholangiography (IOCG) may be performed as alternative,

Table 1. Predictors of common bile duct stones

Positive likelihood ratio	Predictors
> 10	Cholangitis, jaundice, ultrasound detected common bile duct stones
4-7	Ultrasound detected dilatation of the common bile duct, hyperbilirubinemia (> 2 the upper limit of normal)
< 3	Elevated alkaline phosphatase, pancreatitis, cholecystitis, elevated amylase or lipase

if ERCP facility is unavailable. However, its role for diagnosing choledocholithiasis is controversial.[51, 52]

Cholecystectomy is often conducted after ERCP and extraction of common bile duct stones. Compared to conservative management after ERCP, cholecystectomy results in lower mortality and a decreased risk of recurrent biliary pain or cholecystitis, jaundice or cholangitis, and need for ERCP or other forms of cholangiography. Conservative management may be justified in patients with important comorbidity.[53] The optimal timing of LC after ERCP is still unclear. A randomized trial showed that LC within 72 hours after ERCP results in decreased risk of recurrent biliary symptoms compared to LC after 6-8 weeks.[54] Removal of both gallbladder stones and common bile duct stones can be performed in a single operation by open or laparoscopic cholecystectomy with choledochotomy. LC combined with laparoscopic common bile duct exploration showed comparable morbidity and mortality as ERCP followed by LC, but hospital stay is shorter after single-stage treatment.[55, 56] Since the experience with common bile duct exploration decreases, postoperative morbidity increases.[57] Therefore, ERCP remains the therapy of first choice. If ERCP with stone extraction fails, open surgical transcystic stone extraction is a safe second option with low morbidity and a high success rate.[56] Other options include radiological endoscopic rendez-vous procedure or percutaneous gallstone removal, but no trials have been performed that assessed the role of these procedures.[58] Transcystic stone extraction is also a safe option with a success rate of 75% in case choledocholithiasis is diagnosed intraoperatively. Postoperative ERCP is indicated if transcystic stone extraction fails.[59, 60]

Acute cholecystitis

Acute cholecystitis is characterized by at least one local abnormality (a positive 'Murphy sign,' pain in right upper quadrant) and at least one systemic abnormality (fever, leukocytosis, elevated CRP). The diagnosis can be confirmed with ultrasound. If any discussion exists regarding confirmation of the diagnosis of acute cholecystitis a CT-scan can be performed. The severity is divided into severe, moderate or mild acute cholecystitis. Severe acute cholecystitis is characterized by organ dysfunction. Moderate acute cholecystitis is characterized by leukocytosis ($>18*10^3$ cells / mm^3), a palpable, sensitive resistance in the right upper quadrant, duration of at least 72 hours, or evident

local inflammation (biliary peritonitis, pericholic or hepatic abscess, gangrenous or emphysematous cholecystitis). Mild acute cholecystitis is characterized by absence of criteria for a more serious grade.[61]

Treatment options of acute cholecystitis included conservative management with or without antibiotics, cholecystectomy or percutaneous cholecystostomy (gallbladder drain). Antibiotic treatment of acute cholecystitis patients is empirical. In most patients with mild acute cholecystitis intravenous antibiotic treatment does not improve early outcome.[62] Only in immune compromised patients or patients with moderate or severe cholecystitis antibiotics may be applied. Another point of discussion is whether cholecystectomy should be performed in an acute setting (<1 week) or in a delayed setting (>6 weeks). Acute cholecystectomy results in faster recovery compared to delayed cholecystectomy.[63] Small-incision or laparoscopic technique will be preferred, because of faster recovery compared to conventional open cholecystectomy.[64-66] For patients unfit for cholecystectomy because of severe comorbidity, percutaneous cholecystostomy is an alternative treatment option. Routine use is not recommended in these patients.[67, 68] Cholecystostomy can be performed transhepatically or transperitoneally with no evidence-based preference for either one of the techniques. The drain can be removed after two weeks when using transhepatic drainage or after three weeks when using intraperitoneal drainage, because bile leakage will not occur after this period.[69]

Cholangitis

In patients with bile duct stones, clues suggesting systemic inflammation are fever (T > 38 °C) or cold chills or an inflammatory response (leukocytes <4 or > $10*10^3$ /mm^3, CRP ≥ 10 mg/L). Items characterizing cholestasis are jaundice (Total Bilirubin 34 µmol/L) or elevated liver biochemical tests (Alkaline phosphatase 1.5x the upper limit of normal value, gamma-glutamyltransferase 1.5x the upper limit of normal value, aspartate aminotransferase 1.5x the upper limit of normal value, alanine aminotransferase 1.5x the upper limit of normal value). Radiological signs that may accompany cholangitis are biliary dilatation or proof of the etiology (stricture, stone, stent, etc.). Cholangitis is suspected in patients with at least one item suggesting systematic inflammation, and at least one item showing cholestasis or radiological signs of cholangitis. The diagnosis is confirmed if one item in each category is present. Similar to the gradation of acute cholecystitis, the severity of cholangitis was divided into severe, moderate or mild. Severe cholangitis is characterized by organ dysfunction. Moderate cholangitis is characterized by leukocytosis (>12 or <$4*10^3$ cells/mm^3), a temperature ≥ 39 °C, age ≥ 75 years, hyperbilirubinemia (total bilirubin ≥ 85 µmol/L), or hypoalbuminemia (< lower limit of normal value x 0.7). Mild acute cholangitis is characterized by absence of criteria for a more serious grade.[70]

Treatment of cholangitis consists of administration of antibiotics and bile duct decompression. Endoscopic decompression, irrespective of proven choledocholithiasis, results in lower morbidity and mortality compared to surgical decompression. No randomized trial has been performed that compared endoscopic drainage with percutaneous drainage. Stent insertion is preferred for initial drainage of severe acute

cholangitis.[71] In addition, broad spectrum antibiotics need to be administered because of the polymicrobial nature of cholangitis.[72-74] Consequently, the mortality rate of cholangitis has dropped to 2.7-10%.[75]

Acute biliary pancreatitis

It was beyond the scope of this guideline to discuss the complete management of acute pancreatitis. This guideline aimed to discuss the treatment of acute biliary pancreatitis. Acute pancreatitis is characterized by two items of the following features: Upper abdominal pain, serum amylase or lipase > 3x the upper limit of normal, or signs of pancreatitis on imaging. Pancreatitis is likely of biliary origin if gallstones or sludge have been detected. Clinical assessment and monitoring of potential complications is essential.[76] In mild acute biliary pancreatitis without signs of cholangitis ERCP with sphincterotomy does not reduce the incidence of early complications, nor mortality and is not recommended.[77, 78] ERCP does need to be conducted in patients with acute biliary pancreatitis with cholangitis within 24 hours.[78] For patients with severe acute biliary pancreatitis without cholangitis it remains unclear if ERCP leads to less complications and mortality.[77-79] In patients with severe comorbidity unfit for surgery ERCP solely for the treatment of recurrent acute biliary pancreatitis is sufficient.[80]

In all other patients cholecystectomy is recommended to prevent recurrent symptoms. The optimal timing of cholecystectomy is dependent on the severity of the pancreatitis. Cholecystectomy for mild biliary pancreatitis is recommended as early as possible with no increase in peroperative morbidity.[81] Early cholecystectomy in patients with severe acute biliary pancreatitis may lead to an increased incidence of infected collections. Cholecystectomy for these patients should, therefore, be delayed until the peripancreatic collections have been dissolved or after six weeks if the collections persist.[82]

OTHER CHAPTERS

Bile duct injury

Bile duct injury is defined as any type of injury of the bile duct system including bile leakage of the intrahepatic bile duct system and cystic duct. The incidence of bile duct injuries in open cholecystectomy varies between 0-0.5%, whereas the incidence in laparoscopic cholecystectomy is assumed to be higher varying between 0.04-1.5%.[32, 33, 83-86] Currently, no clinical evidence with a low risk of bias exists suggesting higher or lower incidence of bile duct injuries in new cholecystectomy techniques including SILC or TVC compared to conventional laparoscopic cholecystectomy. Factors that may be associated include learning curve, insufficient overview, anatomical variations, and not reaching the critical view of safety.[83] Only 42% of bile duct injuries is identified during primary operation.

Multiple classification systems of bile duct injuries exist. In this guideline the Amsterdam classification (Table 2) was applied because treatment results directly from this classification.[87] If bile duct injury is detected during cholecystectomy without lost tissue, closure of the duct using end-to-end anastomosis over a T-drain is a good option. An experienced surgeon should perform the operation after conducting a cholangiogram.

Table 2. Amsterdam classification of bile duct injuries

Typ A	Cystic duct leakage
Type B	Bile duct leakage
Type C	Bile duct stricture
Type D	Bile duct transection

An acute hepaticojejunostomy could be performed, if tissue of the bile duct is lost. Drainage of bile ducts and subhepatic fossa and treatment of sepsis is warranted, if bile duct injury is suspected after surgery. Bile duct injury type A should be treated by lowering the pressure gradient between the common bile duct and duodenum. Stenting, nasobiliary drainage with or without papillotomy can be considered. There is no evidence with low risk of bias that shows a preference of any of the options or combinations. Bile duct injuries type B and C should be treated preferably by endoscopic stenting (type B without leakage) and stenting with dilations up to 12 months (type B with leakage and type C) with recurrent replacements of the stents. If an elective operation remains indicated, a delay of 6 to 8 weeks delay should be followed, especially with bile duct injuries type B with leakage. A surgical reconstruction after 6-8 weeks also applies for bile duct injuries type D.[83]

Gallbladder polyps, unsuspected gallbladder carcinoma and routine histopathology

Gallbladder polyps are often found with ultrasound incidentally. Patients with gallbladder polyps of ≥ 10 mm should be offered cholecystectomy due to a higher risk on gallbladder cancer.[88] Polyps smaller than 10 mm have a benign natural history.[89] Polyps ≤ 6 mm do not need follow-up and for polyps ≥ 7 mm follow-up frequency is unclear.[90] In addition, sensitivity of ultrasonography for detecting gallbladder polyps is limited leading to a positive predictive value of 10.5%.[91]

The incidence of unexpected gallbladder carcinoma during or after cholecystectomy because of cholelithiasis is 0.4% in Western Europe. Approximately two third of all gallbladder cancers are diagnosed this way. The postoperative management of these patients depends on classification of the carcinoma.[92] Patients with incidentally diagnosed gallbladder cancer Tis, T1a, T3, T4 after cholecystectomy do not need additional surgical treatment. Additional lymph node dissection is recommended in case of T1b gallbladder cancer, with an additional liver segment resection in case of T2 gallbladder cancer. In case of suspicion of gallbladder carcinoma with local infiltration conversion of laparoscopic to open cholecystectomy has no evidence-based benefit.[93]

Routine histopathological examination for carcinoma in cholecystectomy specimen is not evidence-based. Histopathological examination of gallbladder specimens reviewed as macroscopically normal during cholecystectomy does not change treatment or outcome of patients with unsuspected gallbladder carcinoma.[92] Therefore, routine histopathological examination seems inappropriate.

Intraperitoneal loss of gallstones

Occasionally during cholecystectomy, the gallbladder is perforated resulting into loss of gallstones. These lost stones cause complications in 0.5-1.4% of cases. The most frequently described complications are abscesses and fistulas. Nevertheless, there is no need for extensive search of lost gallstones during the surgery.[94]

Persistent symptoms after cholecystectomy

In some patients symptoms persist after cholecystectomy. Causes of these persistent symptoms are very heterogeneous ranging from irritable bowel syndrome, functional dyspepsia to reflux disease. Risk of persistent symptoms strongly depends on the indication of cholecystectomy. Incidences of up to 33% have been described for persistent abdominal pain of variable intensity.[31] We recommend to inform patients about the relatively high rate of persistent symptoms after cholecystectomy in order to create realistic expectations.

Sludge

Sludge is defined as precipitation of cholesterol crystals or calciumbilirubinate granules embedded in mucin in the gallbladder or bile ducts. Sludge is usually diagnosed by ultrasonographical findings of echogenic material without shadowing. It is considered to be a gallstone equivalent. Sludge should, therefore, in general be treated identical to macroscopic cholelithiasis.[95] Nevertheless, it should be realized that under certain circumstances (e.g. after pregnancy or after rapid weight loss), sludge will likely disappear spontaneously.

Pregnancy and cholelithiasis

Pregnancy is a risk factor for developing sludge or cholesterol gallstones. Incidences vary between 2-4% for asymptomatic and 0.16-0.8% for symptomatic cholelithiasis. Conservative treatment carries a risk of 38-69% for recurrent symptoms or complications. Cholelithiasis during pregnancy should be managed similarly to non-pregnant patients with cholelithiasis taking into account the first trimester. The second trimester or start of the third trimester seem to be the most appropriate semester for potential surgical intervention, because organogenesis has ended and the uterus size is still limited.[96]

The future

Along with the introduction of mini-LC, SILC and TVC, the ongoing development of less invasive surgical interventions will continue. The challenge of better cosmetics with less postoperative pain will lead to new cholecystectomy techniques. In addition, due to financial constraints stricter indications and timing of cholecystectomy will be assessed decreasing variations in practice. Studies will focus on ways of making management of cholelithiasis more efficient and cost-effective. Patient-reported outcomes will likely play an important role to accomplish this aim.

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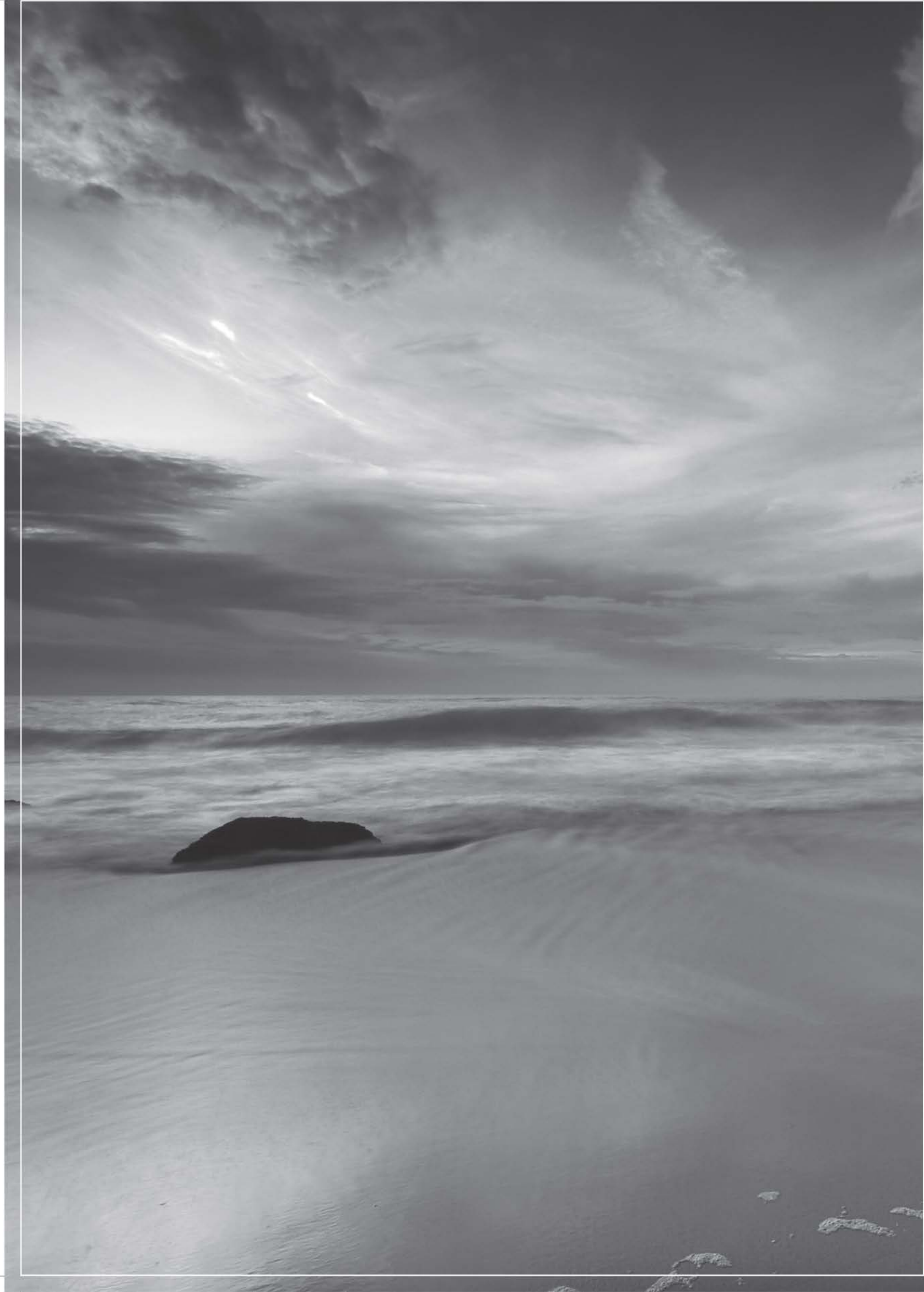

DISCUSSION

CHAPTER 10

DISCUSSION & FUTURE PERSPECTIVES

DISCUSSION

The main aim of this thesis was to assess which patients diagnosed with uncomplicated symptomatic cholecystolithiasis will benefit from cholecystectomy in terms of patient-reported outcome measures. In addition, we aimed to evaluate a strategy to reduce the number of non-beneficial cholecystectomies to avoid unnecessary treatment and health care expenses. The possible implications of our findings for diagnosis and treatment of cholecystolithiasis are discussed and suggestions for future research are offered. For this purpose, the journey of a patient with abdominal symptoms and gallstones from diagnosis to treatment is scrutinized.

Diagnosing and treating cholecystolithiasis

Approximately 15 to 20% of the general population experience episodes of abdominal pain annually.[1] Some 30% of these patients will visit a general practitioner (GP) which comprises 2 to 4% of all visits to GPs.[1, 2] Abdominal, presumed gallstone-related, pain may vary from typical acute colicky upper abdominal to more nonspecific chronic non-colicky pain with or without concomitant dyspeptic symptoms.[3-5] Watchful waiting, empirical treatment with antacids, or transabdominal ultrasonography are some of the options a GP may consider.[6] If ultrasound has been performed and gallstones have been detected, the GP will have to decide whether the stones are an incidental finding or are associated with the abdominal pain and subsequently refer the patient to a surgeon.[7] Evidence for watchful waiting or empirical treatment with antacids or transabdominal ultrasonography is lacking, which introduces variations in general practice.[8] In addition, criteria for appropriate referral of patients with abdominal symptoms and gallstones are absent. Consequently, the number of patients with abdominal symptoms and gallstones visiting the departments of surgery differs per hospital and region, likely adding to the variation of hospital practice.[9]

For surgeons it remains a challenge to determine if the abdominal symptoms are associated with the ultrasound proven gallstones. Some of the options a surgeon may consider are conservative treatment, esophagogastroduodenoscopy (EGD) or elective cholecystectomy. Conservative treatment can be applied if comorbidity enhances the risk of significant complications due to cholecystectomy or if the probability of persistent symptoms is estimated to be high. However, which high-risk patient will benefit from cholecystectomy and which high-risk patient will benefit from watchful waiting is currently not known.[10] In addition, conservative treatment can also be applied to observe symptoms that are transient or would lead to clues suggesting other diagnoses. However, this option may be challenging to propose. Although the probability of persistent symptoms is high in some patients, patients expect to be scheduled for surgery.[11] Not fulfilling these expectations may put the surgeon at risk for extensive conversations in the limited amount of time at the outpatient clinic.[12] Many patients have upper abdominal pain that might warrant further investigation. A strategy that has been used by physicians is to perform EGD early in the diagnostic process. However, EGD should be considered selectively for those who have a clear indication. Our analysis demonstrated

that endoscopy rarely avoids cholecystectomy as the endoscopic findings often did not point to abdominal symptoms (Chapter 6).[13] Guidelines reported that EGD should only be considered in case of alarm symptoms or in Helicobacter pylori negative patients of ≥ 50 years with persistent or recurrent symptoms despite antacid treatment.[14, 15] No studies reported characteristics that warrant change of these criteria for patients with gallstones in order to improve the efficiency of EGD.

Guidelines are lacking to guide surgeons which patient to offer an elective cholecystectomy and which patient to treat conservatively. Therefore, the indication to perform a cholecystectomy lies within the surgeons' preference. This leads to variations in hospital practice and often unnecessary cholecystectomies in terms of postoperative symptoms.[16-18] In this thesis, we distinguished postoperative symptoms in persistent and de novo symptoms (Chapter 2).[19] This distinction is probably less strict in daily practice and should rather be seen as part of a spectrum. Symptoms may have recurred or be more expressed and therefore considered as new-onset while in fact being persistent.[20] The distinction of persistent and de novo symptoms may be valuable to render the group of patients with postoperative symptoms less heterogeneous.

This thesis discusses absence of symptoms as most appropriate patient-reported outcome to measure benefit of cholecystectomy. We found that the factors that showed an association varied across patient-reported absence of postoperative pain, improved abdominal symptoms, positive surgery results, or health status improvement (Chapters 4, 5, 8).[21-23] These discrepant associations call for an explanation. First, answers are dependent on which patient-reported outcome measurement (PROM) questionnaire that was used (Chapter 3).[24] Several confounders such as co-morbidities, mood, timing of measurement, and expectations of the treatment influence patient' responses on questionnaires.[25] A single comprehensive PROM that is consistent across comorbidities, mood, timing, and expectations may be challenging to develop. An additional challenge is not only the episodic nature of abdominal pain associated with gallstones in some, but also the heterogeneous phenotype of abdominal symptoms in others.[3-5]

The different results between PROMs also applies for the decision model. The cost-effectiveness of a new strategy to select patients for cholecystectomy is dependent on the PROM that is used. Absence of abdominal pain was used as PROM in the decision model (Chapter 7). Applying other PROMs such as patient-reported improved abdominal symptoms or positive surgery results would certainly influence the cost-effectiveness of cholecystectomy. Strict selection by the treating surgeon based on the episodic nature of abdominal pain or having abdominal pain 1 year or less, whilst advocating the merits of a watchful waiting approach is the best way to avoid unnecessary surgery in uncomplicated cholecystolithiasis patients and seems cost-effective in terms of absence of abdominal pain.

Limitations and strengths

There are some limitations of this thesis that need to be addressed. First, the definition of uncomplicated symptomatic cholecystolithiasis varies substantially among clinicians,[5, 26] limiting the generalizability of study results. A preoperative classification homogenizing

this heterogeneous patient group may have been helpful. Second, we experienced that the response rate of cholecystolithiasis patients to complete and return the questionnaire set was limited (Chapters 4, 5, and 8). In retrospect, we might have increased the response rate by using internet-based questionnaires in addition to paper-based questionnaires.[27] We would also liked to have asked patients to complete the questionnaire at the outpatient clinic instead of at home to prevent questionnaire set completion and return to be forgotten. However, the medical ethics committee emphasized that we had to offer patients time for reflection prior to taking part in this study. Finally, we performed decision analytic modelling using a treatment arm of usual care and a treatment arm of restrictive care (Chapter 7). Watchful waiting was one of the treatment options in the decision model. Decision analytic modeling is based on assumptions which approach reality as closely as possible. Unfortunately, very few studies have been conducted adopting a watchful waiting period in patients with cholecystolithiasis and abdominal symptoms.[28] This makes it challenging to extrapolate our findings in a real world setting.

Strengths of this thesis included the use of the Gastrointestinal Quality of Life Index (GIQLI) as generic and the McGill questionnaire (MPQ) as disease specific questionnaire.[29-32] Other studies used the GIQLI as a disease specific questionnaire and the Short Form 36 as generic questionnaire.[33-35] By using a pain questionnaire as disease specific questionnaire we valued the main predictor of patient-reported success of surgery.[36] The diagnosis of uncomplicated symptomatic cholecystolithiasis is based on abdominal pain adding significance to the use of a pain questionnaire as disease specific questionnaire.[5, 26] The MPQ and GIQLI are standardized and validated and therefore our study results can easily be used for comparisons with future studies. Other strengths are our attempt to substantiate broad-established healthcare based on evidence. In this time of austerity the effectiveness of resources should be considered.[37] Many costs could and should be saved by not performing unnecessary procedures with associated complications. Increasing evidence of effectiveness would limit room for interpretation by clinicians concerning the use of a certain procedure.

Guidelines are eminently a tool to reduce practice variations by offering recommendations for diagnosis and treatment. The Dutch national guideline for diagnosis and management of gallstone disease was revised during the writing of this thesis (Chapter 9). Compared to the original guideline the revised guideline not only included higher levels of evidence concerning treatment of biliary pancreatitis and acute cholecystitis, but also reported about the effectiveness of cholecystectomies. The right indication for cholecystectomy for patients with uncomplicated symptomatic cholecystolithiasis is in accordance with the ROME III criteria for symptomatic gallstone disease combined with radiological detected gallstones. Currently, the level of evidence for this conclusion is rated to be low. However, studies included in this thesis and upcoming studies will certainly improve the level of evidence and thereby improve the effectiveness of cholecystectomies.

Future perspectives

Although we aimed to increase the patient benefit and effectiveness of cholecystectomies, this thesis is only one piece of a large puzzle of personalizing healthcare for patients

with cholecystolithiasis. There are some potential areas for future research we would like to discuss. First, a randomized trial should be performed to assess if a restrictive care strategy with a stepwise selection for cholecystectomy is at least as effective as usual care for patients with features of symptomatic cholecystolithiasis. In fact, such a randomized controlled trial is being performed at the time of finishing this thesis.[38, 39] Second, the focus of practice variations has been limited to hospitals, while inappropriate cholecystectomies may be prevented by limiting unnecessary referrals from general practices to surgery departments. The extent of general practice variation and determinants associated with these variations should be part of future studies.[40] Third, cholecystectomy and watchful waiting are treatment options most often applied in clinical practice. Remarkably, the lack of evidence supporting watchful waiting strategy suggest there is much evidence to gain for this option. For example, dietary restrictions to reduce abdominal symptoms should be studied. Many patients report that fatty or spicy nutrition provoked episodes of abdominal pain in our daily clinical practice. Patients who initiated a strict diet eliminating these nutritional components resulted in lessening of complaints in some of these patients. In addition, watchful waiting is often applied in patients with cholecystolithiasis and comorbidity who are considered high-risk for surgery. However, evidence to justify this option is insufficient.[10, 41] Fourth, as mentioned in the limitations and strengths section, a classification of uncomplicated symptomatic cholecystolithiasis needs to be developed. The clinical presentation of patients with uncomplicated symptomatic cholecystolithiasis is very heterogeneous, complicating effective application of diagnostic and therapeutic options. Uncomplicated symptomatic cholecystolithiasis may be part of a spectrum with asymptomatic cholecystolithiasis and severe acute cholecystitis on the ends of the spectrum. In line with the Tokio Guidelines,[42, 43] criteria for diagnosis and severity should be determined and validated. In addition, predictors of patients with cholecystolithiasis at risk for complicated cholecystolithiasis should be determined as these patients may benefit from earlier cholecystectomy. Finally, PROMs should be measured routinely to assess which patient benefits from a certain treatment. By using internet-based questionnaires at follow-up and tablet-based questionnaires at the outpatient clinic the response rate may increase, limiting potential selection bias.

If symptoms due to cholecystolithiasis are so difficult to disentangle and cholecystectomy is far less successful as we always thought, it becomes comprehensibly that cholecystolithiasis is not a phenomenon on itself. Maybe cholecystolithiasis is merely a surrogate diagnosis of a much broader diagnosis of 'metabolic syndrome.' This metabolic syndrome causes a great variation of symptoms related to the digestive tract. With this awareness we need not to focus on diagnosing and treating a subdiagnosis (e.g. cholecystolithiasis), but the whole scale of related symptoms. This urges us to refocus on the secondary prevention and especially primary prevention of the cause of the metabolic syndrome, such as life style, food overconsumption, and physical exercise. As modern healthcare becomes more and more expensive, standardized measurement of patient-reported outcomes combined with clinical parameters is key to increase the cost-effectiveness and appropriateness of healthcare resources. Outcome driven and patient-centred care should therefore be put at the heart of clinical decision-making.

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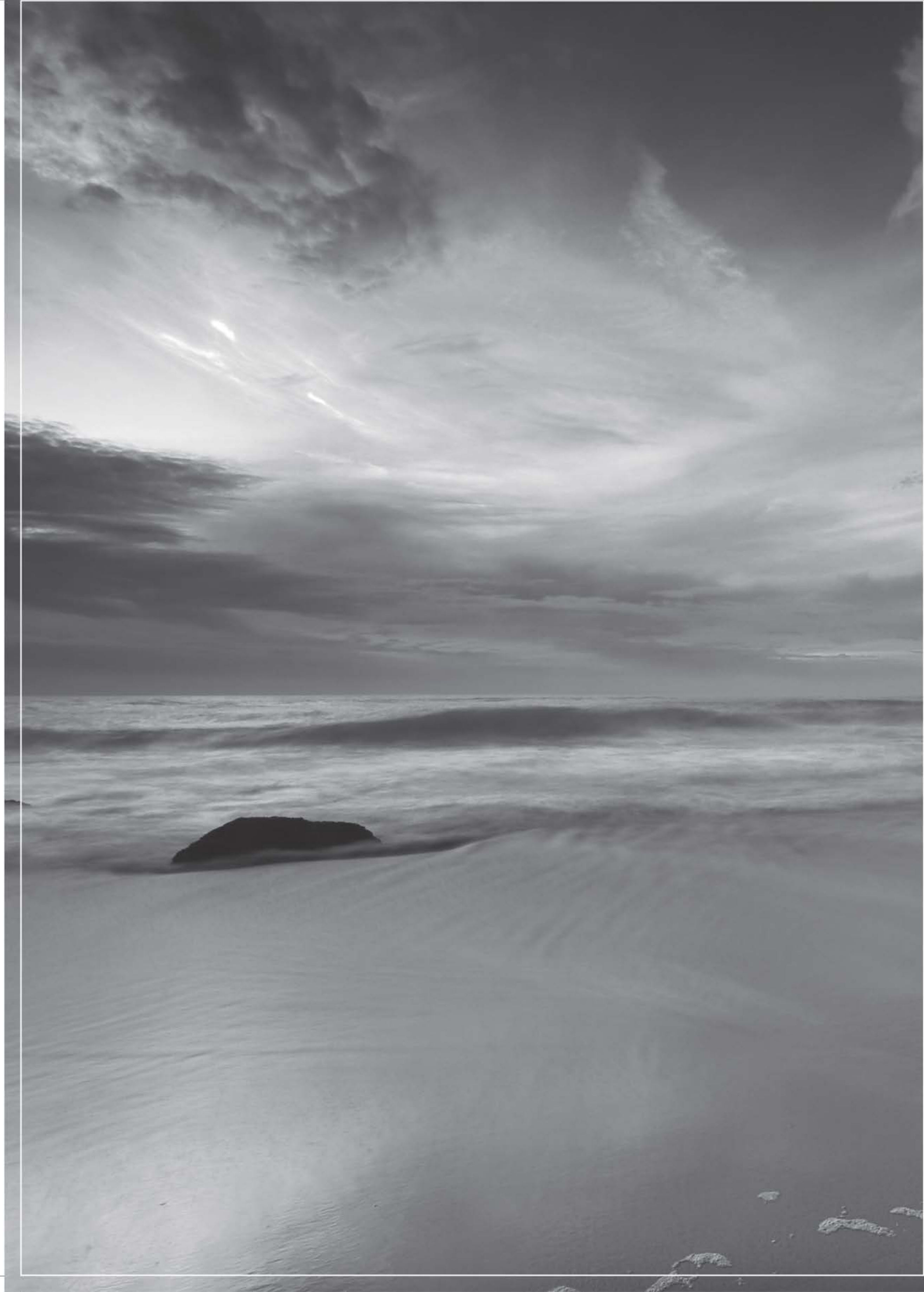


SUMMARY

SUMMARY IN ENGLISH

Chapter 1 is the first part of the introduction of this thesis and presents an overview of gallstone disease, the treatment options and the phenomenon called practice variations.

Chapter 2 is the last part of the introduction systematically reviewing the effect of cholecystectomy on abdominal symptoms. The aim of cholecystectomy in a large share of patients is to relieve abdominal symptoms that are caused by gallstones. However, a cholecystectomy is frequently ineffective in terms of postoperative abdominal symptoms. These postoperative abdominal symptoms can be divided into persistent and de novo symptoms. This distinction may be useful to better predict which patient will likely benefit from cholecystectomy from patients that will not.

Chapter 3 describes the methods to reduce variations in practice by asking patients routinely if they have benefited or not from a certain treatment. The volume of medical actions and the results strongly vary between countries, but also between regions within one country. The quality of healthcare is suboptimal, patients risk complications because of unnecessary interventions and there are unnecessary healthcare expenses, because of these variations. In this chapter a perspective is described on how to reduce variations in practice by using patient-reported outcome measures (PROMs). If data of differences in outcomes are combined with data of regional variations in practice, it will be elucidated in which region too many or too few interventions are being conducted.

Chapter 4 describes the results of a multi-centre prospective cohort study in which pain characteristics are assessed that predict which patient will benefit of cholecystectomy and which patient will not using PROMs. Patients with a better health status with episodic abdominal pain lasting for a year at the most have the highest risk of being free of pain after a cholecystectomy. However, these characteristics are not associated with improvement of abdominal symptoms or with the surgery results. This discrepancy shows that there are variations of patients' expectations of cholecystectomy. Selection of patients most likely to benefit from cholecystectomy based on preoperative patient characteristics, whilst advocating the merits of a watchful waiting approach, is, for the present, the best way to avoid unnecessary surgery in patients with uncomplicated cholecystolithiasis.

In **chapter 5** the results are described of a prospective cohort study of the effects of cholecystectomy on long-term abdominal symptoms, that are measured with PROMs. Abdominal pain associated with gallstones frequently appears in episodes, sometimes with intervals of several years. Therefore, a cholecystectomy may seem to have cured abdominal pain at short-term follow-up, but symptoms may reappear at long-term follow-up. Approximately 90% of patients rated their abdominal symptoms to have improved compared to before the operation and considered the surgery result to be good, despite residual pain in a significant part of these patients. None of the characteristics were consistently associated with all three outcome measures. Absence of pain at three months after cholecystectomy is associated with absence of pain at long term follow-up.

In **chapter 6** the results are described of a systematic review and meta-analysis of the value of esophagogastroduodenoscopy (EGD) in patients with gallstones that have been referred for cholecystectomy. EGD can be a diagnostic modality to detect alternative causes for the abdominal symptoms. In addition, there is discussion if EGD should be applied selectively or routinely in patients that have been referred for cholecystectomy. In this study 36.3% of patients that received an EGD, had an abnormality in the upper digestive tract. In 3.8% of the total number of patients cholecystectomy was avoided because treatment had cured the symptoms. Most patients in whom a cholecystectomy was avoided had a gastrointestinal ulcer. The value of EGD to prevent unnecessary cholecystectomies is limited and should therefore only be applied selectively.

Chapter 7 described the results of a cost-effectiveness study of a new strategy to select patients that will benefit of cholecystectomy. The selection criteria for the new strategy are abdominal pain being present for a maximum of one year and having pain in episodes. The new strategy of using one out of two selection criteria may be an effective but also a cost-effective method to reduce the proportion of patients with pain after cholecystectomy compared to a strategy of applying no strict criteria as in current practice.

Chapter 8 shows the results of a subgroup analysis of the prospective multi-centre cohort study. Cholecystolithiasis represents a clinical spectrum that ranges from asymptomatic gallstone disease to uncomplicated symptomatic gallstone disease to acute cholecystitis. Patients with asymptomatic gallstone disease benefit least from cholecystectomy in terms of improvement of health status and should receive conservative care. Those with acute cholecystitis benefit most and should receive surgery. The optimal timing that results in the highest benefit for patients with uncomplicated symptomatic cholecystolithiasis remains less clear. Classically, uncomplicated symptomatic gallstone disease is characterized by biliary colicky pain. The frequency, maximum duration and intensity of these colics are variabele. This analysis assessed whether these characteristics of biliary colicky pain were associated with a clinically relevant improvement of health status after cholecystectomy. No association was shown, causing the timing of cholecystectomy with the highest benefit to be individualized.

Chapter 9 is the last part of the results of this thesis. In an overview a summary is given of the Dutch guideline of 'diagnosis and treatment of cholelithiasis.' A guideline is eminently a tool to reduce variations in practice by combining the best available evidence as an answer to clinical relevant research questions. The guideline has been updated with respect to the first version that was published in 2007.

Chapter 10 is the discussion of this thesis. In this part suggestions are described for future research to reduce variations in practice with respect to the treatment of variations in practice.

SUMMARY IN DUTCH
(SAMENVATTING IN HET NEDERLANDS)

Hoofdstuk 1 vormt het eerste deel van de inleiding van dit proefschrift en geeft een overzicht van het ziektebeeld galsteenlijden, de behandelingsmogelijkheden en het fenomeen dat praktijkvariatie heet.

Hoofdstuk 2 is het laatste deel van de inleiding waarin het effect van cholecystectomie op buikklachten systematisch wordt beschreven. Het doel van een cholecystectomie bij een groot deel van de patiënten is het verlichten van buikklachten, die door galstenen zouden worden veroorzaakt. Echter, een cholecystectomie is vaak ineffectief in termen van postoperatieve buikklachten. Daarbij kan een onderscheid worden gemaakt tussen persisterende symptomen en nieuwe symptomen. Deze onderverdeling kan mogelijk van nut zijn om beter te voorspellen welk type patiënt baat zal hebben van een operatie en welke niet.

Hoofdstuk 3 beschrijft de methode om variaties in praktijk terug te dringen door routinematig patiënten zelf te vragen of ze wel of geen baat hebben gehad bij een behandeling. De hoeveelheid aan medische handelingen en het resultaat ervan variëren sterk tussen landen, maar ook tussen regio's binnen één land. Door deze variatie is de kwaliteit van zorg suboptimaal, lopen patiënten onnodige risico's op complicaties door onnodige ingrepen en zijn er onnodige kosten. In dit hoofdstuk wordt een perspectief beschreven hoe praktijkvariatie te verminderen door gebruik te maken van patiënt gerapporteerde uitkomstmaten ofwel PROMs (Patient-reported outcome measures). Als men gegevens over verschillen in resultaat combineert met gegevens over regionale praktijkvariaties, wordt duidelijk waar teveel en waar te weinig wordt behandeld.

Hoofdstuk 4 beschrijft de resultaten van een prospectief cohort onderzoek met meerdere centra waarin, gebruikmakend van PROMs, pijn karakteristieken worden bepaald die voorspellen welke patiënt baat heeft bij een cholecystectomie en welke niet. Patiënten met een betere gezondheidstoestand met episodische klachten die maximaal een jaar duren hebben de hoogste kans om pijnvrij te worden na een cholecystectomie. Echter, deze karakteristieken zijn niet geassocieerd met verbetering van buikklachten of met het chirurgie resultaat. Deze discrepantie toont aan dat er verschil is in verwachtingen die patiënten kunnen hebben van een cholecystectomie. Om patiënten te selecteren die waarschijnlijk baat hebben van een cholecystectomie, kan vooralsnog het best gekeken worden naar preoperatieve patiëntfactoren, terwijl ook de voor- en nadelen voor een afwachtend beleid moeten worden meegewogen.

In **hoofstuk 5** worden de resultaten beschreven van een prospectief cohort onderzoek naar de effecten van cholecystectomie op buikklachten op de lange termijn, die zijn gemeten met PROMs. Buikpijn die geassocieerd wordt met galstenen komt vaak in episodes, soms met intervallen van enkele jaren. Daardoor kan het lijken alsof een cholecystectomie de buikpijn heeft genezen op de korte termijn, maar klachten kunnen dan toch weer verschijnen op de lange termijn. Ongeveer 90% van de patiënten oordeelde dat hun

buikklachten beter waren ten opzichte van voor de operatie en het chirurgie resultaat als positief, terwijl een groot deel van deze patiënten niet vrij van pijn was. Geen van de karakteristieken was voorspellend voor al deze drie uitkomstmaten. Als patiënten geen buikpijn meer hebben na 3 maanden is dit voorspellend voor afwezigheid van pijn op de lange termijn.

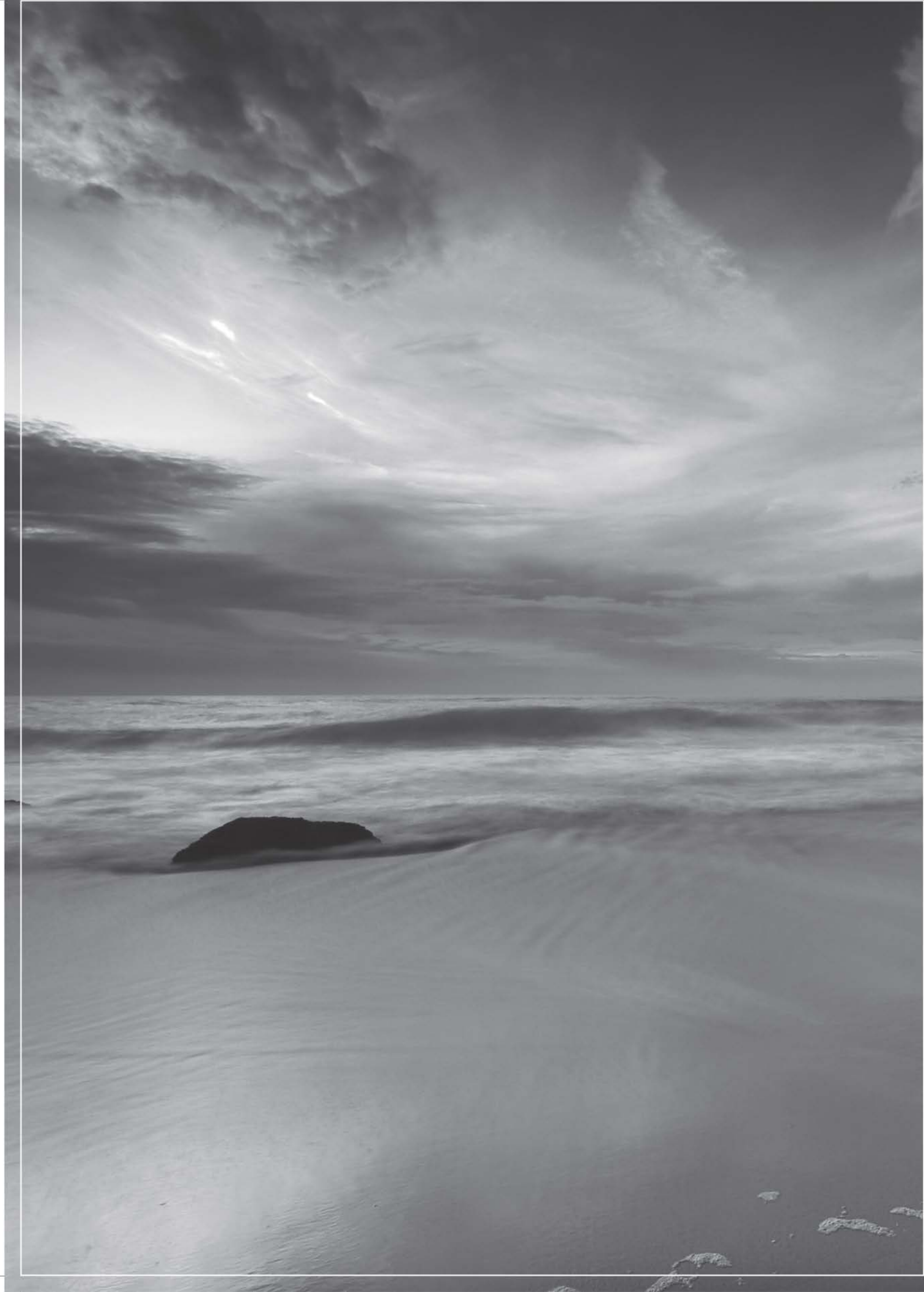
In **hoofdstuk 6** worden de resultaten beschreven van het systematisch literatuuronderzoek en de meta-analyse van de waarde van een oesophagogastroduodenoscopie (EGD) bij patiënten met galstenen die verwezen zijn voor een cholecystectomie. EGD kan een diagnosticum zijn om alternatieve oorzaken voor de buikklachten op te sporen. Ook is er discussie over het feit of dat EGD selectief of routinematig moet worden toegepast bij patiënten, die voor een cholecystectomie worden verwezen. In deze studie komt naar voren dat 36,3% van de patiënten, die een EGD ondergingen, een afwijking heeft in de bovenste tractus digestivus. Bij 3,8% van het totale aantal patiënten werd een cholecystectomie voorkomen. De meeste van de patiënten waarbij een cholecystectomie voorkomen werd hadden een gastro-intestinaal ulcus. De waarde van EGD ter voorkoming van onnodige cholecystectomieën is beperkt en zal daarom alleen selectief moeten worden toegepast.

Hoofdstuk 7 beschrijft de resultaten van een kosteneffectiviteitsonderzoek van een nieuwe strategie om patiënten te selecteren die baat zullen hebben van een cholecystectomie. De selectie criteria voor de nieuwe strategie zijn buikpijn die maximaal een jaar aanwezig is en het hebben van episodische pijn. De nieuwe strategie gebruikmakend van 1 van de 2 criteria lijkt niet alleen een effectieve, maar ook kosteneffectieve methode om het aantal patiënten met pijn na een cholecystectomie te verminderen ten opzichte van een strategie waarbij geen strikte criteria worden gehanteerd zoals in de huidige praktijk.

Hoofdstuk 8 toont de resultaten van een subgroep analyse van het prospectieve cohort onderzoek met meerdere centra. Galsteenlijden kan worden gezien als een klinisch spectrum dat varieert van asymptomatisch galsteenlijden naar ongecompliceerd symptomatisch galsteenlijden naar een acute galblaasontsteking. Patiënten met asymptomatisch galsteenlijden hebben in het algemeen geen baat van een cholecystectomie en worden doorgaans conservatief behandeld. Patiënten met een acute galblaasontsteking hebben juist veel baat hebben van een cholecystectomie en worden doorgaans geopereerd. Wanneer patiënten met ongecompliceerd symptomatisch galsteenlijden het meeste baat hebben van een galblaasoperatie is minder duidelijk. In het klassieke geval wordt ongecompliceerd symptomatisch galsteenlijden gekarakteriseerd door kolieken. Deze kolieken variëren in frequentie, maximale duur en intensiteit. In deze analyse werd onderzocht of deze karakteristieken van kolieken geassocieerd waren met een klinisch relevante verbetering van de gezondheidstoestand na een cholecystectomie. Er werd geen associatie aangetoond, waardoor het tijdstip van de cholecystectomie waarbij de meeste gezondheidswinst kan worden behaald per individu moet worden afgewogen.

Hoofdstuk 9 vormt het laatste deel van de resultaten van dit proefschrift. In een overzicht wordt een samenvatting gegeven van de Nederlandse richtlijn 'onderzoek en behandeling van galsteenlijden.' Een richtlijn is bij uitstek een middel om praktijkvariatie te doen beperken door het best beschikbare bewijs te bundelen als antwoord op klinisch relevante onderzoeksvragen. De richtlijn is geactualiseerd ten opzichte van de eerste versie verschenen in 2007.

Hoofdstuk 10 vormt de discussie van dit proefschrift. In dit deel worden suggesties voor toekomstig onderzoek beschreven om praktijkvariatie ten aanzien van de behandeling van galsteen patiënten te verminderen.



ADDENDUM

DANKWOORD
CURRICULUM VITAE
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DANKWOORD

Het is klaar!

Na afronding van de studie geneeskunde kreeg ik de gelegenheid om me te storten in de voor mij grotendeels onbekende wereld van het onderzoek. Ik heb daarbij met zeer veel plezier in de verschillende ziekenhuizen gewerkt. Ik wil graag allen bedanken die me hebben geholpen met de totstandkoming van dit proefschrift. Hierbij wil ik graag een aantal personen in het bijzonder noemen:

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CURRICULUM VITAE

Mark Lamberts werd geboren op 10 september 1986 te Nijmegen en groeide op in een gezin met 5 kinderen. In 2004 behaalde hij zijn VWO-diploma aan het Stedelijk Gymnasium te Nijmegen. Dat jaar startte hij vervolgens de studie geneeskunde aan de Radboud Universiteit Nijmegen. Hij heeft een masterclass interne geneeskunde gevolgd. Verder heeft hij tijdens zijn studie onder andere onderzoek gedaan naar polymorfismen bij chronische pancreatitis en naar celmodellen bij polycysteuze leverziekten. In 2010 is hij 3 maanden werkzaam geweest als co-assistent in Sengerema Designated District Hospital in Tanzania.

In 2011 ontving hij zijn diploma geneeskunde en startte hij met zijn promotie onderzoek naar doelmatigheid van galblaasoperaties onder supervisie van zijn promotoren prof. dr. J.P.H. Drenth, prof.dr. C.J.H.M. van Laarhoven en prof.dr. G.P. Westert. De resultaten van dat onderzoek staan beschreven in dit proefschrift. Hij heeft zich daarnaast ook ingezet als commissielid van de Clinical PhD Council. Hij heeft verder bijgedragen aan de update van de richtlijn galsteenlijden uit 2007.

In januari 2015 is hij de opleiding tot Maag-Darm-Leverarts gestart. Momenteel volgt hij de vooropleiding interne geneeskunde in het Rijnstate ziekenhuis te Arnhem (opleider dr. Louis Reichert).

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