Management options

What should I do about my patient's gall stones?

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Summary

The problem of benign biliary disease is one that causes significant morbidity and social economic strain in the western world. The classical treatment, cholecystectomy, has been challenged by various medical and surgical techniques in a seemingly random nature. The development of the treatment of gall stone disease is reviewed by analysis of published studies over the last 20 years. The advantages and disadvantages are discussed as an overview and summary of the current management of gall stone disease in the light of our knowledge of its malignant potential.

Keywords: gall stones, management options, cholecystectomy

The last two decades have witnessed extraordinary pharmacological and technical advances which have dramatically altered our approach to the management of gall stones. These developments drew the attention of the medical profession and general public alike to the significant morbidity associated with classical cholecystectomy. Nevertheless it remains difficult to define clear indications for many of the alternative treatments, particularly in view of the lack of long-term studies and details not only of procedure-related complications but also of problems associated with the diseased gall bladder being *in situ* for a prolonged period. The situation is further complicated in some countries where market forces seem to play an inordinate part in the management of this particular problem.

It is nevertheless remarkable that the known association between gall stones and the development of gall bladder cancer has seemed to play such a small part in the decision-making process regarding the treatment of symptomatic gall bladder disease. The aim of this article is to review the alternatives to traditional cholecystectomy in the light of what is presently known about the process leading to carcinoma of the gall bladder.

Open cholecystectomy

The option of open cholecystectomy for symptomatic gall stones has been with us since the surgical revolution in late 19th century following the advent of anaesthesia and Lister's introduction of his principle of antisepsis. First performed successfully in 1882 by CJA Langenbuch,¹ chief surgeon in the Lazarus Hospital of Berlin, by 1886 this had become a routine procedure in the hands of surgeons such as Hans Kehr² who had performed over 1000 by his death in 1916. The cause was further championed by both Moynihan in England and Mayo in America and by the early 1920s became the procedure of choice for symptomatic gall stones despite a significant mortality and morbidity.

Early mortality rates were reported at 6.6%³ although by 1952 this had decreased to 1.8%⁴ and recent studies show it to be dropping to around 0.5%.^{4–6} Pulmonary embolism and deep vein thrombosis were reported at 1%,^{7–9} adding to specific complications such as common bile duct damage,^{7,10,11} retained stone,¹² and bile leak.^{7,9} Wound complications included infection, herniation and dehiscence,^{7,9,10,13–15} with both the classical Kocher subcostal incision or the right paramedian incision causing respiratory compromise with subsequent risk of atelectasis or pneumonia.^{9,10,14,16}

As a reaction to this morbidity the classical incisions gave way in the 1980s to that of the 'minilap' using a 5-cm muscle-splitting incision and a no-touch technique in a 'well'.^{17,18} Improving both local and systemic morbidity¹⁹ breathed life into the open cholecystectomy in the face of advances in dissolution therapy and extracorporeal shock-wave lithotripsy.

Dissolution therapy

It is nearly 20 years since the study from Danzinger *et al* showed that oral chenodeoxycholic acid could produce cholesterol stone dissolution.²⁰ This report was responsible for stimulating many groups in the confident expectation that non-operative methods for managing gall stones would eventually become firmly established. Consequently, after a number of small studies, a large randomised multicentre study the National Co-operative Study was embarked upon in the US to define in particular the efficacy and indication for chenodeoxycholic acid. Unfortunately this study failed to confirm much of the initial enthusiasm and whilst demonstrating that, in selected cases, gall stones were eradicated, it also revealed that even when treatment was reserved for 'ideal' candidates, after two

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Cholecystectomy: complications	
• mortality	0.1% < 50 years 0.6% 50–70 years 2.5% > 70 years
• pulmonary embolism	0.4%
• deep vein thrombosis	1–3%
• wound infection (paramedian > subcostal)	2–10%
• hernia	5–13% (vertical > subcostal)
• atelectasis	5–20% (subcostal > vertical) (minilap < 4%)
• common bile duct damage	0.1%

Box 1

Dissolution therapy: the ideal patient	
• stones: cholesterol, < 15 mm diameter, non calcified	
• functioning gall bladder	
• compliant	
• non-obese	

Box 2

Principles of lithotripsy	
• acoustic waves are transmitted into the body if generated within a medium of similar impedance to the soft tissues, ie, water	
• waves will pass harmlessly through soft tissues and release energy to areas of different density, eg, bone, air, calculi	
• waves are focused to protect normal structures and maximize destructive power	
• acoustic coupling was initially ensured by immersing the patient in a water bath but now utilises a membrane and ultrasonographic jelly	

Box 3

Figure 1 Treatment options for symptomatic gall stones (E.S.W.L. = extracorporeal shock-wave lithotripsy)

years the rate of disappearance was a disappointing 13%.²¹ This low response rate in combination with frequent side effects did not indicate an effective alternative therapy to traditional cholecystectomy which persisted unchallenged as the treatment of choice until the advent of extracorporeal shock wave lithotripsy. However, the more recent availability of ursodeoxycholic acid, which is believed to be more effective and less troubled by side effects than chenodeoxycholic acid,²² and the use of extracorporeal shock-wave lithotripsy and dissolution together, has expanded the potential use of these agents.²³

Extracorporeal shock wave lithotripsy

It was not until 1986 that Sauerbruch *et al* in Munich published a report showing that, in combination with oral bile acids, extracorporeal shock-wave lithotripsy had completely eradicated the stones from gall bladders in six out of nine subjects.²⁴ In 1988 encouraging results were reported by the same group on the first 175 patients. This study not only showed the stones were no longer present in over 90% of the subjects within eight months of treatment, but also demonstrated the most suitable patients by showing that when single stones of less than 2 cm were treated, the rate rose to 95%. Perhaps more significant, however, was the finding in the study that only 28% of all patients reviewed were considered to fulfil the criteria for treatment.²³ It has subsequently become evident that relaxing the treatment criteria dramatically reduces the effectiveness of extracorporeal shock-wave lithotripsy and may explain why preliminary reports of studies from the US have been less encouraging than those from Munich.²⁵

It is likely that the natural history of the gall stone fragments after treatment will in part explain differences in early studies. The treatment aims to fragment stones to less than half a centimetre in diameter which, in theory at least, should then be naturally eliminated. The belief that this was uncommon (indeed if this were true why did all gall stones not do the same during their formation) led the Munich group to include oral bile salts in the original protocol. A study from Schoenfield *et al* confirmed that the addition of ursodeoxycholic acid doubled the effectiveness of the treatment.²⁵ These findings cast some doubt on the future of the treatment, especially in view of the advances occurring concomitantly in other areas. The main problem was the inability to fragment stones to less than half a centimetre in diameter in more than 50% of the patients treated. Furthermore, at six months only 20% of patients originally considered suitable (5% of all patients referred) demonstrated complete stone clearance.²⁵

Percutaneous gall bladder stone treatment

The development of ‘mother and baby’ endoscopes (initially developed for the clearance of stones from the common bile duct²⁶) facilitated the introduction of solvents into the cystic duct. Agents such as methyl-tert-butyl ether will effectively dissolve cholesterol stones²⁷ and this method seems likely to be fraught with less problems than previously attempted percutaneous approaches.²⁸ Unfortunately these percutaneous approaches, enthusiastically adopted by radiologists and urologists, are limited by the composition of the stones when attempting dissolution, and the size and composition when attempting extraction in a dilated duct.²⁸ These limitations led to the investigation of devices capable of destroying gall stones *in situ*, but even early reports with this type of equipment have indicated that significant morbidity might be expected.²⁹

The lack of a wholly successful treatment for gall stones *in situ*, combined with fears about long-term problems from damaged mucosa (both recurrent stone disease and malignancy) contributed to the enthusiasm with which laparoscopic cholecystectomy was greeted.

Laparoscopic cholecystectomy

Since its introduction in France by Phillippe Mouret in Lyon in 1987, laparoscopic cholecystectomy has emerged as an attractive alternative to traditional cholecystectomy for symptomatic gall stone disease. The main advantages of this technique are the cosmetic aspects, minimal wound pain with complete resolution within a few days, the short hospital stay, the ability of many patients to return to work within a week of operation³⁰ and the improvement of postoperative respiratory function compared to both classical^{31,32} and ‘mini-lap’ cholecystectomies.³³ Initially, the proportion of patients suitable for laparoscopic cholecystectomy was believed to be approximately 80%.³⁴ However, with increasing experience the list of absolute contraindications has clearly diminished, making laparoscopic cholecystectomy suitable for nearly all patients

Figure 2 Radiograph of 'baby' endoscope passing up common bile duct from 'mother' endoscope. Inset: view of mouth of cystic duct. From *Practical Gastrointestinal Endoscopy*, PB Cotton and CB Williams, by kind permission Blackwell Scientific Press

Figure 3 Complications of open vs laparoscopic cholecystectomy (CBD = common bile duct; misc = miscellaneous, gu = genitourinary; gastro = gastrointestinal; haem = haematological; resp = respiratory)

with symptomatic cholelithiasis. At present, patients requiring concomitant upper abdominal operations or not tolerating general anaesthesia are excluded (the latter condition could be overcome, at least in selected cases, with the use of epidural anaesthesia).³⁵

There is a remarkable consistency in the figures produced by different series. The Southern Surgeons Club in the US conducted a prospective study of 1518 patients who underwent laparoscopic cholecystectomy by a total of 59 surgeons. The overall complication rate was 5.1% with a bile duct incidence of 0.5% and a conversion rate to traditional open cholecystectomy of 4.7%.³⁶ Cuschieri *et al* reported the European experience by performing a retrospective survey of seven European centres involving 20 surgeons who undertook 1236 laparoscopic cholecystectomies. The total postoperative complication rate was 1.6% while conversion to open cholecystectomy was necessary in 45 patients (3.6%).³⁷

Despite the rapid and widespread acceptance, early data suggest that some complications are more common after laparoscopic cholecystectomy when compared to traditional cholecystectomy. The main area of concern with this procedure is bile duct injury, and the experience from several institutions reporting an overall rate between 0.3% and 0.6%³⁶⁻³⁹ compared to only 0.1% in patients with traditional cholecystectomy.⁴⁰ It must be remembered, however, that the above figures are those for surgeons still familiarising themselves with the technique. Whether this risk translates into a significant problem with bile duct strictures or patients with long-term sequelae of undetected bile duct injuries remains to be seen. It is generally accepted that only fully trained general surgeons with expertise in biliary surgery and an adequate training in laparoscopy should perform laparoscopic cholecystectomy.⁴¹ With a background of previous similar discussions for flexible endoscopy, the Board of Directors of the Society of American Gastrointestinal Endoscopic Surgeons has introduced guidelines for *Granting of Privileges for Laparoscopic General Surgery*.⁴² In accordance with this and with a view to influencing the widespread adoption of this new procedure, clinical laparoscopic training has been introduced into general surgery residency programmes.⁴³

Finally, in the present era of National Health Service reforms and widespread redistribution of funds, the financial implications of laparoscopic cholecystectomy are clear with a cost-saving capital per patient (largely due to reduced hospital stay) of £900.³⁷ Utilising selection criteria which eliminate most high-risk patients it is estimated that 60% of all patients undergoing laparoscopic cholecystectomy could be done as true out-patients leading to even less expense and greater convenience for the patient.⁴⁴

Gall bladder carcinoma

The last 30 years has seen 41 studies of gall bladder cancer appear in the literature giving details of almost 45 000 patients.⁴⁵⁻⁸⁵ The motivation for most of these studies hinges not on the frequency of the tumour (which although the commonest biliary tract malignancy is still a rare tumour) but upon the dismal prognosis, irrespective of treatment, in all but the earliest lesions due to direct liver spread. The difficulty in achieving early detection of gall bladder cancer lies in the lack of any specific biochemical, clinical or radiological features. It is usually only advanced cases that present with suspicious symptoms (jaundice and unremitting pain), and 75% are found to be inoperable.⁸⁶ Indeed the overall survival at between 0 and 12.5% at five years (median 1.7%) is only improved in those 15% of patients with tumours discovered incidentally subsequent to histological examination.⁸⁷ In this respect the report of Bergdhal is typical in stating that in 32 patients with only mucosal or submucosal involvement, there was a 63.6% five-year survival and 45.5% 10-year survival following cholecystectomy alone.⁸⁸ A similar series of Nevin *et al* was more encouraging, reporting an 86% five-year survival in patients with mucosal disease.⁴⁶ These results probably explain the 30% increase in mortality from gall bladder carcinoma that has occurred in Sweden in the last 20 years where the rate of cholecystectomy has been reduced dramatically. The falling rate of cancer in the UK, USA and Canada⁸⁸ where cholecystectomy rates have risen, suggest that approximately one gall bladder carcinoma will be cured or prevented per 100 cholecystectomies for gall stones.⁸⁹ The available literature confirms the known predisposing factor for gall bladder cancer (choledochal cysts,^{90,91} long-standing inflammatory bowel disease,⁹² xanthogranulomatous cholecystitis,⁹³ 3,3-chlorobenzidine exposure,⁹³ previous biliary surgery,⁹⁴ chronic salmonellosis,⁹⁴ diffuse calcification,⁹⁵ abnormal pancreaticobiliary anatomy,⁹⁶ certain ethnic groups,⁹⁷ and gall stones (40-100%).^{86,97} Although studies of the effect of gall stones have been hindered by their prevalence in developed countries, the relationship is not only a constant finding but depends upon the nature of the

Figure 4 Carcinoma of gall bladder. A fungating, partly papillary tumour with three small pigment stones. From *An atlas of gross pathology*, CDM Fletcher, by kind permission Edward Arnold Ltd

Key points

- Conservative therapy*
- few ideal candidates
 - high recurrence rate
 - pathology left *in situ*
 - known associations with gall bladder cancer
 - minimal morbidity
- Open surgery*
- significant morbidity/mortality
 - pathology removed
 - 1% incidence of early cancer cured
- Laparoscopic cholecystectomy*
- decreased mortality/morbidity
 - rise in common bile duct injuries
 - learning curve
 - close control of training required

Box 4

stones. The incidence of carcinoma increases two- to four-fold for 2.0–2.9 cm stones compared to stones of 1 cm and increases 10-fold for stones greater than 3 cm.⁹⁸ It has also been shown that cholesterol stones are most likely to be associated with the development of carcinoma. Despite the strong correlation between the two the causity of gall stones in the pathogenesis of gall bladder cancer is not yet fully understood. It is postulated that the chronic trauma and mucosal inflammation caused by gall stones lead to dysplasia and hence frank malignancy, with the accumulative risk of eventually developing carcinoma in a gall bladder containing stones estimated at 8% over the age of 50.⁹⁹ These findings, together with work tracing the sequence from gall bladder adenoma to *in situ* malignancy,⁸⁶ forms a basis for some reservations about the move away from traditional cholecystectomy.

The present position

The traditional upper abdominal cholecystectomy incision is unsightly, painful and associated with postoperative respiratory complications. Patients usually require a hospital stay of at least a week and full normal activity (particularly heavy manual work) is typically not restarted for several weeks. This latter problem infrequently produces considerable domestic and financial problems and is one of the main arguments in favour of the move to laparoscopic cholecystectomy.

Whilst laparoscopic cholecystectomy is a new procedure which has a considerable way to go before its' place in the surgical armamentarium is clearly defined,^{25,100} it nevertheless has clear advantages over traditional cholecystectomy. Further, unlike non-surgical options, removal of the gall bladder not only cures the disease, but at the same time eliminates the possibility of recurrence and the development of carcinoma due to diseased mucosa remaining *in situ*. The role of recurrent disease is indeed significant as, after destruction of stones or their removal, if follow-up is long enough, reformation occurs in about 66% of patients,¹⁰¹ although bile salts and prostaglandin inhibitors seem to reduce this problem.¹⁰² It seems reasonable to assume that this approach is likely to increase the risk of malignant transformation further by prolonging the period of chronic irritation. This has led to attempts to ablate the gall bladder mucosa by installation of a variety of agents after occlusion of the cystic duct¹⁰³ but this approach could have predictably disastrous consequences if the cystic duct were imperfectly occluded.

The simultaneous development of a number of completely different gall bladder preserving conservative approaches had many critics who were worried about the lack of long-term data. It is extremely unlikely that, had a 'multicentre study' been constructed in similar fashion, clinicians would have accepted it. Fortunately the emergence of laparoscopic cholecystectomy as a safe, simple procedure in confident hands is likely to redress the balance between non-operative treatments and traditional cholecystectomy.

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