A Randomised Controlled Trial Comparing Laparoscopic to Mini Cholecystectomy

Jeffrey S. Barkun

Department of Epidemiology and Biostatistics

McGill University, Montreal

December, 1993

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfilment of the requirements for the degree of M Sc.

Laparoscopic

vs

Mini Cholecystectomy:

a randomised trial

Abstract

To better define the differences between laparoscopic (LC) and mini cholecystectomy (MC) in treating cholelithiasis, we conducted a randomized controlled trial with 70 patients (LC:38, MC:32).

Both groups were comparable at baseline. The median length of post- operative hospital stay and time to full diet were significantly shorter in LC than MC ($p<0.005$ for both). Mean duration of convalescence was 11.9 ($\pm$ 9.1) days for LC and 20.2 ($\pm$ 16.5) days for MC ($p=0.04$). Kaplan - Meier survival analysis confirmed these results. Using Cox's proportional hazards model, duration of convalescence was only found to be associated with the type of cholecystectomy performed. Three quality of life scores showed that LC patients improved more quickly than MC patients after cholecystectomy.

Surgeons underestimated convalescence on average by 25% ($p<0.01$) when compared to nurses' measurements.

In conclusion, even though recovery after MC was shorter than generally anticipated, time to recovery from LC was still shorter and more predictable than MC.

ABRÉGÉ:

Afin de mieux évaluer les différences entre la cholécystectomie par voie laparoscopique (CL) et la mini cholécystectomie dans le traitement de la cholélithiase, nous avons fait appel à une étude randomisée à laquelle ont participé 70 patients (LC:38, MC:32).

Les caractères de base des patients étaient semblables dans les deux groupes. La durée médiane d'hospitalisation ainsi que la durée de temps jusqu'à ce que les participants puissent manger furent plus courtes chez les patients LC. La durée moyenne de convalescence fut de 11.9 ($\pm$ 9.1) jours pour le groupe LC et 20.2 ($\pm$ 16.5) jours pour MC ($p=0.04$). Ces résultats furent confirmés par une analyse de type Kaplan Meier. En utilisant la méthode d'analyse des hazards proportionels de Cox, la durée de la convalescence put être imputée au type de cholécystectomie pratiqué. Trois échelles de qualité de vie confirmèrent la direction de ces résultats.

Les chirurgiens sous-éstimèrent de 25% en moyenne ($p<0.01$) cette valeur par rapport aux mesures effectuées par les infirmières.

Pour conclure, quoique les temps de récupération des patients MC furent plus courts qu' anticipé, la récupération après LC fut plus rapide et plus prévisible.

TABLE OF CONTENTS

Appendices:

Introduction:

Cholelithiasis is one of the most common diseases of the adult North American population, affecting at least 20 million people in the US alone (1). Similarly, the surgical treatment of gallstones is only second to hysterectomy as the most common surgical procedure performed in North America. It therefore comes as no surprise that the treatment of gallstones is the most costly treatment related to digestive diseases in the United States with an estimated cost of more than $5 billion dollars per year (2). Open cholecystectomy (removal of the gallbladder) was introduced nearly one hundred years ago to treat gallstone disease. It succeeded cholecystostomy (opening the gallbladder but not removing it) in the early twentieth century and its safety as well as its proven efficacy have made it the modern gold standard to treat cholelithiasis (3). This status has however recently been challenged. Recent advances in fiberoptics and camera technology have revolutionized much of Medicine and Surgery. These refinements as well as much improved instrumentation, have helped to further the applications of what has been called "keyhole surgery". In particular, laparoscopic cholecystectomy (LC) has taken the general surgical world by storm and has become, in the eyes of many, the method of choice to remove a diseased gallbladder electively.
The purpose of the investigation to be presented is to

assess whether laparoscopic cholecystectomy deserves this preferred status when it is objectively compared to the previously best available treatment.

STATE OF THE ART

a) Cholelithiasis: the disease.

The exact prevalence of cholelithiasis in the general population may be difficult to determine, and in fact may vary significantly with respect to the population studied, or to the method used to determine it (autopsy, surveys, ultrasound screening,...). It has long been known to be affected by gender, being two-fold greater in women, and can also be seen to increase with age (4,5-13). In a study looking at a small area in Northern Italy, the overall prevalence of gallstone disease was found to be 6.7% in men and 14.6% in women (7). This female predominance persisted while the prevalence increased with age in both gender groups from 18 to 65 years: from 1.1% to 11% in men, and from 2.9% to 27% in women.

Over the past 50 years, the documented prevalence of cholelithiasis seems to have increased (4,14) although it is not clear whether this is a true phenomenon or the result of greater detection. Indeed, diagnostic modalities to discover gallstones have improved markedly over the past 15 years, especially with the introduction of ultrasonographic techniques. Nevertheless, increases in the prevalence of the disease had already been reported over the first half of this century (4,14), and other factors such as increasing median age of the population, improved

access to medical care, and popularity of surgical techniques may be responsible for an apparent change.

RISK FACTORS:

Cholelithiasis is one of the so-called "Western diseases", and has thus been postulated to somehow be related to industrialization (15). There are important racial differences which affect the prevalence of cholelithiasis: the prevalence among Black Africans in many areas of Africa is less than 1% (16), whereas it climbs to 35% in Chile (17) and peaks at close to 50% among Pima Indians in the Southeastern US. Such differences have been attributed to both hereditary and environmental factors and can even be detected locally between different regions of a given country such as India or Great Britain (18,19).

Other contributing factors seem to be: Family history, obesity (especially with central body fat distribution), parity, rapid significant weight loss (with dieting), ileal disease, total parenteral nutrition, possibly estrogen replacement therapy, and diabetes mellitus. Haemolytic anemia can lead to pigment stones which are however different from the more common cholesterol-mixed stones.

In spite of these facts, however, no specific dietary factor has been identified and thus, there is no specific prophylactic therapy possible at this time. One exception to this may be the case of morbidly obese patients about to

undergo sudden significant weight reduction as part of a diet. In this group, which has long been known to be at risk, the prophylactic use of ursodeoxycholic acid (a bile acid obtained from polar bears) may prevent the development of gallstones (20) .

CLINICAL BURDEN:

Although the prevalence of cholelithiasis is relatively high among North American adults, the mortality attributable to gallstone disease is in fact small: gallstones account for 6000 deaths per year in the USA (21), and this number has fallen dramatically between 1950 and 1980 (22).

Recently, a classification of cholelithiasis has been suggested which may correspond to its natural history. Three stages of the disease have been identified: the asymptomatic stage, the symptomatic stage, and the complicated stage (23). This classification, although not universally accepted is thought to reflect the observation that gallstones are initially silent for some time after they have formed. In one study using radioactive carbon to date gallstones, the minimum delay between the development of gallstones and the appearance of symptoms was 2 years; the average was 8 years (22).

1)Asymptomatic gallstones:

Several cohort studies spanning over 20 years have helped

to define the risk of developing symptoms (biliary colic) in several previously asymptomatic patient populations. On average the conversion rate from silent to symptomatic groups is 1-4% per year and conversion directly to a complicated stage occurs with an incidence of 0.8% per year (24-33). The yearly risk of requiring a cholecystectomy in at least one study was 1.3% per year (30).

Because of these figures and the results of decision-tree analysis (34), it is generally agreed that asymptomatic gallstone disease is not an indication for surgical treatment unless other mitigating factors are present, such as the suspicion of a gallbladder cancer.

Risk factors for the development of symptoms have not yet been clearly defined although it is known that women develop symptoms more often than men (9,13,32). Other factors such as smoking, age less than 55, the presence of floating stones, nulliparity, and greater weight have occasionally been proposed (30,35).

2) Symptomatic gallstones:

Several longitudinal studies have followed patients with symptoms. These have been variously defined as biliary colic, or the presence of other ("non specific") symptoms. The results are quite disparate owing to the population studied, the defined endpoint (usually the need for cholecystectomy) and the episodic nature of gallstone symptoms. The average risk of developing a complication (ie

acute cholecystitis, cholangitis, pancreatitis, or cholecysto-enteric fistula) is 1-3% per year, and the risk of requiring surgery is 6-8% per year although it decreases over longer follow-up (20,27,30,35,36). Because of these figures, it is almost universally agreed that patients with specific biliary symptoms should undergo treatment of their gallstones (2).

3)Complications:

Complications of gallstone disease include the following: acute cholecystitis, pancreatitis, choledocholithiasis, and cholangitis, cholecysto-enteric fistula, and gallbladder cancer. As previously stated, the presence of symptoms seems to correlate with the subsequent development of complications, and as such is an indication for cholecystectomy. The presence of a complication is an absolute indication for operation in almost all groups. Acute cholecystitis has been shown on average to occur in up to 11% of all cases over 10 years (23). Choledocholithiasis, cholangitis, and pancreatitis (all signifying symptomatic gallstone migration to the common bile duct) remain unusual, occurring in less than 2% of gallstone patients (23).

The complications of gallstone disease are more devastating in elderly patients because of the frequent presence of concurrent medical diseases, or because of their atypical presentation and subsequent delayed diagnosis. In

gallbladder empyema, fever or pain can be absent, which explains the high mortality of this entity in the aged (37). Age is widely recognized as a poor prognostic factor in acute pancreatitis (38), and in at least one study, a 9% mortality was associated with the first episode of acute pancreatitis in patients under 60, as opposed to a 28% mortality in those over 60 (39).

The risk of developing a gallbladder cancer has been described in the cohort analysis of a stable population of gallstone patients from the Mayo Clinic, and found to be 1 per 1000 per year (40).

b) The Surgical Treatment of Cholelithiasis

CHOLECYSTOSTOMY:

The first surgical treatment of cholelithiasis can be traced back to a case report by Von der Weil in 1667 (41) where an abdominal wall abscess was drained and gallstones concomitantly evacuated. In 1733, Petit, a French surgeon, advocated a two-stage procedure to incise and drain a gallbladder in the context of an acute cholecystitis. In the 1800's, Lawson Tate published a series of 14 cholecystostomies (simple incision of the gallbladder with removal of the gallstones), and reported a single death (42). Surgical cholecystostomy is at present only indicated

if a cholecystectomy may be technically hazardous, or if the patient's overall state of health is thought to be too precarious to allow the surgeon to perform a cholecystectomy.

OPEN CHOLECYSTECTOMY:

In 1882, Carl Langenbuch performed the first cholecystectomy (43) and this procedure gained increasing acceptance over the start of this century. It eventually supplanted cholecystostomy because the latter was associated with a substantial rate of gallstone recurrence. Interestingly, this is the same advantage which cholecystectomy confers today over all non-surgical alternatives to treat cholelithiasis. We will not concern ourselves with non surgical therapy for gallstone disease in this dissertation even though our institution has completed a randomized trial comparing lithotripsy to both laparoscopic and mini cholecystectomy.

Short term results:

Open cholecystectomy has become a very popular procedure worldwide because of its safety and effectiveness in many hands. A recent study in centres with a special interest in cholelithiasis reviewed the current status of biliary tract surgery in the USA and worldwide (21). Overall mortality for open cholecystectomy was 1.1% in the USA cohort, and 0.6% worldwide. These figures changed markedly, however,

when the surgical treatment of common bile duct stones was added to the simple removal of a gallbladder. Indeed, when common bile duct exploration was also performed, the mortality rose to 5.8% in the USA, and 4.4% overall. No iatrogenic bile duct damage was noted in this study but it has been estimated to be of 0.2-0.3% with open cholecystectomy (44). The low incidence of this complication in the above study may have been the reflection of particularly good technical results because only centres with a special interest in biliary tract disease had participated. The exact incidence of common bile duct injury following cholecystectomy in the community has been difficult to grasp, partly because of under-reporting, and partly because of the possibility that an iatrogenic stricture may only appear many years after the cholecystectomy has been performed (44).

Because the world population is aging, and the prevalence of cholelithiasis increases with age, we must specifically look at the mortality of gallstone surgery in this group of patients. The overall mortality of elective cholecystectomy is threefold higher in the elderly (45); morbidity is also higher due to sepsis (3-5% rate of wound infections), cardiovascular complications, and venous thromboembolism. Published studies have reported cholecystectomy mortality rates of 2.5-3.3% in patients over 65 (45,46), compared to 0.1% in patients under 50.

Performing a cholecystectomy as an emergency operation has also been found to be associated with a greater mortality rate in all groups: up to 16.7% in elderly patients versus 0.4% in patients under 50 years of age (47). When common bile duct exploration is performed in that context, mortality increases to as much as 29% in some series in patients over 70, as compared to 0.4% in patients under 50 (although some difference is attributable to whether a supra- or transduodenal approach is used).

One of the most controversial aspects of cholecystectomy remains the frequency with which this procedure should be carried out. This operation remains today the second most commonly performed surgical procedure in the U.S.A. where it is carried out several times more often than in other areas such as in the United Kingdom, without obvious benefit to the patient (48). The higher surgical rates have in fact been thought to increase overall gallstone disease mortality (34,48). We will not address this issue further but to point out that "excesses" in the performance of cholecystectomy stem mostly from liberalization of the recognized indications which have been described above.

Long term results:

Although cholecystectomy is a popular operation, 35-50% of patients express dissatisfaction with their surgery. This includes only 5% complaining of "specific" symptoms following cholecystectomy, with all other patients

complaining of the persistence of nonspecific symptoms (49,50). Biliary causes for persistent post-operative right upper quadrant pain include retained common bile duct stones, common bile duct strictures, and the poorly understood syndrome of sphincter of Oddi dyskinesia. Retained stones are related to the persistence of stones in the common bile duct after surgery. These stones are, for the most part, thought to have originated in the gallbladder and either have been undetected or passed into the common bile duct at the time of surgery. In the previously described multi-centre, multi-national study involving several biliary centres (21), the incidence of retained stones was measured to be 4.5%. The incidence of retained stones will however vary markedly depending on the age of the population (the prevalence of choledocholithiasis increases with age), the duration of post-operative follow-up, or the practice of the surgeon performing the cholecystectomy. It can be as high as 10% if surgeons do not perform systematic intra-operative cholangiography although the routine use of this practice is debated (51).

MINI CHOLECYSTECTOMY:

The mini cholecystectomy (MC) is a variant of the conventional open cholecystectomy which eludes any specific definition. It has appeared in the literature in many

forms: as a muscle-sparing subcostal incision, as a muscle-splitting 5 cm transverse incision , or even as a small midline incision (52-55,56,57). In fact, it has been so loosely defined that the 1993 NIH consensus conference on gallstone disease concluded that too little information was available about this technique to evaluate it properly (2). As opposed to laparoscopic cholecystectomy, mini-cholecystectomy only requires minor modifications in technique over conventional cholecystectomy and does not necessitate sophisticated technology. Of six English language papers available in peer reviewed literature over the past 22 years, only three were available for large series analysis. This allowed for the assessment of 169 patients undergoing MC (57). The rate of conversion, ie the need to perform a classic open cholecystectomy, on average was 11%, and the overall morbidity was 6% with no mortality. The average length of hospital stay was 3.5 days and, although poorly documented, the average duration of convalescence was 27 days. These results are all comparable to standard open cholecystectomy except for the durations of hospital stay and convalescence which are less than those traditionally attributed to open cholecystectomy (one week hospitalization and six weeks convalescence) though no comparative trial is available for review. MC thus appears to compare very favourably to traditional open cholecystectomy and it is for this reason that MC was

chosen in the present trial as the best "open" surgical technique against which to compare laparoscopic cholecystectomy. This had also become the cholecystectomy of choice in our group of surgeons.

LAPAROSCOPIC CHOLECYSTECTOMY:

Laparoscopic cholecystectomy was first reported to have been used in France (58) and then spread simultaneously to the rest of Europe and North America (59,60). In theory this operation combines the century-proven efficacy of surgical gallbladder removal with the theoretical advantages of laparoscopic surgery as pertain to post-operative pain and patient convalescence. Many large patient series, mostly from University affiliated centres, have shown that the laparoscopic technique can be mastered by many surgeons, and that this technique is consistently associated with short hospital stays and duration of post-operative convalescence (61). Moreover, this procedure can be performed with an average risk of conversion to open cholecystectomy of around 5%. The overall morbidity rate has also been shown to be under 5% in most series, now totalling over 84,000 patients (61), and the mortality rate is under 0.3%.

The main drawback to LC seems to be the issue surrounding the increased risk of common bile duct injury. A great many large American and Canadian series (61,62) which have

addressed this issue have been reported. These are based on both university and community data and report rates of common bile duct (CBD) injury essentially similar to those of historical studies looking at open cholecystectomy (2,63). In spite of these, there is a "consensus" that more common bile duct injuries have been referred to large biliary surgical centres since the advent and diffusion of LC. It is thought that these reports represent a true increase in the incidence of CBD injury rather than a change in referral patterns.

Most laparoscopic cholecystectomy patient series have reported a single day of hospitalization , and an average convalescence of 7 days (61). Initially, these encouraging results were thought to have been the result of patient selection but further studies which included "all-comers" duplicated these results (61,64). The generalizability of the initial LC results is best demonstrated in a recent study looking at a single surgeon's experience over time. In a prospective series of patients operated on, before and after the introduction of LC, the authors were able to show that the results achieved initially in highly selected patients could be duplicated even when all consecutive cholelithiasis patients were referred for LC (64).

JUSTIFICATION OF THE STUDY

Although previous evidence has suggested that laparoscopic cholecystectomy is more advantageous than conventional open cholecystectomy (59,65,66,67), the patient benefits of LC over open cholecystectomy, and mini cholecystectomy in particular, have never been clearly demonstrated or precisely documented. In fact, at the time that the described trial was instituted, the enthusiasm for this approach stemmed from the results of many personal experiences, case series, and its appealing modern technology (58,66,68,69). A carefully controlled study had been repeatedly called for in numerous reports and editorials (53,70,71,72,73).

Some authors had contested that none was needed, since the benefits were so obvious, and others had in fact deemed such a trial to be idyllic or even unethical (74). It was our belief that a trial comparing open to laparoscopic cholecystectomy was necessary, but that the "best" open cholecystectomy against which to compare it should be the mini-cholecystectomy which had become the procedure of choice for many of the surgeons at our institution. Proponents of this technique (MC), even prior to the advent of LC, had claimed results comparable to those subsequently achieved with LC (52-55). Based on data reported in the literature, a clear determination of which technique is superior was not possible because the few published

comparative trials had used unmatched concurrent or historical controls, usually compared to a self-selected group of patients (59,65,66,67). With the introduction of laparoscopic cholecystectomy, we were provided with a window of opportunity to conduct a randomized trial comparing LC to MC.

It was important to commence the trial as early as possible before lay diffusion of LC among physicians and patients alike would make patient accrual a near impossible task. The design of this study was chosen to correct what we thought were important limitations of previous comparative assessments: particularly to balance out potential effects of patient motivation, occupation, or personal disposition and expectations, which may strongly affect outcome. These had previously been suggested as possible confounding factors in a descriptive analysis comparing the duration of convalescence in North American and European patient populations following LC (75).

It has been argued that the main issues surrounding LC have been the increased risk of CBD injury over traditional cholecystectomy, and the more problematic management of CBD stones; and that the resolution of these issues could not come from a randomized trial with limited patient accrual. These concerns, however make it all the more imperative that the presumed laparoscopic advantages be definitively proven or discarded.

The absence of any randomized trial comparing surgical cholecystectomies has clearly created a void in the literature which the following trial will attempt to fill.

OBJECTIVES

The goals of the study are manifold:

1- Descriptive: To document whether the measured pre-operative quality of life of cholelithiasis patients is improved after LC and MC.
Any further descriptive objective regarding LC is outside of the scope of the trial (see below).

2- Analytical: a) To compare the effects of LC to those of mini-cholecystectomy in patients randomly assigned to each treatment using convalescence as primary outcome variable. Secondary outcome variables will be the duration of hospital stay, quality of life and post-operative discomfort.
b) To compare the measurements of clinical endpoints performed by treating surgeons to those taken by research nurses.

Notes:

a) There are other descriptive objectives which are related to events with a very low expected frequency of occurrence.

These include mortality and morbidity rates, in particular that of peri-operative common bile duct injury, and the incidence of post-operative retained common bile duct stones. Comparisons of these events which have a low incidence would require a much larger sample size, and are therefore outside of the scope of this study.

b) In order to evaluate such outcomes with a low frequency of occurrence, a laparoscopic cholecystectomy registry was started at the time that this procedure first began to be performed at McGill. In the discussion section, data from this separate, surgeon-generated, data base will be used as an external validation criterion to which the patients in this trial may be compared.

c) At the time of this trial, lithotripsy with gallstone dissolution was considered another feasible alternative treatment for gallstone disease other than the two surgical modalities to be compared within this trial. Lithotripsy was assessed in a separate randomized trial and it will be considered outside the scope of this trial.

NOTES REGARDING RANDOMISED TRIALS IN SURGERY

Randomized trials in surgery have basic characters which set them apart from other randomized trials (76, 77).

Any surgical procedure is essentially irreversible, and many (in particular LC and MC) involve a general anaesthesia. Consequently any study with a cross-over design cannot, by definition, be used because a patient will never be able to act as his/her own control. This, in a way, fails to allow a patient the right to withdraw from a trial at any time without a change in his/her status. The preparation for a surgical procedure moreover requires the building of a special relationship between patient and surgeon. A large part of this relationship is based on trust and confidence in the abilities of the surgeon as an operator. The extent to which this relationship may affect a given outcome, such as return to full activities, is poorly understood but a placebo effect of varying intensity is especially hard to quantify and can never be ruled out. The admission by a surgeon of uncertainty as to which is the best surgical procedure (in the context of a comparative trial) may lead to a compromise in the confidence which a patient has in him/her. It may thus be damaging both to the process and to its outcome. Moreover, because of the strength of the patient-surgeon bond, any failure may be more likely perceived as a shortcoming of the method rather than the surgeon.

A very fundamental point is that neither the operating surgeon nor the patient can truly be blinded to the procedure to be performed, and this limits some of the

possible control by any investigator over outcome measurement bias. The surgeon in particular determines many outcomes such as discharge from hospital and the time of return to work. It is difficult, either through artificial definitions or through proxy variables to ensure objectivity. As a consequence, measurement of any given outcome by many "objective" observers may be necessary. Finally, quite apart from any placebo effect, surgical procedures, and in particular the technically more demanding ones, require expertise which cannot be a priori expected to be similar in all hands. This may well result in a performance bias which cannot be neutralized by blinding. One way to counter this effect is to start the study only after the "learning curve" of each surgeon will have been completed.

Although many designs have been tried, current justified ethical practices and the nature of surgical methods itself mandate the development of trials which can be particularly suited to the field of Surgery.

STUDY HYPOTHESES

The primary study hypothesis was that laparoscopic cholecystectomy led to shorter durations of hospitalization and convalescence than mini cholecystectomy.

The secondary hypothesis was that the laparoscopic approach is more effective than the mini approach when looking at post-operative quality of life indices and post-operative pain.

STUDY DESIGN

We conducted a prospective randomized clinical trial of mini versus laparoscopic cholecystectomy for symptomatic gallstone patients. We used an "intention to treat approach" to analyze all results.

The patients were randomized to either of two intervention groups:

Group 1: Patients in this group underwent mini cholecystectomy.

Group 2: Patients in this group underwent laparoscopic cholecystectomy.

Each participating surgeon was able to perform both surgical procedures and had completed his "learning curve" for the laparoscopic procedure prior to entering the trial.

PATIENT POPULATION

The patient population consisted of men and women aged 16-85 years and referred to participating surgeons at the Montreal General, Queen Elizabeth, Royal Victoria, and Jewish General hospitals in Montreal, and the Toronto General Hospital in Toronto. Patients were included in the study if all the inclusion and none of the exclusion criteria had been met:

Selection criteria

1. Signed, informed consent to randomisation.
2. A history of at least one episode of biliary colic (defined as right upper quadrant or epigastric pain lasting at least 30 minutes) within the last 18 months.
3. Proven gallbladder stones on ultrasound (echogenic foci within the gallbladder which move with gravity and are responsible for acoustic shadowing) or on oral cholecystography.
4. Each patient was deemed fit for surgery by the referring surgeon after consideration of the patient's overall health

status including co-morbid conditions (for example, the presence of cardiovascular or respiratory diseases, malignancies, etc.).

Exclusion criteria

1. Any concomitant medical condition excluding the patient from being a surgical candidate for cholecystectomy in the treating surgeon's opinion. (We believe that, in the context of the present effectiveness trial, there was no need for more formal exclusion criteria pertaining to a patient's concomitant disease(s) or overall medical condition. This also permitted the study to reproduce as closely as possible the setting encountered in actual clinical practice).

2. Pregnancy, known liver disease (active hepatitis, cirrhosis, hepatoma, liver metastases), acute cholecystitis, known and untreated common bile duct stones, a recent episode of pancreatitis, bleeding disorder, or anticoagulant therapy.

3. Previous upper abdominal surgery.

The final decision on patient inclusion was taken by the project director (JB), to ensure that those who were randomized met two fundamental criteria:

a) each patient was a suitable candidate for each of the two treatments, and

b) each patient was expected to provide the full range of

follow-up data (note that certain of the quality of life measuring tools are not available in languages other than French or English).

RANDOMISATION

Randomisation cards, according to computer generated numbers, were prepared in Montreal and held there in confidence. Randomization followed a 50-50 ratio for the two treatment options, and was blocked (by groups of 12) by surgeon and age (with 50 years of age as cut-off). When a patient was found to meet all eligibility criteria, the investigator involved with the case telephoned the central office for a randomisation assignment. The assignment was made by telephone, with immediate confirmation by fax. The central office was staffed to provide randomization assignments during all regular working hours. Once randomized, the date and number of randomization were irrevocably entered into the patient file.
Note that data analysis involved patient study ID (randomization) numbers rather than names to ensure confidentiality.

SPECIAL PATIENT CASES

Cross-overs and withdrawals

It was possible for a patient to cross-over in either group direction prior to cholecystectomy, but once a patient had

entered the operating room, cross-over could only occur from the laparoscopic cholecystectomy group to the open cholecystectomy group. The latter case has been called "a conversion" in the surgical literature and occurred, in the trial, only for surgical reasons. Based on preliminary published data, the percentage of patients who have to undergo "conversion" had been estimated to be anywhere from 2% to 25% (67,69,72), most likely around 5%.

The cross-over and withdrawal cases were recorded and analyzed under the "intention to treat" principle, whereby each patient remained as part of his/her randomisation group, for the purpose of the overall analysis. In addition, a supplementary analysis was performed with the cross-overs as part of the group other than the one they had been randomized to in order to assess the possible impact of these cross-overs.

Choledocholithiasis after randomisation

A cystic duct cholangiogram was not performed in patients in either group unless there was a suspicion of choledocholithiasis. This suspicion would only have occurred after randomisation (since choledocholithiasis was a criterion for exclusion) or been based on intra-operative findings. If patients had been found on intra-operative cholangiogram to have choledocholithiasis, they would have been followed and subsequent group analysis performed both

with these patients and without them, so as to assess their impact. Indeed, the presence of a single such patient with choledocholithiasis might have strongly affected any measured outcome because of its clinical significance.

CO-VARIATE AND BASELINE MEASUREMENTS

General co-variates included: Referring physician, age (as a continuous variable), sex, ethnic group, occupation group, work status, and other standard socio-demographic information.

The gravity of concomitant illnesses was categorized by the grading of the patient's overall physical condition using the American Society of Anesthesiologists classification (78, see chart on next page) and this was used for stratification in the analysis (by grouping grades one and two together, versus three, four and five together).

Quetelet's index of body mass (expressed in kg/m^2) was calculated for each patient and included as a co-variate in the analysis.

We also recorded the frequency of pre-operative biliary and non-specific abdominal symptoms in order to see if these might help to predict the occurrence of technical difficulties intra-operatively, especially in the laparoscopic group. These were also recorded to see how the interventions affected these symptoms and as they related

Co-morbid disease - estimated ASA score (1 to 5):

ASA CLASSIFICATION	PATIENT STATUS
1	Healthy
2.	Mild illness
3.	Moderate
4.	Severe
5.	Moribund

to patient quality of life.

All pre-treatment evaluations were carried out within the six weeks preceding the intervention if there was no change in the patient's medical condition over that time interval. The initial laboratory data which decided on the patient's eligibility was ordered by the referring surgeon or physician. The nurse clinician, following an initial contact by phone, met the patient at the first gallstone clinic visit and made sure that all appropriate data were ordered; they also entered all relevant data into the patient's study file. The gallstone clinics were established at each participating institution to channel and follow McGill gallstone patients taking part in the trial. They were staffed by a study nurse and a contributing surgeon. These clinics created a favourable environment for optimal recording of study outcomes which was not threatening to the patients and thus could optimize compliance.

Weekly meetings with the project director confirmed that the study files were complete and that the patients recruited would indeed fulfil the selection criteria before any intervention was carried out.

Prior to the intervention, the work-up also included:

-Complete physical examination with pulse, BP, temperature, height and weight, respiratory, cardiac, abdominal, and neurological examinations,

-Chest and abdominal x-rays,

-Beta-Human choriogonadotropin for women of child-bearing age (to rule out pregnancy),

-Complete blood counts,

-Prothrombin and partial thromboplastin times,

-Automated biochemistry profiles (SMAC) including liver function tests,

-Electrocardiogram,

-Urinalysis (including dipstick for blood and leucocytes),

-Abdominal ultrasound

-Serum amylase

-Pulmonary function testing, when appropriate.

Each patient also filled out the German quality of life questionnaire (79), the Quality of Life Visual Analogue Scale (80,see details below), and the Nottingham Health Profile questionnaire (81,82) .

INTRA-OPERATIVE MEASUREMENTS

A member of the study medical team prospectively recorded the following data: Ability to perform the laparoscopic cholecystectomy, cause for failure thereof where applicable (anatomic anomalies, compromised safety. adhesions, patient complication,...); length of the mini cholecystectomy incision, incision site (subcostal versus midline), ability to perform an intra-operative cystic duct cholangiogram and

its results (where applicable), bile spillage, stone spillage into the peritoneum, duration of operation, as well as any intra-operative complication.

OUTCOME MEASURES

The outcomes were noted over two distinct time periods: The short term, which included the immediate post-operative time at 1 and 7-10 days, and again at 30 days following the intervention.

The long term covered the remaining 23 months of the trial (total follow-up 2 years).

Six-monthly follow-up by telephone and yearly follow-up by interview in person was performed for a total of 2 years post-operatively. In order to assess issues related to quality of life and retained common bile duct stone rates, data collection was performed on the day following the intervention, one month later, and thereafter on a yearly basis, at the time of a clinic or office visit, or if an event occurred, until the end of the study.

Study outcomes are described in detail below.

a) Hospital stay and convalescence

These were the primary study outcomes because they are believed to be the most important in clinical practice

(providing all else is equal between both groups).

1)Hospital stay: The duration of hospitalization was recorded from the time of admission (nearly always on the eve of the procedure in both groups) to the time of eligibility for discharge/ actual discharge. Each night spent in hospital counted as one day ("hotel system"). It was expected that the pressure for early patient discharge was equally great following both mini and laparoscopic cholecystectomy. Patients were considered eligible for discharge when they satisfied the following criteria: Afebrile, requiring only oral medication for comfort (from pain or nausea), having active bowel sounds, and able to eat. If a patient was kept in hospital in spite of being eligible for discharge (eg: Social reasons, work-up of concomitant medical problem,...), an "event sheet" was filled out by the study nurse, and the case was reviewed with the study coordinator.

2)Convalescence: The time from admission to post-operative return to employment was recorded at the time of the follow-up visits or by telephone conversation, and counted from the first post-operative day. The endpoint of interest was the return to full employment which was held prior to the surgical intervention. If the patient was not employed, we looked at the time to resumption of full pre-operative daily activities. To ensure an accurate assessment, the number of days of convalescence, as well as the percentage

of usual activities, at work and at home, actually being performed at the time of the interview were recorded. The possible effects of concurrent medical diseases on convalescence (eg: A fractured leg, hypothyroidism,...) were dealt with on an individual basis after an "event form" had been filled out by the study nurse. For the laparoscopic group, there was dual measurement of this outcome: both by the surgeons at the time of office follow-up, and by the study nurses (who were not directly aware of the randomization group) at the time of gallstone clinic follow-up. For logistical reasons, it was not possible to perform this dual measurement in the mini-cholecystectomy patients.

b) Quality of life assessment

We chose two measures which have been proven repeatedly in the literature to be both reliable and valid in a large variety of patient groups.

The Nottingham Health Profile Index (NHPQ) was used as a general index of "quality of life". It has 38 questions, and, in its simplest scoring form, a point is given for each positive response. A more elevated score therefore signifies a worse quality of life (range: 0-38). It is available in English and French and has proven both valid and reliable in both (81,82). The questionnaire was given to each patient before and after the intervention.

Post-test recordings were taken at 7-10 days after operation, then one month, three months, and thereafter at once yearly follow-ups. The nurse clinician or participating investigator administered the questionnaire to each patient at the bedside or in the respective hospital gallstone clinic. See Appendix 1 for a copy of the NHPQ Index.

A functional status scale more specifically developed for patients with biliary disease had been recently validated (79) at the start of the trial and was also utilized. It was called the German Gastro-intestinal Quality of Life (GGQL) Scale and has 26 core items as well as 6 optional organ specific items which relate to biliary diseases. For this scale, a lower score reflects a worse quality of life (range: 24-112 for the core component). Note that certain aspects of this scale were used to record the presence of baseline and long term non-specific symptoms. See Appendix 2 for a copy of the GGQL Scale. This questionnaire was administered before operation, and then one month later.

The third instrument used to document quality of life was a Visual Analogue (VA) Scale (80) which measured 11.5 centimetres and from which a quality of life score was directly measured. High values reflected a good quality of life (range: 0-11.5). It was administered pre-operatively as well as at 7-10 days later, then at one month, 3 months and 12 months follow-up. See Appendix 3 for a copy of the

VA Scale.

It is recognized that quality of life is a very difficult quantity to define or measure, and it was hoped that a combination of the three stated indices which seemed to cover different aspects of "quality of life" may help to assess it better than any single instrument.

c) Post-operative pain

The McGill pain score has been shown to be valid and reliable in a number of clinical circumstances (83). It is based on adjectives to describe the intensity of pain and an overall assessment. It is available in English, French, and Italian. Scores were recorded immediately following the procedure, then at 7-10 days, and at one month follow-up. High values reflected greater post-operative pain (range: 0-198, but very unlikely to ever be that elevated). See Appendix 4 for a copy of the McGill Pain Score.

We also recorded the amount of morphine equivalents (in milligrams) required in the first post-operative week, and a pill count was made based on the exit prescriptions which the patients had been given.

d) Morbidity, persistent symptoms, conversion

In the short term, we recorded in each treatment group the following indicators which may have required active treatment:

Atelectasis, pneumonia, wound infection, venous thrombosis, pulmonary embolism, cardiac dysrhythmia or infarct, intraabdominal sepsis, or UTI.

In the long term, we compared the incidence of retained common bile duct stones using clinical and, if indicated, biochemical assessment, as well as ultrasound, or even ERCP. The persistence or recurrence of biliary colic and non-specific upper abdominal symptoms was assessed and compared to each patient's pre-operative complaint.

The ability to perform the laparoscopic procedure was documented and correlated with factors such as gallbladder wall thickness on abdominal ultrasound; obesicy, age, or symptoms.

e) Mortality

Overall mortality was compared both over the short term (within the 30 days following cholecystectomy) and long term follow-up periods (any time thereafter for the duration of the trial). In addition, a group of independent observers was set to determine the condition-specific mortality (defined as that attributable to the intervention, the underlying gallstone disease, or a complication thereof) for all deaths. The likelihood of the relationship of death to treatment, gallstone disease or complications thereof would have been recorded on a quantitative percentage scale.

FOLLOW-UP

1) Short term:

Ten days, and again one month following the randomisation, every patient was seen in one of the gallstone clinics. At each clinic visit, the patient was assessed by the physician in charge of the clinic, and a nurse who administered to each patient both the quality of life and pain questionnaires. Moreover, the nurses entered all information pertaining to days of convalescence away from work and time during which the patient had been unable to perform daily activities. Surgeon data pertaining to convalescence were entered by the treating surgeon at the time of a separate office visit, and were recorded as part of a separate ongoing McGill laparoscopic cholecystectomy registry which was alluded to earlier.

2) Long term:

The cholecystectomy patients were assessed 3 months after operation, and every year thereafter in the gallstone clinics, and further documentation of the quality of life scores were performed as well documentation of any possible ongoing convalescence.

Any patient requiring immediate attention because of possible ongoing biliary disease, or intervention-related complication, was instructed to get in touch with the

physician or nurse on call for the study at any time. Appropriate relevant laboratory data and outcome were documented by the nurse clinician and an event form filled out if such a situation arose.

The study ended for all patients two years after the date of operation, or at the time of death if it preceded this date.

FLOW OF THE PATIENTS

The five centres agreeing to partake in the trial (including surgical, gastroenterological and radiological staff) were the Montreal General, Queen Elizabeth, Royal Victoria, and St Mary's hospitals in Montreal. The Toronto General Hospital in Toronto also agreed to recruit patients. All patients referred to a surgeon participating in the study was a potential candidate. If referred from a general practitioner or gastroenterologist to the gallstone clinic itself, the patient was sent to a participating surgeon of their choosing. After the initial clinical assessment, the surgeon explained the study to the patient with regards to the possible treatment alternatives. The candidates for elective cholecystectomy were asked to undergo an abdominal ultrasound if none had been performed yet. If the patient was shown to have cholelithiasis and

agreed to be part of the trial, she/he was then assessed by the physician or surgeon in charge of the clinic, and the study was explained in more detail. If the patient fulfilled all of the selection criteria, he/she was then asked to sign the consent form to participate in the study and be randomised. A study nurse (or physician) then gathered all necessary baseline information and contacted the coordinating centre for the randomisation assignment. The patient usually entered the hospital on the afternoon prior to surgery and was asked to sign the standard operative consent form for the procedure to which she/he had been randomized. The on-site project coordinator ensured that complete data were collected and entered into the patient's study file. The surgical procedure was carried out the following day.

Further data were recorded on the first post-operative day, during the admission, at seven to ten days, at 30 days and then long-term in the Gallstone clinics.

STATISTICAL CONSIDERATIONS

1) Sample size calculations

The sample size calculations were based on unpaired t-tests with a power of 0.8 and an alpha value of 0.05 while looking at differences in duration of hospitalization and

differences in time until return to full employment or level of functioning. We did not calculate the required sample sizes on the basis of expected rates of mortality, morbidity or retained stones because of the anticipated very low incidence of any of these in either group.
In our experience prior to the trial, mini cholecystectomy patients required 2-3 days of hospitalization whereas laparoscopic cholecystectomy patients could usually be discharged home on the day following the procedure. Moreover, return to work in young patients could occur 1 week after the laparoscopic procedure as opposed to 3-4 weeks following the conventional approach: We estimated a difference in convalescence of 18 days. By estimating standard deviations (9 d vs 16 d) and variances, based on these numbers, we concluded that around 50 patients would be required in each group to provide significant differences in duration of hospital stay and convalescence.

2) Statistical analysis

Continuous descriptive variables were expressed as mean ± standard deviation. For the duration of hospital stay, which is a skewed measure, the median and interquartile ranges were also given. Between group differences for continuous variables were assessed for statistical significance by the use of Student's t-test and the

nonparametric Wilcoxon's rank sum test. The Chi-square statistic or Fisher's exact test were used for comparison of categorical variables. Changes from baseline values for the quality of life measures were evaluated using paired tests whereas between group differences were assessed by non paired procedures.

For the primary study outcome, i.e. time to full convalescence, the Kaplan-Meier method was used to construct life tables, and the nonparametric log-rank test to evaluate the statistical significance of between group differences. Cox's proportional hazards model was also used to evaluate the specific contributions of key variables to between group differences with respect to convalescence.

FEASIBILITY

In view of the combined patient volumes at all participating institutions, it was estimated that, with a 15% refusal rate of randomisation, the accrual phase of the study should take 9-12 months. The long-term follow-up would then take one more year.

ETHICAL CONSIDERATIONS

Copies of the utilised consent form have been included in Appendix 5.

RESULTS

During the initial 12 month study period, consecutive patients fulfilling the previously described criteria were approached for randomization, and 70 of these patients consented to participate in the study. Of these 70 patients, 38 were randomized to LC and 32 to MC. Two thirds of all study patients were contributed by 3 surgeons in equal proportions. These surgeons came from 3 different hospitals. In all cases, individual surgeons contributed similar numbers of patients to each group.

Only the results up to a follow-up of 12 months will be presented at this time.

Baseline values:

Baseline characteristics of the patient groups were similar specifically with respect to age, weight, ethnic group, body mass index (Quetelet index), and gender, as can be seen in table I. The distribution of patients according to occupation was also similar in both groups: 40% performed most of their activities at home, 15% were involved in manual labour, and less than 10% were professionals. Patients in the two groups were also comparable with respect to the duration of symptoms, baseline measurements of quality of life (table I), and ASA scores (84% LC class I and 91% MC class I). Also, there was no statistical difference in the duration and types of symptoms, as well

TABLE I - BASELINE PATIENT CHARACTERISTICS

	Mean (SD)	
	LC (n=37)	MC (n=25)
Age (yr)	51.4 (16.1)	52.3 (18 7)
Weight (kg)	70.5 (12.7)	74 7 (17.9)
Quetelet index (kg/m^2)	25.8 (4.6)	27.5 (5.8)
NO(%) MALE/FEMALE	11 (30%)/26 (70%)	6 (24%)/19 (76%)
NHPQ*	8.01 (6.2)	7.8 (7.3)
GGQL*	66.9 (18.2)	61.1 (21 1)
VA	7.4 (2.5)	6.4 (3.2)

*For quality of life measures: LC n=35, MC n=23.

as baseline laboratory or radiological tests which the patients initially presented with.

Exclusions after randomisation:

Of the 38 patients randomised to LC, 37 (97%) underwent operation compared to only 25 of 32 (78%) randomised to MC. This difference was not statistically significant.

Four patients, one in the LC group and 3 in the MC group, declined participation in the study after randomization and refused any follow-up.

Three other patients in the MC group also refused to participate following randomisation and opted to have their open cholecystectomy performed by non-participating surgeons who did not use a "mini" technique.

One other MC patient eventually declined participation and underwent LC at a non participating institution.

There was no difference in baseline characteristics of the patients who dropped out in each group and they also did not differ from the rest of the study patients. It was not possible to get follow-up on the drop-outs and therefore none was included in the results. The final analysis is therefore based on 37 LC and 25 MC patients. Analysis according to "intention to treat" or "treatment received" yielded the same results. In view of this, only the "intention to treat analysis" will be presented.

Intra-operative measurements:

The mean duration of surgery tended to be shorter ($p=0.08$)

TABLE II - POSTOPERATIVE ASSESSMENT

	Mean (SD)		P
	LC (n=37)	MC (n=25)	
Duration of Surgery (min)	85 9 (23)	73 1 (24 5)	0.08
Hospital stay (days)*	3 (1-13;2-3)	4 (1-6;3-5)	0.001
Time to full diet (days)	1.1 (0.7)	1.7 (0.8)	0.004
No (%) with right shoulder pain	12 (33%)	1 (5%)	0.015
McGill pain score	15.7 (12.6)	22.2 (18.4)	0.18
Duration of convalescence (days)	11.9 (9.1)	20.2 (16.5)	0.04

* Median (range; interquartile range).

for MC than LC by over 12 minutes (table 2). A single patient in the LC group required conversion to open cholecystectomy (2.7%) because of the inability to recognize the anatomy safely. A single patient in the MC group elected to have LC just prior to being taken to surgery. Differential analysis of the latter patient did not have any effect on the results described below, ie all results were similar whether the patients were classified by intention to treat or treatment received. Intra-operative cholangiography was used in only one patient, in the MC group, and it did not show choledocholithiasis. There was no untoward event during surgery in any patient in the trial.

Primary outcome measures:

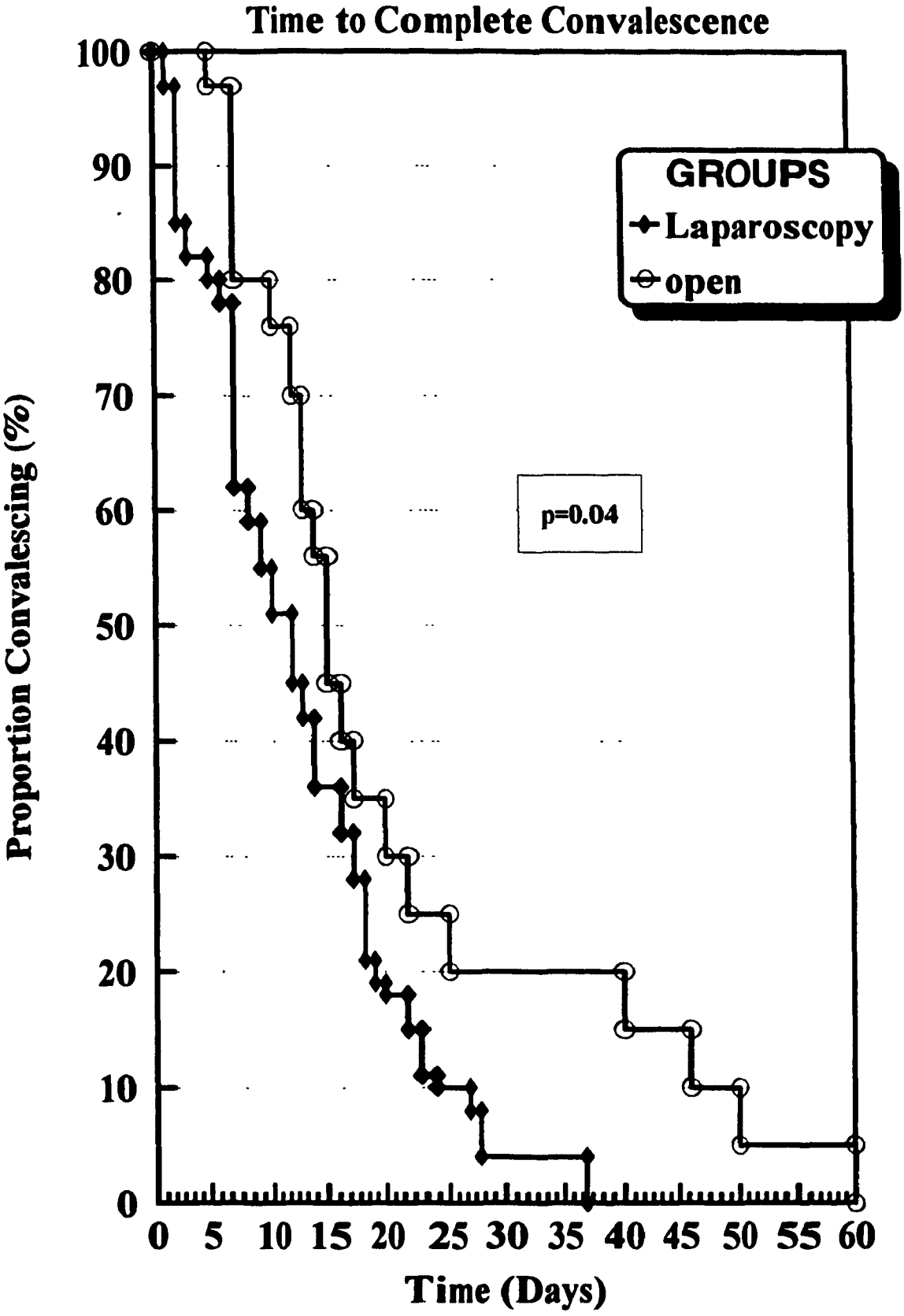
Duration of hospital stay:

The patients who underwent laparoscopic surgery had a shorter mean hospital stay by approximately one day (table II). For the LC patients, the median stay was 3 days (range 1-13 d, 2nd quartile 2 d, 3rd quartile 3 d). For the MC patients, the median was 4 days, (range 1.5-6 d, 2nd quartile 3rd, 3rd quartile 5 d). In addition, 16 (43%) LC patients were discharged on the first post-operative day compared to only 3 (12%) MC patients (p=0.02).

Convalescence:

Figure 1 shows the Kaplan-Meier survival curves describing

figure 1


Time to Complete Convalescence
100
90
80
70
60
50
40
30
20
10
0
Proportion Convalescing (%)
GROUPS
Laparoscopy
open
p=0.04
0 5 10 15 20 25 30 35 40 45 50 55 60
Time (Days)

the time to full convalescence in each group. Fifty percent of the patients in the LC group had completed convalescence by 9 days compared to 14 days for the MC patients (the mean ± standard deviation and range of time to full convalescence for the LC and MC groups respectively were 11.9±.1 days, ranging from 1 to 37 days, and 20.2±16.5 days ranging from 2 to 62 days, $P<0.05$). Between group comparison, using the Mantel-Cox statistic, showed that the patients in the LC group required significantly shorter convalescence compared to those in the MC group ($p=0.036$). Cox's proportional hazards analysis showed that the rate ratio of return to normal activities for the LC group compared to the MC group was 1.77 (95% Confidence Interval = 1.01 to 3.11, $p=0.03$). This indicates that the LC patients convalesced at a rate which was 77% greater than the MC patients. In Cox's proportional hazards model, the only variable which was significantly associated with the speed of convalescence was the type of cholecystectomy used. The other variables in the model, including age, gender, Quetelet index, occupation, or interactions of any of the above, were not significant predictors of the duration of convalescence. Inclusion of a variable to represent the surgeon or the centre in the model also did not affect these results. This would have adjusted for the potential effect of the surgeon or centre on the outcome, thus controlling for performance bias.

We compared duration of full convalescence of the LC patients as measured independently by the study nurses and by the treating surgeons. The surgeons' estimates were found on average to be four days, or 25%, shorter than that of the nurses' ($P<0.01$). Furthermore, the intra-class correlation coefficient measuring the nurses' and surgeons' estimates of convalescence was 0.78 (lower 95% CI=0.64) indicating moderate agreement in this setting. It was not possible, as previously stated, to perform a similar outcome comparison for the MC patients.

Secondary outcomes:

The LC patients were able to return to a full diet just over one half day earlier than patients who had undergone MC (table 2). Right shoulder pain occurred more frequently in the patients who had undergone LC (33% in LC vs 1% in MC, $p=0.015$).

Post-operative pain:

Post-operative use of narcotics during hospital stay and over the first post-operative week was significantly greater in the MC group (LC: 17.4 ± 12.5 morphine mgEq, MC: 79.2 ± 83.8 morphine mgEq, $p<0.001$). Post-operative pain on the day following surgery was greater in the MC patients, as measured by McGill pain scores, but this difference failed to achieve statistical significance (table 2).

Quality of life:

* Paired analysis: Paired analysis within each group of post-operative compared to baseline quality of life scores showed that all patients improved significantly following surgery no matter what type of cholecystectomy they had undergone. Significant improvement in the laparoscopic group was detected as early as 10 days after surgery with the VA Scale (mean change: 1.9 ± 3.2, $p=0.047$), and at one month with both the NHPQ (mean change: -5.8 ± 5.4, $p=0.0001$) and the GGQL (mean change: 18.4 ± 20.1, $p=0.0001$). The patients in the MC group experienced a significant improvement at later times: only one month following surgery with the GGQL (mean change: 16.5 ± 20.3, $p=0.004$) and the VA Scale (mean change: 2.6 ± 2.8, $p=0.002$), and at 3 months with the NHPQ (mean change: -5.7 ± 7.6, $p=0.03$).

* Unpaired analysis: The results of unpaired analysis are illustrated in Table 3 where the raw means of quality of life indices in both patient groups at the various times of measurement are indicated. Differences between these means were not found to be statistically significant.

Therefore the extent of improvement in quality of life scores following surgery was not significantly different in both groups although the improvements were noted more quickly in LC patients.

Morbidity and mortality:

There were two complications noted in the MC group (8%):

TABLE III - QUALITY OF LIFE

	Mean (SD)		
	NHPQ	GGSQLI	VAS
BASELINE			
MC (n=23)	7.8 (7.9)	66.9 (19.2)	7 4 (2.5)
LC (n=35)	8.0 (6.2)	61.1 (21.5)	6.4 (3.2)
10 Days			
MC (n=21)	6.9 (6.6)	68.8 (16.1)	7.4 (3.7)
LC (n=18)	5.3 (5.2)	73 6 (17.6)	9.3 (1.8)
1 Month			
MC (n=15)	3.1 (4.3)	78.4 (18.3)	8.9 (2.2)
LC (n=21)	1.4 (2.6)	85.7 (12.8)	9.9 (1.6)
3 Month			
MC (n=15)	1.8 (3.2)	89.5 (20.0)	8.8 (1.5)
LC (n=21)	2.9 (4.7)	87.7 (15.8)	10.0 (1 5)

One patient developed a wound infection which was slow to heal; the other patient presented 10 days post-operatively with an acute abdomen. Free intraperitoneal bile was found and drained at laparotomy, without a demonstrable leak. One complication was noted in the LC group (2.7%) where a patient developed a persistent ileus and pain 4 days post-operatively. She underwent laparotomy but no abnormality was found and the patient subsequently improved. She stayed in hospital a total of 13 days.

No mortality was recorded in the study.

No retained stone was detected in either patient group after a one year follow-up.

Reference population:

Over the period of accrual of the randomized trial, 1278 laparoscopic cholecystectomy patients were included in the McGill laparoscopic cholecystectomy registry. This registry is based on surgeon-generated data from four different hospitals representing over 12 surgeons. The characteristics of these patients are shown in table 4. These data are included herein because they will be used for comparison in the discussion section below. There is unfortunately no information available as to the socio-economic status of these patients, or the referral patterns of the contributing surgeons.

(Note: This data base was used to obtain the surgeon-

generated measurements of patient convalescence which were compared to the nurses' measurements).

Table IV

McGill Laparoscopic Cholecystectomy Population

Size	1278 patients
Mean age	49 years
% women	73%
% previous abdominal surgery	36%
Median ASA score	1

DISCUSSION

Both patient groups were similar with respect to baseline parameters thus suggesting that randomisation seems to have been successful, at least as pertains to measured baseline variables. The use of a randomized design also allowed for the subsequent unconstrained application of statistical testing.

Hospital stay, time to full diet, and duration of convalescence in the MC group were comparable to previously published results using mini-cholecystectomy (52-55) thus confirming that the effectiveness of this technique in our hands is similar to that in the literature. Duration of convalescence in the MC group was markedly shorter than that described in at least one previous comparative trial comparing LC to MC (59). Results in that non-controlled trial were most likely affected by pre-determined surgeon expectations. This underscores the importance of utilizing a suitable control group for comparative analysis, which was the main impetus for our trial, in the first place. The results obtained with LC in this study were similar to those reported by other investigators (57), also suggesting effectiveness of that technique in our hands. Overall, despite the optimal results obtained with MC, patients in the LC group still fared better with regard to almost all measured outcomes. A statistically and clinically

significant difference in convalescence between both groups was demonstrated using survival analysis. It is particularly of interest to compare patients who had convalesced fully by 30 days. The slope of each curve up to this time is steeper in the LC group (figure 1), showing that these patients are recovering from surgery 1.77 times more rapidly than MC patients. All patients requiring longer than one month convalescence had usually suffered a complication. These patients therefore represented a separate subset which is more difficult to compare, because of the heterogeneity of the complications and the small number of patients involved.

Although the number of patients in the study was small, we used multivariate regression analysis to determine which variables could best explain the observed durations of convalescence. The type of operation performed was found to be the only variable significantly associated with duration of convalescence, even when controlling for the possible confounding effects of age, gender, co-morbidity, Quetelet index, and occupation of the patient. The length of the MC incision was also not found to affect significantly the duration of convalescence. Surgeon and centre effects were not found to be determinant of outcome but some of these relationships may be hidden by the size of our sample.

The meaning of the results concerning mortality and morbidity is not totally clear, again because of the small

sample size, but they were nevertheless quite comparable to previous reports in the literature (69,84) and similar in both groups. It is interesting to note that an MC patient developed a post-operative bile leak, which is a complication more frequently reported with LC than with an open technique (69). The LC patient who underwent laparotomy for a persistent ileus and required a long hospital stay might now be managed differently, given our greater experience with LC. As expected because of the sample size, there was also no reported common bile duct injury or retained common bile duct stone.

Post-operative pain was quantified in each group with "objective" (amount of narcotics used) and "subjective" (McGill Pain Score) measures. Mean total doses of post-operative narcotics required within the first week were significantly less in the LC group. Interestingly, the reported figure was almost, to the last mgEq of morphine, equal to that reported in a study by the UCLA group (85). Although median McGill Pain Questionnaire scores did not significantly differ at 24 hours, there was a trend favouring LC which was indeed validated by the one week narcotic consumption figures. The lack of significance achieved in the patients' post-operative pain scores warrants some attention. This seemed to go against the overwhelmingly common belief that this may be the single most clinically obvious benefit of LC over any of its open

counterparts. It is possible that the McGill Pain Score is poorly suited for the use which we made of it (ie post-operative abdominal pain). However, it is also quite plausible that the McGill Pain Score results across both groups are similar as a result of the significantly greater amount of narcotics used in the MC group. Therefore, we think it is important to interpret the pain data both in terms of the amount of pain reported and the quantity of pain relievers consumed at that time.

The multiple quality of life indices were chosen to reflect both general and specific aspects of health status and quality of life. All were found to be sensitive enough to detect an improvement following operation irrespective of the surgical technique used (paired, intra-group, analysis). Although the magnitude of the change in quality of life scores between groups did not differ significantly (unpaired, inter-group scores), the LC patients showed improvement in mean scores more quickly than the patients in the MC group (paired scores). This was found, albeit to varying degrees, using all three indices, and is compatible with the direction of the results observed for the duration of convalescence which also favoured LC over MC.

In spite of these results, a number of factors in our trial may limit the scope of its conclusions.

External validity: The present study population is not necessarily fully representative of all patients with symptomatic gallstones because of the exclusion of lithotripsy candidates and patients suspected of common bile duct stones. One might also argue that there is an intrinsic bias towards the types of patients who accepted to be included in a randomized trial. Moreover, since only 8 of the 40 surgeons performing cholecystectomy at McGill were involved in the study, and 2/3 of patients were contributed by 3 surgeons in differing institutions, it is not possible to determine exactly the size or characteristics of the population from which the study sample size is taken. One way of assessing these points is to compare the characteristics of patients in this study with the overall patient population from which they were taken. Over the period of accrual of the trial, 1278 laparoscopic cholecystectomies were performed at McGill, and the following table V summarizes some characteristics of these patients with respect to those in the randomised trial. As previously mentioned, there are no data available from the registry as to patient socio-demographic variables or referral patterns. This, albeit flawed, is the best source of information on the contributing surgeons and the overall patient population from which the study sample was taken. We are unaware of any characteristics of the referral system which should lead to significant bias.

Table V

Characteristics of Trial and Registry patients

	Trial	Registry
Number of patients	70	1278
Mean age (years)	51.8 yrs	49 yrs
% women	71 %	73%
% previous abdominal surgery	32 %	36%
Median ASA score	1	1

Table 5 illustrates that there is no obvious significant difference in any of the standard descriptive baseline categories. In view of these results, there is no strong biological reason to assume that the generalizability of the study may be compromised by a subselection of patients.

Exclusions: There were more drop-outs in the MC than in the LC group, however all were accounted for by factors which seemed to be similar in both groups. Overall, 11.4% of study patients dropped out after randomization. This may well reflect the poor acceptance of surgical randomisation by patients. It is unlikely that bias was involved in the decision of patients to drop out because four patients (one from the LC and three from the MC group) declined to take any part in the trial after having been randomised, for a variety of reasons: Because of extended leaves (two cases), because of a concomitant sudden psychiatric disturbance (one case), and for unknown reasons in the last. These were thought to be the result of errors in the investigator's judgment by poorly assessing the anticipated compliance of these patients. Interestingly, these cases all occurred early on in the trial experience. Thereafter, four patients in the MC group refused further participation. It is again unlikely that treatment bias played a role in these decisions because three of these four patients (75%)

underwent an open (albeit not "mini") cholecystectomy anyway with their referring surgeon. The latter had initially referred the patients for LC and, upon learning that an "open procedure" was going to be carried out, elected to operate on the patients themselves. Unfortunately, none of these surgeons performed an operation which would in any way have been considered to qualify as a MC. Because of this consideration, these patients were also excluded from the analysis.

Trial termination: One point of contention relates to the timing of the termination of the trial. It was terminated mainly because ongoing patient accrual had become very difficult in view of the concomitant diffusion of LC both in the lay press and particularly among referring physicians. It was also not felt to be ethical to pursue the trial because statistically (and clinically) significant differences in major outcomes had been reached at the first analysis. There is at least one report which relates to the ability to terminate a trial early with respect to the pre-calculated sample size. According to Hwang et al, (86) any result achieved after 70% accrual where a p-value is inferior to 0.039 can be considered to be significant. Most of the major outcomes of our study satisfy this condition.

Outcome measurement bias:

As in every other reported post-operative assessment, surgeons were involved in both administering the intervention (the surgical procedure) and measuring the outcome (for eg: Full convalescence). In order to determine to what extent this may have affected the assessment of duration of convalescence, this outcome was measured in the LC group both by surgeons at the time of office follow-up, and by research nurses in the gallbladder clinics. There was a 25% discrepancy in these assessments with the surgeons tending to underestimate the patients' return to full activities by over four days. The surgeons' estimates are similar to results in the literature (59,87). Such surgeon-generated observer bias will need to be considered in future unblinded surgical trials where outcomes are measured by the treating surgeons themselves.

As previously mentioned, patient and surgeon blinding is not likely to be effective, practical, or ethical ("sham" operations) when an operative procedure is involved. Moreover the nurses, who made the measurements which were considered as the "true" outcomes, were not formally blinded to the patient group, even though they were instructed to document duration of convalescence prior to any other data which may have informed them of the patient's randomization group (especially when they were measuring the length of the MC incisions). Thorough

blinding of the observers in the future, where feasible, may strengthen the objectivity of this measurement. That there may have been bias in the outcome measurements therefore remains a matter of speculation. Nevertheless, cross validation of outcomes which were less subject to observer bias (eg: Quality of life, amount of narcotics used,...) seem to confirm the direction of the convalescence data. In order to try to utilize potential observer bias in the same direction in both groups, while maintaining some of the strengths of the randomized design, some authors have suggested that only patients should be randomized, rather than clinicians or treatments (88). This would allow each surgeon group to operate according to preference or expertise.

Long term outcomes:

This trial was not designed to address important points related to the ability of either the mini or the laparoscopic approach to deal with common bile duct stones, or the incidence of post-operative common bile duct strictures. In order to assess the comparative overall impact of each procedure on both patients and Society, these issues certainly need to be addressed. The incidences of both these outcomes are relatively rare (1-5% for retained common bile duct stones, and 0.1-0.6% for common bile duct injury) and require lengthy follow-up (several

years) to be accurate. These issues are therefore best dealt with in the context of a large multi-institutional biliary registry, which is ongoing at present at most McGill University teaching hospitals.

Conclusion:

The present randomised controlled clinical trial comparing laparoscopic to mini-cholecystectomy demonstrates superior effectiveness of the laparoscopic procedure with regards to duration of hospital stay and convalescence in patients with symptomatic gallbladder stones not suspected of having choledocholithiasis. Its limitations appear to be representative of the shortcomings characteristic of most surgical randomised trials, suggesting that alternatives to conventional randomisation schemes and multiple "blinded" party outcome measurement may be required.

ACKNOWLEDGEMENTS

I am indebted to the following people in helping me to successfully complete this thesis:

Diane Thibeault and Christine Wickham without the caring attention and devoted work of whom the study could not have been performed.

Ethicon Corporation who, through an MRC University Industry partnership grant, helped to support the trial financially.

The members of the McGill laparoscopic group who contributed their time and helped to recruit their patients.

Dr J.Sampalis whose statistical support was invaluable.

Dr JL. Meakins whose intellectual support and encouragement helped to maintain many standards of excellence.

Dr Pierre Tousignant who, as a thesis supervisor, knew the correct ingredients to help me complete this work.

Drs Alan Barkun and Gerry Fried whose ongoing stimulation and unquestioned support have created the environment necessary to undertake this and other studies successfully.

My parents, who showed me the importance of trying to get the most out of every accomplishment.

Most of all, my wife Susan whose constant support and direction continues to be my greatest source of inspiration.

STATEMENT OF ORIGINALITY

The study to be described in this thesis has represented an original contribution to the field of biliary surgery. It is one of the only three randomised trials comparing open to laparoscopic cholecystectomy. Moreover, it is the largest one, and the only one to use mini cholecystectomy as standard for comparison in the "open" cholecystectomy group.

BIBLIOGRAPHY

1. Ingelfinger FJ. Digestive diseases as a national problem. Gallstones. Gastroenterol 55:102-104, 1968.

2. National Institute of Health Consensus Development Conference Statement on Gallstones and Laparoscopic Cholecystectomy. Am J Surg Vol 165:390-396, April 1993.

3. Strasberg SM, Clavien PA: Cholecystolithiasis: Lithotherapy for the 1990s. Hepatology Vol 16 No 3:820-839, 1992.

4. Brett M, Barker DJP. The world distribution of gallstones. Int J Epidemiol 5:335-341, 1976.

5. Bennion LJ, Grundy SM. Risk factors for the development of cholelithiasis in man. N Engl J Med 299:1161-1167, 1221-1227, 1978.

6. Rome group of the epidemiology and prevention of cholelithiasis (GREPCO). Prevalence of gallstone disease in an adult female population. Am J Epidemiol 119:796-805, 1984.

7. Barbara L, Sama C, Labate AMM, Taroni F, Rusticalli AG, Festi D, Sapio C, et al.: A population study on the prevalence of gallstone disease: The Sirmione Study. Hepatology 7:913-917, 1987.

8. Gamblek I, Kvaale G, Arnesjo B, Soreide O: Prevalence of gallstones in a Norwegian population. Scand J Gastroenterol 22:1089-1094, 1987.

9. Rome group of the epidemiology and prevention of cholelithiasis (GREPCO). The epidemiology of gallstone disease in Rome, Italy. Part I: prevalence data in men. Hetpatology 8:904-906, 1988.

10. Rome group of the epidemiology and prevention of cholelithiasis (GREPCO). The epidemiology of gallstone disease in Rome, Italy. Part II: factors associated with the disease. Hepatology 8:907-913, 1988.

11. Jorgensen T: Gallstones in a Danish population: relation to the weight, physical activity, smoking, coffee consumption, and diabetes mellitus. Gut 30:528-534, 1989.

12. Maurer KR, Everhart JE, Ezzati TM, Johannes RS, Knowler WC, Larson DL, Sanders R, et al.: Prevalence of gallstones disease in hispanic populations in the Unites States. Gastroenter. 96:487-492, 1989.

13. Heaton KW, Braddon FEM, Mountford RA, Emmett PM: Symptomatic and silent gallstones in the community. Gut 32:316-320, 1991.

14. Guttierrez Y, Ransohoff DF, Gracie WA. Frequency of gallstone disease: trends over time at autopsy. Gastroenterology 86:1103, 1984 (abstract).

15. Burkitt DP, Trowell H. Refined carbohydrate foods and disease: Some implications of dietary fibre. London, Academic Press, 1985.

16. Becker BJP, Chatgidakis CB. Carcinoma of the gallbladder and cholelithiasis on the Witwatersrand; autopsy survey of racial incidence. S Afr J Clin Sci 3:1-22 1952.

17. Marinovic I, Guerra C, Larach G. Incidencia de lithiasis biliar en material de autopsias y analysis de composicion de los calculos. Revista Medica de Chile 100:1320-1327, 1972.

18. Ma Photra SM. Epidemiological study of cholelithiasis among railway workers in India with special reference to causation. Gut 9:290-295, 1968.

19. Barker DJP, Gardner MJ, Power C, Hutt MSR. Prevalence of gallstones at necropsy in nine British towns: A collaborative study. Br Med J 4:189-1992, 1979.

20. Broomfield PH, Chopra R, Sheinbaum RC, et al. Effects of ursodeoxycholic acid and ASA on the formation of lithogenic bile and gallstones during loss of weight. N Engl J Med 319:1567-1572, 1988.

21. DenBesten L, Berci G. The current status of biliary tract surgery: an international study of 1072 consecutive patients. World J Surg 10:116-122, 1986.

22. Charlton JRH, Velez R. Some international comparisons of mortality amenable to medical intervention. Br. Med J 292:295-301.

23. Friedman GD: Natural history of asymptomatic and symptomatic gallstones. Am J of Surg 165:399-404, 1993.

24. Lund J: Surgical indications in cholelithiasis: Prophylactic cholecystectomy elucidated on the basis of long term follow up on 626 non operated cases. Ann Surg 151:153-162, 1960.

25. Wenckert A, Robertson B: The natural course of gallstone disease: eleven-year review of 781 nonoperated cases. Gastroenter. 50:376-381, 1966.

26. Peterson R: Gallstones during the course of 1066 abdominal sections for pelvic disease. Surg Gynecol Obstet 20:284-291, 1951.

27. Truesdell ED: The frequency and future of gallstones believed to be quiescent or symptomless. Ann Surg 119:232-245, 1944.

28. Comfort MW, Gray HK, Wilson JM: The silent gallstone: a ten to twenty year follow-up study of 112 patients. Ann Surg 128:931-937, 1948.

29. Gracie WA, Ransohoff DF: The natural history of silent gallstones: the innocent gallstone is not a myth. N Engl J Med 307:798-800, 1982.

30. Thistle JL, CLeary PA, Lachin JM, Tyor MP, Hersh T: The natural history of cholelithiasis: The National Cooperative Gallstone Study. Ann Intern Med 101:171-175, 1984.

31. McSherry CK, Ferstenberg H, Cahoun WF, Lahman E. Wirshup M: The natural history of diagnosed gallstone disease in symptomatic and asymptomatic patients. Ann Surg 202:59-63, 1985.

32. Friedman GD. Problems in determining the prognosis of asymptomatic gallstones. In Capocaccia L, Ricci G, Angelico F, Attili MF editors. Epidemiology and prevention of gallstone disease. Proceedings of an international workshop on epidemiology and prevention of gallstone disease, Rome, December 1983. Boston: MTP Press Limited, 1984: 158-167.

33. Schoenfield LJ, Carulli N, Dowling RH, Sama C, Wolpers C. Asymptomatic gallstones: definition and treatment (working team report). Gastroenterol Int 2:25-29, 1989.

34. Ransohoff DF, Gracie WA, Wolfenson LB, Neuhauser D. Prophylactic cholecystectomy or expectant management for silent gallstones. Ann Int Med 99:199-204, 1983.

35. Friedman GD, Raviola CA, Firman B: Prognosis of gallstones with mild or no symptoms: 25 years of follow-up in a health maintenance organization. J Clin Epidemiol 42:127-136, 1989.

36. Newman HF, Northup JD, Rosenblum M, Abrams H: Complications of cholelithiasis. Am J Gastroenterol 50:476-496, 1968.

37. Rhornton JR, Heaton KW, Espiner HJ, Eltringham WK. Empyema of the gallbladder-reappraisal of the neglected disease. Gut 24:1183-1185, 1983.

38. Ranson JHC, Pasternack BS. Statistical methods for quantifying the severity of clinical acute pancreatitis. J Surg REs 22:79-91, 1977.

39. Corfield AP, Cooper MJ, Williamson RCN. Acute pancreatitis: a lethal disease of increasing incidence. Gut 26:724-729, 1985.

40. Maringhini A, Moreau JA, Melton LJ. Gallstones, gallbladder cancer, and other gastrointestinal malignancies: an epidemiologic study in Rochester, Minnesota. Ann Int Med 107:30-35, 1987.

41. Robinson JO: Silvergirl's Surgery: Biliary Tract. Austin, Silvergirl Inc., p 85, 1985.

42. Sparkman RS: Bobbs centennial: The first cholecystotomy. Surg Gynecol Obstet 61:965-971, 1967.

43. Langenbuch C. Ein Fall von Extirpation der Gallenblase wegen chronischer Cholelithiasis. Berliner Klin Wschr 18:725-727, 19882.

44. Lillemoe KD, Pitt HA, Cameron JL: Postoperative Bile Duct Strictures. Surgical Clinics of North America Vol 70 No6:1355-1380, 1990.

45. Houghton PWJ, Jenkinson LR, Donaldson LA. Cholecystectomy in the elderly: a prospective study. Br J Surg 72:220-222, 1985.

46. Crocker JR. Biliary tract disease. In Gastrointestinal disorders of the elderly. Clin in Gastoent; 773-809, 1985.

47. Vellacott KD, Powell PH. Exploration of the common bile duct, a comparative study. Br J Surg 66:389-391, 1979.

48. Bates, Godfrey PJ, Harrison M, Walsh B, Levien DH. Cholecystectomy rates in the US and the UK compared: does the difference matter? Gut 25:A1147-1147, 1984.

49. Ros E, Zambon D. Post-cholecystectomy symptoms: a prospective study of gallstone patients before and two years after surgery. Gut 28:1500-1504, 1987.

50. Moody F. The post cholecystectomy syndrome in surgical treatment of digestive diseases. Yearbook Medical Publishers, Chicago 296-305, 1986.

51. Tompkins RK: Surgical management of bile duct stones. Surgical Clinics of North America Vol 70 No 6:1329-1339.

52. Ledet Jr. WP. Ambulatory cholecystectomy without disability. Arch Surg 125:1434-1435, 1990.

53. Saltzstein EC, Mercer LC, Peacock JB et al. Outpatient open cholecystectomy. Surg Gyn Obst 174:173-175, 1992.

54. Armstrong PJ, Burgess RW. Choice of incision and pain following gallbladder surgery. Br J Surg 77:746-748, 1990.

55. Cheslyn-Curtis S, Russell RCG. New trends in gallstone management. Br J Surg 78:143-149, 1991.

56. Personal communication re: vertical mini-cholecystectomy, unpublished data, Wexler, M.

57. Olsen DO: Mini-lap cholecystectomy. Am J of Surg 165:440-443, 1993.

58. Dubois F, Icard P, Berthelot G, et al. Coelioscopic Cholecystectomy. Ann Surg 211:60-62, 1990.

59. Reddick EJ, Olsen DO. Laparoscopic laser cholecystectomy. Surg Endosc 3:131-133, 1989.

60. Cameron JL, Gadacz TR.: Laparoscopic cholecystectomy. Ann Surg 213:1-2, 1991.

61. Gadacz TR: US experience with laparoscopic cholecystectomy. Am J of Surg 165:450-454, 1993.

62. Litwin DEM, Girotti MJ, Poulin EC, et al. Laparoscopic cholecystectomy; trans Canada experience with 2201 cases. Can J Surg 35:291-296, 1992.

63. Barkun JS, Fried GM, Barkun AN, Sigman HH et al.: Cholecystectomy without operative cholangiography: implications for common bile duct injury and retained common bile duct stones. Ann of Surg Vol 218 No 3:371-379, 1993.

64. Sanabria JR, Clavien PA, Cywes R, Strasberg SM: Laparoscopic versus open cholecystectomy: a matched study. JCC Vol 36 no 4:330-336, 1993.

65. Gadacz TR, Talamini MA. Traditional vs laparoscopic cholecystectomy. Am J Surg 161:336-338, 1991.

66. Grace PA, Quereshi A, Coleman J, et al. Reduced Postoperative Hospitalization After Laproscopic Cholecystectomy. Br J Surg 78:16-162, 1991.

67. Frazee RC, Roberts JW, Okeson GC, et al. Open versus laparoscopic cholecystectomy. Ann Surg 213:651-654, 1991.

68. Peters JH, Ellison EC, Innes JT, et al. Safety and efficacy of laparoscopic cholecystectomy. Ann surg 213:3-12, 1991.

69. Meyers WC, Branum GD, Farouk M, et al. A prospective analysis of 1518 laparoscopic cholecystectomies. NEJM 324:1073-1078, 1991.

70. Paterson-Brown S. Laparoscopic Cholecystectomy. Br J Surg 78:131-132, 1991.

71. Cholecystectomy Practice Transformed. The Lancet 338:789-90, 1991.

72. Walsh TN, Russell RCG. Cholecystectomy and gallbladder conservation. Br J Surg 79:4-5, 1992.

73. Tompkins RK. Laparoscopic cholecystectomy - Threat or opportunity. Arch Surg 125:1245, 1990.

74. Neugebauer E, Troidl H, Spangenberger, et al. Conventional versus laparoscopic cholecystectomy and the randomized controlled trial. Br J Surg 78:150-154, 1991.

75. Vitale GC, Collet D, Larson GM, et al. Interruption of professional and home activity after laparoscopic cholecystectomy among French and American patients. Am J Surg 161:396-398, 1991.

76. Barkun JS, Barkun AN, Mulder DS, Battista RN: Technology Assessment. Principles and Practice of Research, Second Edition 313-321, 1991.

77. Chang C, Lancet, Oct 9, 1993; vol 3423:929, letter,

78. Owen WD, Felts JA, Spitznagel EL Jr, et al. ASA physical status classification: a study of consistency ratings. Anaesthesiology 49:239-43, 1978.

79. Eypasch E, Troidl H, Wood-dauphinee S, et al. Quality of life in gastrointestinal surgery. A clinimetric approach to development of a measure. Theoret Surg 5:3-10, 1990.

80. Streiner DL, Normal GR. Chapter 4: Scaling responses. In: Health measurement scales. A practical guide to their development and use. Oxford: Oxford Medical Publications 23-25, 1989.

81. McDowell I, Newell C. Measuring Health, a guide to rating scales and questionnaires. 1987, Oxford Press.

82. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. J R Coll Gen Ract. 35:185-8, 1985.

83. Melzack R. The McGill pain questionnaire: Major properties and scoring methods. Pain 1:277-299, 1975.

84. Larson GM, Vitale GC, Casey J, et al. Multipractice analysis of laparoscopic cholecystectomy in 1983 patients. Am J Surg 163:221-226, 1992.

85. Woolf B, personal communication.

86. Hwang IK, Weichung JS. Statistics in Medicine 9:1439-1445, 1990.

87. Schirmer BD, Edge SB, Dixs J, et al: Laparoscopic cholecystectomy. Ann Surg 213:665-677, 1991.

88. Korn EL, Baumrind S. Randomised clinical trials with clinician preferred treatment. Lancet 337:149-152, 1991.

APPENDIX - 1 -

Note: EL = energy level P = pain, ER = emotional reactions, S = sleep
SI = social isolation PA = physical abilities

- Listed below are some problems people can have in their daily life.
- Please read each one carefully
- If it is TRUE for you, put a tick (✓) in the box under Yes.
- If it is NOT TRUE, put a tick (✓) in the box under No
- If you are not sure whether to answer yes or no to a problem, ask yourself whether it is true for you *in general*

Note: it is important that you answer every question

	Yes	No	Section
I'm tired all the time	☐	☐	EL
I have pain at night	☐	☐	P
Things are getting me down	☐	☐	ER
I have unbearable pain	☐	☐	P
	Yes	No	
I take tablets to help me sleep	☐	☐	S
I've forgotten what it's like to enjoy myself	☐	☐	ER
I'm feeling on edge	☐	☐	ER
I find it painful to change position	☐	☐	P
I feel lonely	☐	☐	SI
	Yes	No	
I can walk about only indoors	☐	☐	PA
I find it hard to bend	☐	☐	PA
Everything is an effort	☐	☐	EL
I'm waking up in the early hours of the morning	☐	☐	S
	Yes	No	
I'm unable to walk	☐	☐	PA
I'm finding it hard to make contact with people	☐	☐	SI
The days seem to drag	☐	☐	ER
I have trouble getting up and down stairs or steps	☐	☐	PA
I find it hard to reach for things	☐	☐	PA
	Yes	No	
I'm in pain when I walk	☐	☐	P
I lose my temper easily these days	☐	☐	ER
I feel there is nobody I am close to	☐	☐	SI
I lie awake for most of the night	☐	☐	S
	Yes	No	
I feel as if I'm losing control	☐	☐	ER
I'm in pain when I'm standing	☐	☐	P
I find it hard to dress myself	☐	☐	PA
I soon run out of energy	☐	☐	EL
	Yes	No	
I find it hard to stand for long (e.g. at the kitchen sink, waiting for a bus)	☐	☐	PA
I'm in constant pain	☐	☐	P
It takes me a long time to get to sleep	☐	☐	S
I feel I am a burden to people	☐	☐	SI
Worry is keeping me awake at night	☐	☐	ER
I feel that life is not worth living	☐	☐	ER
	Yes	No	
I sleep badly at night	☐	☐	S
I'm finding it hard to get on with people	☐	☐	SI
I need help to walk about outside (e.g. a walking aid or someone to support me)	☐	☐	PA
	Yes	No	
I'm in pain when going up and down stairs or steps	☐	☐	P
I wake up feeling depressed	☐	☐	ER
I'm in pain when I'm sitting	☐	☐	P

APPENDIX - 2 -

GASTROINTESTINAL QUALITY OF LIFE (GIQL) SCALE

Troidl H, Eypasch E, Wood-Dauphinee S, Williams J I

CORE ITEMS

1. How often during the last 2 weeks have you been troubled by pain in the abdomen?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

2. How often during the last 2 weeks have you been troubled by a feeling of fullness in the upper abdomen?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

3. How often during the last 2 weeks have you been troubled by bloating (sensation of too much gas in the abdomen)?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

4. How often during the last 2 weeks have you been troubled by the excessive passage of gas?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

5. How often during the past 2 weeks have you been troubled by strong burping or belching?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

6. How often during the last 2 weeks have you been troubled by gurgling noises from the abdomen?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

7. How often during the last 2 weeks have you been troubled by frequent bowel movements?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

8. How often during the last 2 weeks has eating been a pleasure for you?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

9. Because of your illness, how often have you had to restrict the kinds of food you eat?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

10. During the last 2 weeks, how well have you been able to handle everyday stress?

( )	( )	( )	( )	( )
extremely poorly	poorly	moderately	well	extremely well

11. How often during the last 2 weeks have you felt sad about being ill?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

12. How often during the last 2 weeks have you felt nervous or anxious about your illness?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

13. How often during the last 2 weeks have you been happy with life in general?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

14. How often during the last 2 weeks have you felt frustrated about your illness?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

15. How often during the last 2 weeks have you been tired or fatigued?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

16. How often during the last 2 weeks have you felt unwell?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

17. Over the past week, how many nights have you woken up during the night?

( )	( )	( )	( )	( )
every night	5 to 6 nights	3 to 4 nights	1 to 2 nights	never

18. Since becoming ill, to what extent have you been troubled by changes in your appearance?

( )	( )	( )	( )	( )
a great deal	a moderate amount	somewhat	a little bit	not at all

19. Because of your illness, how much strength have you lost?

( )	( )	( )	( )	( )
a great deal	a moderate amount	somewhat	a little bit	none

20. Because of your illness, to what extent have you lost your endurance (the ability to keep doing an activity over time)?

( )	( )	( )	( )	( )
a great deal	a moderate amount	somewhat	a little bit	not at all

21. Because of your illness, to what extent do you feel unfit?

( )	( )	( )	( )	( )
extremely unfit	moderately unfit	somewhat unfit	a little unfit	feel fit

22. During the last 2 weeks, how often have you been able to complete your normal daily activities (school, work, household activities)?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

23. During the last 2 weeks, how often have you been able to take part in your usual leisure or recreational activities?

( )	( )	( )	( )	( )
all of the time	most of the time	some of the time	a little of the time	never

24. During the last 2 weeks, how much have you been troubled by the medical treatment of your illness?

( )	( )	( )	( )	( )
very much	quite a bit	somewhat	a little	not at all

25. To what extent have your personal relations with people close to you (family or friends) worsened because of your illness?

( )	( )	( )	( )	( )
very much	quite a bit	somewhat	a little	not at all

26. To what extent has your sexual life been impaired (harmed) because of your illness?

( )	( )	( )	( )	( )
very much	quite a bit	somewhat	a little	not at all

ORGAN SPECIFIC ITEMS

1. How often during the last 2 weeks, have you been troubled by fluid or food coming up into your mouth (regurgitation)?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

2. How often during the last 2 weeks have you felt uncomfortable because of your slow speed of eating?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

3. How often during the last 2 weeks have you had trouble swallowing your food?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

4. How often during the last 2 weeks have you been troubled by urgent bowel movements?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

5. How often during the last 2 weeks have you been troubled by diarrhea?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

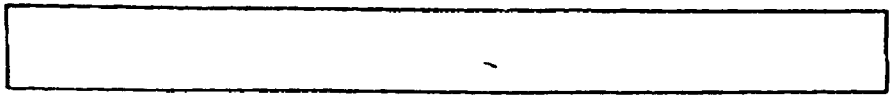
6. How often during the last 2 weeks have you been troubled by constipation?

( ) very often ( ) often ( ) sometimes ( ) rarely ( ) never

APPENDIX - 3 -

QUALITY OF LIFE UNISCALE

LOWEST QUALITY



HIGHEST QUALITY

CD

APPENDIX - 4 -

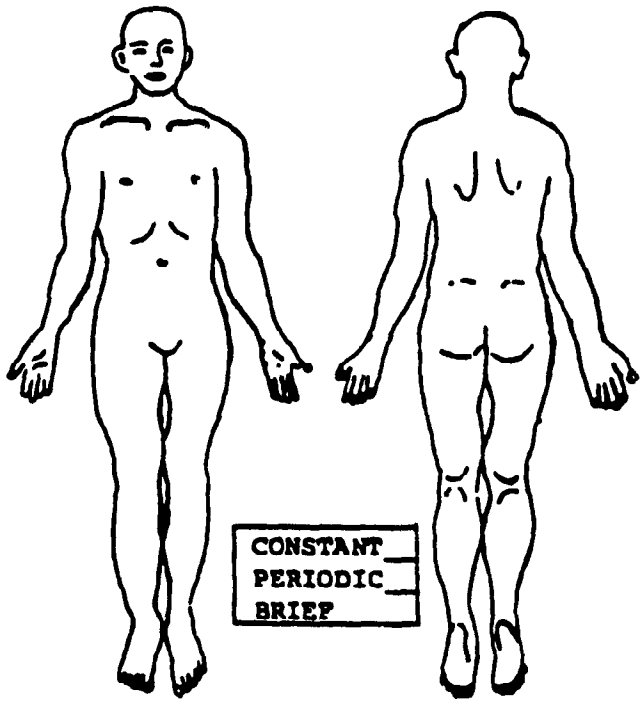
McGill - Melzack Pain Questionnaire

Patient's Name_____ Date_____ Time_____ am/pm
Analgesic(s) _____ Dosage_____ Time Given _____ am/pm
_____ Dosage_____ Time Given_____ am/pm

Analgesic Time Difference (hours): +4 +1 +2 +3
PRI: S_____ A_____ E_____ M(S)_____ M(AE)_____ M(T)_____ PRI(T)____
(1-10) (11-15) (16) (17-19) (20) (17-20) (1-20)

1 FLICKERING		11 TIRING
QUIVERING		EXHAUSTING
PULSING		12 SICKENING
THROBBING		SUFFOCATING
BEATING		13 FEARFUL
POUNDING		FRIGHTFUL
2 JUMPING		TERRIFYING
FLASHING		14 PUNISHING
SHOOTING		GRUELLING
3 PRICKING		CRUEL
BORING		VICIOUS
DRILLING		KILLING
STABBING		15 WRETCHED
LANCINATING		BLINDING
4 SHARP		16 ANNOYING
CUTTING		TROUBLESOME
LACERATING		MISERABLE
5 PINCHING		INTENSE
PRESSING		UNBEARABLE
GNAWING		17 SPREADING
CRAMPING		RADIATING
CRUSHING		PENETRATING
6 TUGGING		PIERCING
PULLING		18 TIGHT
WRENCHING		NUMB
7 HOT		DRAWING
BURNING		SQUEEZING
SCALDING		TEARING
SEARING		19 COOL
8 TINGLING		COLD
ITCHY		FREEZING
SMARTING		20 NAGGING
STINGING		NAUSEATING
9 DULL		AGONIZING
SORE		DREADFUL
HURTING		TORTURING
ACHING		PPI
HEAVY		0 No pain
10 TENDER		1 MILD
TAUT		2 DISCOMFORTING
RASPING		3 DISTRESSING
SPLITTING		4 HORRIBLE
		5 EXCRUCIATING

PPI_____ COMMENTS:



CONSTANT
PERIODIC
BRIEF

ACCOMPANYING SYMPTOMS:	SLEEP:	FOOD INTAKE:
NAUSEA	GOOD	GOOD
HEADACHE	FITFUL	SOME
DIZZINESS	CAN'T SLEEP	LITTLE
DROWSINESS	COMMENTS:	NONE
CONSTIPATION		COMMENTS:
DIARRHEA	ACTIVITY:	COMMENTS:
COMMENTS:	GOOD	
	SOME	
	LITTLE	
	NONE	

APPENDIX - 5 -

(JGH-laparo/open-eng)

CONSENT FORM - THE McGILL GALLBLADDER STONE TREATMENT PROTOCOL

I have been found to have gallstones which are thought to be the cause of my abdominal pain. Patients with abdominal pain caused by gallbladder stones are at risk for developing symptom recurrence over the next few years and may develop serious complications of gallstone disease such as pancreatitis (an inflammation of the pancreatic gland), cholecystitis (an inflammation of the gallbladder), or ascending cholangitis (an infection of the bile and bile ducts) Treatment of stones in the gallbladder is therefore indicated. The goal of this study is to determine whether certain patients will benefit from a modification of the standard treatment now available.

At present, surgical removal of the gallbladder, the conventional cholecystectomy, is the most commonly used treatment . However, recently, a new operative technique has also been developed which is called laparoscopic cholecystectomy. This operation has now been performed on over 500 patients worldwide and offers the benefits of a very small scar while removing the gallbladder.

I require therapy for my gallbladder stones, and the tests indicate that I may benefit from either treatment. The risks of each treatment are described below.

The risks involved with surgery, and its general anaesthesia are very small and on average over 90% of patients will have no complications. About one patient in 200 may die from the surgery. Most patients will remain in the hospital for four to seven days after the operation. After discharge, a one month convalescent period because of pain at the incision site is usually required. Some of the more common post-operative complications of abdominal surgery include wound infection, atelectasis (a condition where part of a lung may not work for a short while), and venous thrombosis (when a clot forms in the veins of the legs).

Laparoscopic cholecystectomy is an operation where the gallbladder is removed using a tube called a laparoscope through a small hole made around the umbilicus or navel. In addition, three smaller holes (5-10mm) are made to allow for surgical instruments to be passed into the abdomen in order to perform the procedure. Laparoscopy has been used widely to perform tubal ligation in women. The potential advantages of this technique as it applies to removal of the gallbladder with stones include a smaller scar, a shortened hospital stay, and a more rapid return to usual daily activities following discharge than with conventional cholecystectomy. The potential risks of this surgery include those inherent to a general anaesthesia, and abdominal surgery as mentioned above. There may also be a higher risk of injury to the bile ducts, blood vessels or bowel. If a complication should occur, or should my anatomy be unsuitable for this type of approach at the time of surgery, I agree to let my surgeon convert the procedure to a conventional cholecystectomy.

At present, we do not know which is the better treatment for gallstones ; but since treatment is indicated, the type of therapy I receive will be decided by chance alone; in other words, neither I nor my physician will decide beforehand which treatment I will get.

In order to assess the effectiveness of each treatment and the impact of gallstones on lifestyle, initial X-ray tests will be performed and follow-up visits will be performed over the next three years. Two small samples of blood will be drawn on two occasions during the month following the treatment as part of my routine care. I will fill out questionnaires about how I am getting on with my life every three to six months at the time of follow-up visits; they should last no more than 15-20 minutes. The surgery will take place in the hospital where my surgeon operates. I will be signing another seperate consent form at the time of treatment.

I understand that all information gathered in this study will remain confidential as required by law. My participation is voluntary, and I am free to refuse to participate, or to withdraw from participation at any time, while still receiving optimal treatment.

The responsible physician at the Sir Mortimer B. Davis , Jewish General Hospital is Dr. HARVEY SIGMAN (Tel.:340-8287); the patient representative is ROSLYN DAVIDSON (Tel.:340-8222, ext.5833).

As a part of the monitoring of hospital operations, a member of the Research Committee may contact me requesting that I answer questions about my participation. I will be free at the time to refuse to answer these questions.

I, the undersigned, have been given a copy of this consent form, and agree to participate in the McGill clinical project investigating the treatment of patients with symptomatic gallbladder stones.

SIGNED: _____

DATE: _____ WITNESS: _____

FORMULE DE CONSENTEMENT - LE PROTOCOLE DE McGILL POUR LE TRAITEMENT DES CALCULS DE LA VESICULE BILIAIRE

On a découvert que je suis porteur de pierres dans la vésicule biliaire qui sont probablement la cause de mes douleurs abdominales. Les patients atteints de douleurs abdominales causées par des calculs de la vésicule ont de grandes chances de récidives et peuvent développer de serieuses complications telles la pancréatite (une inflammation de la glande du pancréas), la cholécystite (une inflammation de la vésicule biliaire), ou une cholangite (une infection de la bile et des voies biliaires). Le but de cette étude est de déterminer si les malades bénéficieront d'un changement du traitement standard en vigueur en ce moment.

L'ablation chirurgicale de la vésicule biliaire, la cholécystectomie conventionelle, est en ce moment le traitement utilisé le plus couramment. Cependant, récemment, un nouveau traitement chirurgical a été développé: la cholécystectomie par laparoscopie. Cette opération a maintenant été pratiquée sur plus de 500 malades dans le monde et offre les avantages d'une très petite incision tout en enlevant la vésicule.

Il faut que mes pierres dans la vésicule soient traitées, et les tests montrent que je pourrai bénéficier de l'un ou l'autre des deux traitements. Leurs risques sont décrits plus bas.

Les risques de la chirurgie et de l'anésthésie générale sont très faibles, et en moyenne plus de 90% des malades n'auront aucune complication. Un malade en 200 meurt par suite d'une cholécystectomie; une hospitalisation de 4 à 7 jours est requise, et la période de convalescence dure d'habitude un mois à cause de la douleur de l'incision. Les complications post-opératoires les plus fréquentes d'une chirurgie abdominale incluent des infections de plaie, l'atélectasie (lorsqu'une partie du poumon fonctionne mal pour une courte durée de temps), et une thrombose veineuse (lorsqu'un caillot de sang se forme dans les veines des jambes).

Lors de la cholécystectomie par laparoscopie, la vésicule est enlevée à l'aide d'un tube part un trou fait juste au dessus du nombril. De plus, trois autres plus petites incisions (5-10mm) sont faites pour permettre de passer des instruments dans l'abdomen pendant l'opération. La lapaioscopie est couramment utilisée pour la ligature de trompes chez les femmes. Les avantages potentiels de cette technique lorsqu'appliquée à la vésicule incluent une plus petite incision, une durée d'hospitalisation plus courte, et un retour plus rapide aux activités journalières lorsque comparés à la cholécystectomie conventionelle. Les risques présentés sont ceux d'une anesthésie générale et d'une chirurgie abdominale tels que mentionnés plus hauts. Il existe aussi possiblement un risque accru de blessures opératoires aux voies biliaires, vaisseaux sanguins et aux intestins. S'il arrive une complication, ou si mon anatomie ne permet pas cette opération,lors de la chirurgie, j'accepte de laisser mon chirurgien la convertir à une cholécystectomie conventionelle.

Personne ne sait à date lequel des deux traitements est le meilleur mais un traitement est indiqué pour mes pierres vésiculaires. Le choix sera donc fait au hasard sans que mon docteur ou moi en sache le résultat préalablement..

Pour juger de l'efficacité de chaque traitement ainsi que l'impact des pierres de la vésicule biliaire sur ma vie de tous les jours, des tests de rayons-X initiaux et des visites chaque 3-6 mois seront complétés lors des trois années qui suivent. Deux petits tubes de sang seront prélevés deux fois lors du premier mois de suivi, et aucun après cette date. Quel que soit mon traitement, je remplirai des questionnaires qui aideront à refléter ma qualité de vie chaque trois à six mois lors des visites à la clinique qui ne devraient dépasser 15-20 minutes. La chirurgie aura lieu à l'hôpital de mon chirurgien. Je signerai une différente formule de consentement au moment du traitement choisi.

Je comprends que toute information découlant de l'étude restera strictement confidentielle, sauf pour ce qui est requis de par la loi; ma participation est volontaire, et je suis également libre de refuser de participer, ou d'interrompre ma participation en tout temps sans porter préjudice à mon traitement.

Le médecin responsable à l'hôpital Sir Mortimer B. Davis - Général Juif de Montréal est le Dr. HARVEY SIGMAN (Tél: 340-8287); la représentante des malades est ROSLYN DAVIDSON (Tél.:340-8222, poste 5833).

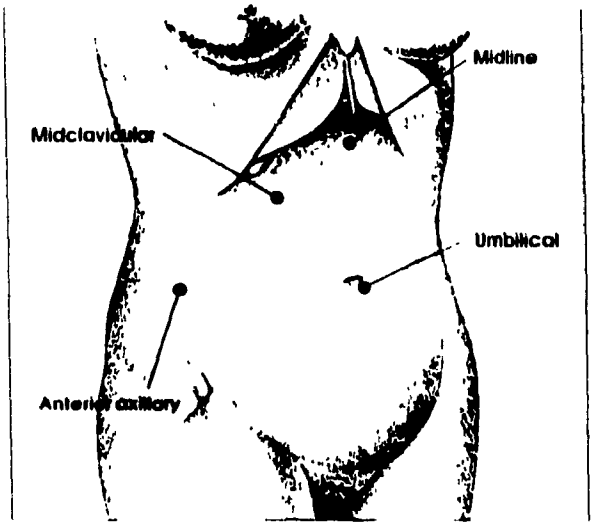
Dans le contexte de la surveillance des activités hospitalières, un membre du comité de Recherches me contactera peut-être pour me poser des questions au sujet de ma participation. Il me sera alors libre de refuser de répondre à ses questions.

Je, soussigné(e), après avoir reçu une copie de la présente formule de consentement, accepte de participer à un projet clinique de l'université McGill visant à étudier le traitement des pierres de la vésicule biliaire.

SIGNATURE: _____

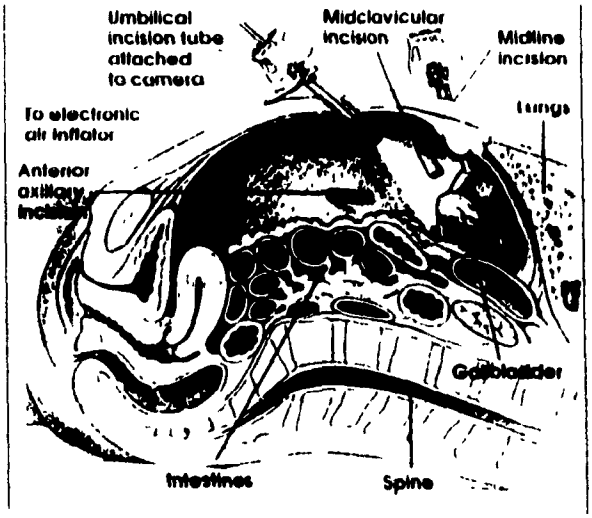
DATE: _____ TEMOIN: _____

LAPAROSCOPIC CHOLECYSTECTOMY



Drawings by LTI Medical /William B Westwood

INCISION SITES FOR LAPAROSCOPIC CHOLECYSTECTOMY



SIDE VIEW OF INSIDE OF ABDOMEN