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Long-term outcomes and quality of life after surgical or conservative treatment of benign simple liver cysts

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Abstract
Background Benign liver cysts are common and are often detected incidentally. Most patients do not require intervention. Occasionally, large dominant or multifocal small cysts cause symptoms as a result of rapid growth, secondary infection, intra-cystic bleeding or compression of adjacent organs.
Aim To compare presenting symptoms and outcomes of a consecutive series of patients with benign liver cysts treated either conservatively or by surgical intervention. Long-term quality of life (QoL) was also assessed.
Methods Retrospective analysis of prospectively collected data was conducted. Long-term general and disease-specific quality of life was also documented.
Results Ninety-five patients were included in the study (46 treated operatively, 49 treated conservatively). 80% were female, and the mean age of the cohort was 58 years. Those who had surgical intervention were older (62 vs 55 years, $p = 0.004$), were more likely to have shortness of breath at presentation (11 vs 5%, $p = 0.018$) and had larger cysts (12 vs 4 cm, $p < 0.001$) compared with those offered conservative treatment. Laparoscopic stapled excision was the most common operative procedure (70%) and the overall complication rate was 20%. At a median follow-up of 64 months, 17% (8/46) of the surgically treated patients had radiological evidence of cyst recurrence but only 9% (4/46) were symptomatic. At median follow-up of 71 months, 37% (14/38) of conservatively treated patients had unchanged or new symptoms compared to the first presentation. Furthermore, 10% (4/38) of this group had additional radiological or surgical intervention for persistent symptoms during the follow-up period. Overall, there was no difference in long-term QoL between the two groups.
Conclusion Surgical intervention for selected patients with symptomatic benign liver cysts results in low long-term recurrence rates and excellent patient-reported outcomes and quality of life. Laparoscopic-stapled excision can be done safely and reliably in carefully selected patients.

Keywords Liver cysts · Long-term outcomes · Quality of life · Laparoscopic stapled excision

Benign, non-infectious cysts are the most common pathology of the liver with an estimated prevalence ranging from 2.5 to 5% [1]. These are simple fluid-filled structures that are frequently multifocal and scattered throughout both sides of the liver. Occasionally a large dominant single cyst may be present. More rarely, widespread cystic change in the liver is due to autosomal dominant polycystic liver or kidney disease.

Simple cysts are biliary malformations containing clear serous fluid and usually there is no communication with the intrahepatic biliary tree [2]. The single layer of cuboidal or columnar epithelial cells of non-parasitic simple cysts and adult-type polycystic liver cysts show similar mucin-histochemical and immuno-histochemical features. There may be a thin attenuated or denuded peri-cystic capsule, and there is no risk of long-term malignant degeneration [3]. Other rarer benign liver cysts include biliary cystadenomas,

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ciliated foregut cysts, peri-ductal hilar cysts and duplication cysts.

Although advanced-stage polycystic liver disease may cause abdominal distension and non-specific upper abdominal pain, most simple liver cysts do not cause symptoms and are usually only found incidentally during imaging for other reasons. Mostly, patients have normal or near normal liver function tests, and the investigations of choice are either transabdominal ultrasound, computed tomography (CT) or magnetic resonance (MR) imaging.

Treatment options for patients with symptomatic liver cysts include percutaneous aspiration (±instillation of a sclerosant) or surgical intervention. Operative intervention may be either open or laparoscopic, and numerous different techniques have been described. These include cyst fenestration, subtotal cyst excision, liver resection and even liver transplantation [4].The primary aim of this study was to assess and compare presenting symptoms and cyst characteristics in patients treated either conservatively or by surgical intervention. A secondary aim was to assess long-term outcomes and quality of life in both groups.

Materials and methods

All patients with liver cysts referred to the Northern Hepatobiliary Unit for a surgical opinion between January 1999 and December 2014 were evaluated. The study groups were divided into patients who were treated conservatively and those who underwent a surgical procedure.

A retrospective review of prospectively collected data was undertaken including the type and duration of operation, overall complications and procedure-related complications. Additional or missing information was obtained by review of clinical records. Long-term follow-up was obtained by direct telephone contact with either the patient, their general practitioner or from outpatient records. Ethics approval for this study was obtained from the Northern Sydney Local Health District Human Research Ethics Committee (AU/7/59D817).

Indications for operative intervention included symptomatic large (>5 cm) dominant cysts located superficially in the liver, cysts that increased in size over time or cysts that developed complications such as an intra-cystic bleed or infection. Patients were investigated exhaustively to exclude other potential causes for the presenting symptoms. Those with incidentally discovered cysts who were asymptomatic or those with small cysts located centrally or posteriorly in the liver were treated conservatively. Occasionally, patients with Gigot type 1 polycystic liver disease [5] were offered operative intervention for a symptomatic dominant cyst or mass effect from a grossly enlarged liver.

The location of the main cyst was assessed on pre-operative CT imaging and classified according to the Couinaud hepatic segmentation [6]. Recorded complications were defined as overall complications and complications specific to the surgical procedure according to the Clavien–Dindo classification summarised as <grade 3 and ≥grade 3 [7].

Surgical technique

A laparoscopic stapled cyst excision was the preferred surgical approach whenever possible. After positioning in the supine position, a pneumoperitoneum was established through an 11 mm supra-umbilical cannula. Additional 12 and 5 mm ports were placed in the right upper mid-clavicular and midline positions, depending on the location of the cyst. After puncture and aspiration, the deflated cyst was fully mobilised including dissection from the diaphragm where necessary in order to maximise cyst wall excision. An articulated 60 mm Echelon Flex™ Endopath® device (Ethicon, Bridgewater, NJ, USA) loaded with 2.5 mm staples was positioned immediately adjacent to normal liver parenchyma and the cyst then circumferentially excised (Fig. 1). Usually 3–5 staple cartridges were necessary depending on the size of the cyst. This technique has been described by others [8] and we have also reported this approach for symptomatic non-parasitic splenic cysts [9]. The final result is a near complete cyst excision with only the base of the cyst remaining in situ. No attempt was made to completely excise the cyst off major vascular or biliary structures. The excised cyst wall was removed in a specimen retrieval bag for histopathological examination in all cases, and drains were only used selectively.

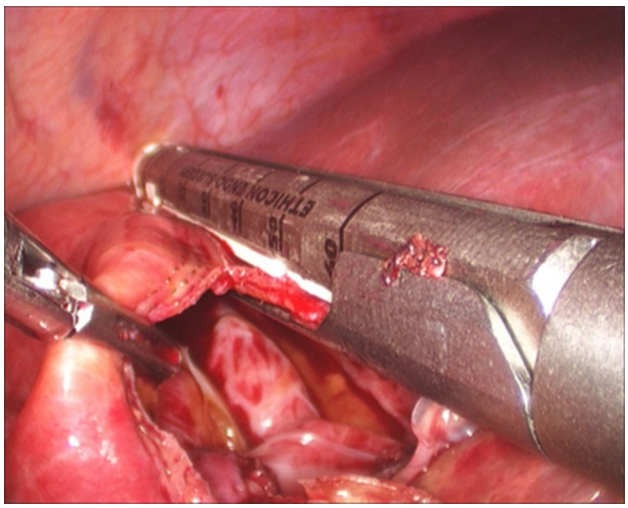

Fig. 1 Laparoscopic stapled excision of a liver cyst in segment 7/8

Long-term follow-up and quality of life assessment

Clinical assessment for the presence of residual or recurrent symptoms was undertaken in all patients. The need for further investigation or intervention was also noted. Radiological assessment was done for all patients in the operative group and for the majority of patients in the non-operative group. Post-operatively, the presence of a large cystic remnant at the treated site was defined as residual disease, and refilling of the treated cyst or an increase in the size of other liver cysts compared with the original presentation was defined as recurrence.

A postal questionnaire composed of two validated instruments assessing generic health-related quality of life and disease-specific quality of life (QoL) including five general questions about treatment satisfaction, persisting symptoms and additional therapy was sent to all patients. If no response was achieved, a follow-up request to complete the questionnaire was made by telephone. Generic health-related QoL was assessed with the 36-item Short-Form Health Survey (SF-36) [10]. This contains 36 items from eight domains: physical functioning, role-physical, role-emotional, vitality, social functioning, mental health, bodily pain and general health. A high score on individual domains or component scores represents better QoL. SF-36 data from the healthy Australian population, matched for age, were obtained from the National Health Survey: SF36 Population Norms, Australia [11].

Disease-specific QoL was assessed using the Gastrointestinal Quality of Life Index (GiQLi). This was developed and validated by Eypasch and colleagues, specifically for use in patients with gastrointestinal disorders [12]. Items were scored on a five-point Likert scale with the total score ranging from 0 to 144. High scores represent better QoL compared with low scores. For both QoL instruments, questions were answered with respect to the last two weeks before completing the questionnaire.

Statistical analysis

Categorical variables are presented as numbers and percentages. Continuous variables are presented as means with standard deviation or median values with interquartile range, as appropriate.

Comparison of categorical clinical characteristics between patients who were treated either conservatively or by surgical intervention was performed using the Chi square test or Fisher exact test and for continuous variables comparison was performed with a Mann–Whitney U or Student t test, where appropriate.

QoL outcome in the two groups were compared using Student t tests. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS® software (SPSS, Chicago, Illinois, USA).

Results

Patient characteristics

From 1999 to 2014, a total of 110 patients with benign liver cysts were referred for surgical review. Fifteen patients were excluded because of other pathology discovered after surgical intervention. These included biliary cystadenomas (11), a mucinous cystic neoplasm (1), a ciliated foregut cyst (1), a peri-ductal cyst (1) and one patient with a duplication cyst (1). A total of 95 patients with simple liver cysts (46 treated operatively, 49 treated conservatively) were analysed for this study. The patient and liver cyst characteristics are outlined in Table 1. Nine patients had polycystic liver disease (5 operative, 4 non-operative).The majority of patients were female (80%), and the mean age of the whole cohort was 58 years. Those in the operative group were significantly older with a mean age of 62 years compared to 55 years for the non-operative group ($p = 0.004$). Seven patients (15%) in the operative group had previously undergone either radiological or surgical intervention compared with only two patients (4%) in the non-operative group ($p = 0.064$).

The most common symptom experienced by all patients was generalised upper abdominal pain (66%). Discomfort localised specifically to the right upper quadrant was the second most common symptom in both groups (50% operative, 33% non-operative group, $p = 0.086$). The operative group included five patients (11%) who presented with shortness of breath, while none of the patients in the non-operative group had this symptom ($p = 0.018$).

Single cysts were diagnosed in only 36% of the patients in the whole cohort ($n = 34$). The size of cysts ranged from 0.5 cm in diameter to 50 cm and the median size of the largest cyst in the operative group was 12 cm compared to 4 cm in the non-operative group ($p < 0.001$). The distribution of location of cysts was even across both sides of the liver.

Peri-operative finding, short- and long-term outcomes in the operative group (Table 2)

Laparoscopic stapled excision was the most common procedure performed (32/46, 70%), followed by open stapled excision or resection (12/46, 26%). Two patients had to be converted to an open procedure because of dense intra-abdominal adhesions and bleeding around the origin of the right hepatic vein. Concomitant cholecystectomy was

Table 1 Patient characteristics, symptomatology and cysts

	Total $N = 95$	Operative group $N = 46$	Non-operative group $N = 49$	p value
Patient characteristics				
Age, years, mean (±SD)	58 ± 13	62 ± 12	55 ± 14	0.004[#]
Gender, male	19 (20%)	7 (15%)	12 (25%)	0.259*
Previous Abdominal Surgery	29 (31%)	17 (37%)	12 (24%)	0.187*
Previous hepatic procedures	9 (9%)	7 (15%)	2 (4%)	0.064*
History of trauma	2 (2%)	2 (4%)	0 (0%)	0.140*
Symptomatology				
Tenderness, or discomfort	63 (66%)	34 (74%)	29 (59%)	0.129*
Right upper quadrant pain	39 (41%)	23 (50%)	16 (33%)	0.086*
Bloating, or a sensation of fullness	15 (16%)	10 (22%)	5 (10%)	0.123*
Shoulder tip pain	8 (8%)	6 (13%)	2 (4%)	0.116*
Shortness of breath	5 (5%)	5 (11%)	0 (0%)	0.018*
Cyst characteristics				
Median size largest cysts, cm (IQR)	8 (4–15)	12 (8–20)	4 (3–8)	<0.001[~]
Single cysts	34 (36%)	14 (30%)	20 (42%)	0.257*
Multifocal cysts	37 (39%)	21 (46%)	16 (33%)	0.194*
Polycystic liver disease	9 (9%)	5 (11%)	4 (8%)	0.653*
Main cyst location[§]				
Segments 1–4	31 (33%)	22 (48%)	9 (18%)	<0.002*
Segments 5–8	34 (36%)	19 (41%)	15 (31%)	0.382*
Most segments involved	30 (31%)	5 (11%)[π]	25 (51%)	<0.001*

* Chi square test operative versus non-operative

[#] Independent T- test operative versus non-operative

[~] Mann–Whitney test operative versus non-operative

[§] According to Couinaud hepatic segmentation

[π] Surgically treated segments: segment 4 in two patients, segment 2 in two patients, segment 5 in one patient

undertaken in 12 patients (26%). For the whole operative cohort, the median operative duration was 90 min.

Post-operative complications occurred in 20% of patients. These included bile leaks in three patients (7%). According to the Clavien–Dindo classification, two patients had a Grade 3 complication; one patient required re-operation, one required ERCP and a stent and the last patient was treated conservatively. In one patient (2%), an intra-abdominal infection was treated with antibiotics (Grade 2).

Median follow-up after operative intervention was 64 months with a range of 15–165 months. Radiological evidence of cyst recurrence occurred in eight patients (17%), four of whom were asymptomatic and were treated conservatively, while four others underwent a repeat operation due to persistent symptoms thought to be due to the recurrent cyst.

Long-term outcomes in the conservative group (Table 3)

Of the total cohort, 49 patients were managed non-operatively with the majority offered either reassurance that no further imaging was required or serial imaging with clinical review. The latter strategy was done in 49% of this group (24/49). The two most common forms of progress imaging were CT scanning ($n = 46$, 93%) and US ($n = 28$, 57%). Five patients had a hepatobiliary iminodiacetic acid (HIDA) scan which suggested either acalculous cholecystitis ($n = 3$) or biliary dyskinesia ($n = 2$). Although tumour markers were ordered in 61% of patients these were within the normal range in all cases. Numerous patients in this cohort were treated for other conditions thought to be the cause for the presenting symptoms (e.g., acalculous cholecystitis, peptic ulcer disease, irritable bowel syndrome).

The median follow-up in the conservative group was 71 months (range 6–187 months) with eleven patients (22%) lost to follow-up. At long-term review, 63% of patients (24/38) in the conservatively treated group reported no current symptoms and 71% (27/38) had no further investigations or intervention since the initial presentation. However, 37% of patients in this group (14/38) were still experiencing either upper abdominal or other non-specific abdominal discomfort. During the follow-up period, seven

Table 2 Operative findings and long-term outcomes ($n = 46$)

Median post op follow-up, months	64 (range 15–165)
Lost to follow-up	6 (13%)
Operation type	
Laparoscopic stapled excision	32 (70%)
Open stapled excision	12 (26%)
Laparoscopic converted to open stapled excision	2 (4%)
Concurrent cholecystectomy	12 (26%)
Median duration of procedure, mins (IQR)	90 (60–120)
Blood loss, ml (IQR)	0 (0–0)
Length of stay, days (IQR)	5 (4–7)
Complications, any	9 (20%)
According to Clavien–Dindo ≥grade III*	2
Bile leak	3
Infection	1
Pneumothorax	1
Ileus	1
Pleural effusion	1
Enterotomy	1
Small bowel obstruction	1
Recurrence	8 (17%)
Symptomatic recurrence	4
Asymptomatic recurrence	4
Indication for re-operation	
Complication	1 (2%)
Recurrence	4 (9%)

* Ref. [7]

patients (18%) had additional radiological investigations, two patients (5%) underwent percutaneous aspiration for residual dominant cysts and two others (5%) had operative intervention for their liver cyst(s) at another institution.

Long-term quality of life and patient-reported outcomes in the whole cohort

From a total of 95 patients, 91 were eligible to participate in long-term assessment of quality of life. Four patients were excluded from the final analysis for the following reasons; deceased ($n = 1$), undergoing palliative care ($n = 1$) or returned to their country of origin ($n = 2$). The response rate was 60% with 55 of the 91 available patients returning the questionnaire. The majority of patients (91%) were satisfied or very satisfied with the initial treatment or advice received. In the operative group, 88% would choose an operation again, and 85% reported complete remission of symptoms. Seventy percent underwent a successful laparoscopic stapled excision, while 30% were either converted to open after starting laparoscopically or had an up-front open-stapled excision. There was no difference in long-term quality of life between these groups. In the non-operative group, only 51% of patients reported complete remission of symptoms during the follow-up period. However, SF-36 generic Quality of life outcomes in both the operative and non-operative groups were comparable to age-matched healthy Australians (Fig. 2A, B).

Discussion

Benign liver cysts are common and have a female predominance as demonstrated in the current study. These cysts are often discovered incidentally and patients who are asymptomatic should be treated conservatively. In those with abdominal symptoms or where complications have developed, the decision to intervene can be difficult and depends on exclusion of other causes for the presenting symptoms as well as the anatomical location of the cyst(s).

The presenting features and long-term outcomes of a consecutive series of patients with simple liver cysts are described. Other than shortness of breath there were no differences in the presenting symptoms between patients treated conservatively and those who had surgical intervention. However, compared with patients in the non-operative group those who had an operation were older (62 vs 55 years, $p = 0.004$), had larger cysts (12 vs 4 cm,

Table 3 Conservative management and long-term outcomes ($n = 49$)

Non-operative group ($N = 49$)	
Median post op follow-up, months	71 (range 6–187)
Lost to follow-up	11 (22%)
Initial investigation/s	
CT	46 (93%)
Ultrasound	28 (57%)
Tumour markers	30 (61%)
Liver function test	9 (18%)
Hydatid serology	5 (10%)
HIDA	5 (10%)
Current symptoms	
None	24 (49%)
Upper abdominal	12 (24%)
Non-specific abdominal	2 (4%)
Further investigation and intervention	
No further investigation and intervention	27 (55%)
Further investigation—no change in cysts	5 (10%)
Further investigation—residual PCLD	2 (4%)
Percutaneous aspiration	2 (4%)
Operative intervention	2 (4%)

$p < 0.001$) and were more likely to have symptoms not accounted for by other pathology (data not shown). This reflects a highly selected surgical group.

At median follow-up of 64 months, 17% (8/46) of the surgically treated patients had radiological evidence of cyst recurrence but only 9% (4/46) were symptomatic. This compares with those treated conservatively where at a median follow-up of 71 months 37% of patients (14/38) had the same or similar abdominal symptoms as when they first presented.

In the conservatively treated patients, 18% (7/38) had further investigations during the follow-up period and 10% (4/38) underwent either radiological or surgical intervention for persistent symptoms.

Although more patients in the surgical group had complete resolution of their abdominal symptoms at long-term follow-up compared with the conservatively treated patients, there was no difference in SF-36 generic quality of life outcomes between the two groups. Furthermore, the outcomes for both groups were comparable to age-matched healthy Australians.

To date, there have been no randomised studies comparing conservative or surgical treatment of patients with liver cysts. Also, there have only been a few studies reporting long-term symptomatic outcomes in terms of cyst recurrence, the need for re-intervention, patient satisfaction and quality of life.

The present series demonstrates that an operative approach is mainly effective in patients with large symptomatic or complicated cysts or in those who have had unsuccessful percutaneous drainage, with or without sclerotherapy. The study was not designed to analyse the advantages or disadvantages of percutaneous aspiration or sclerotherapy.

Interpretation of reported outcomes following different surgical techniques is hampered by multiple treatment algorithms, small patient numbers and relatively short periods of follow-up in many studies [4, 13–20]. A laparoscopic approach is now standard of care but variations in nomenclature and lack of detail about the exact procedure performed have limited comparison of outcomes between centres. The term "de-roofing" is often used but

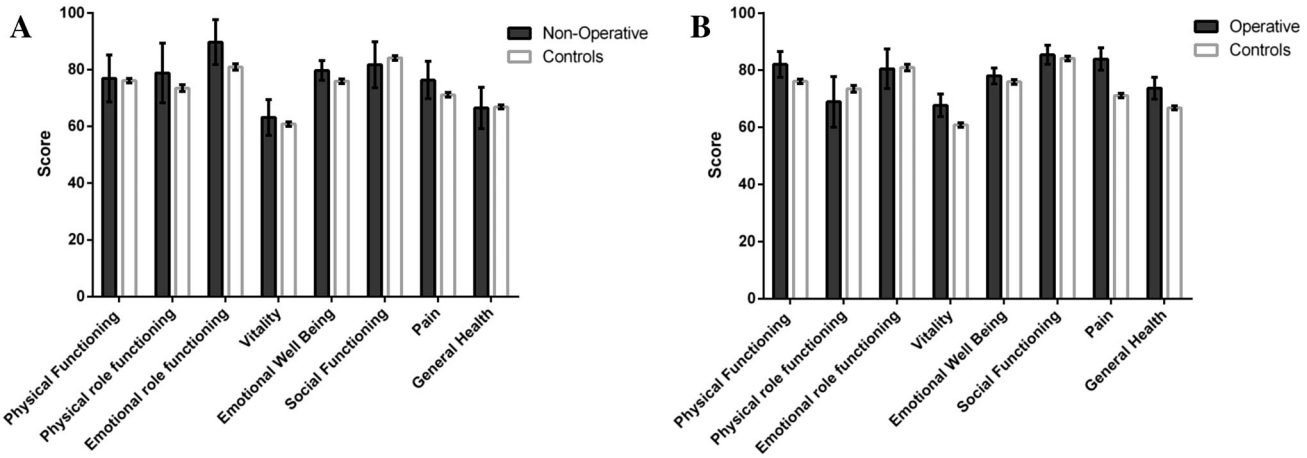

Fig. 2 **A** SF-36 score in SC patients with non-operative management compared to age matched healthy controls. No significant differences between groups. **B** SF-36 score in SC patients with operative management compared to age matched healthy controls. No significant differences between groups

numerous other terms such as "fenestration", "cyst excision", "marsupialisation", "treatment of" or "cyst resection" have also been described [4]. In addition, some groups advocate the use of an omental flap in the cyst cavity [21, 22]; however, there is little evidence that this reduces recurrence rates [23]. Many laparoscopic series have short follow-up, and outcomes vary depending on whether clinical or radiological evidence of cyst recurrence is measured. Following surgical intervention, it has been suggested that patients should be followed for at least two years to adequately exclude symptomatic recurrence [24].

Studies documenting long-term follow-up after laparoscopic treatment of simple liver cysts show a wide range of recurrence rates from 4 to 41% [23–26]. In the present study, long-term radiological recurrence occurred in 17% of patients although only 9% of patients had persistent or recurrent symptoms. Near complete excision of the cyst wall down to normal liver parenchyma was achieved simply and safely by endoscopic stapling (Figs. 3, 4). Occasionally, this required partial liver mobilisation or dissection of the cyst wall from the diaphragm. This approach allowed a near bloodless subtotal excision and wide de-roofing of the cyst, a technical detail that likely reduces the risk of cyst refilling [26]. Electrocautery ablation of the remnant cyst wall or placement of omentum in the cyst cavity was not used in the present series.

In the present study, cyst recurrence was defined as refilling of the index cyst or an increase in the size of other liver cysts compared with the original presentation. Five patients had small remnant cystic changes at the surgically treated site or an increase in the size of other cysts elsewhere in the liver. Only three patients had refilling of the treated cyst and all were located inferiorly in segment 4b of the liver. Large cysts in this location can be difficult to adequately drain without undertaking a formal resection. This might explain why a stapled subtotal cyst excision failed in these patients.

Patients with atypical symptoms underwent detailed gastrointestinal investigations to exclude other pathology. This included upper endoscopy, transabdominal ultrasound, high-quality CT or MR scanning. Hepatobiliary nuclear studies were also used in selected patients to

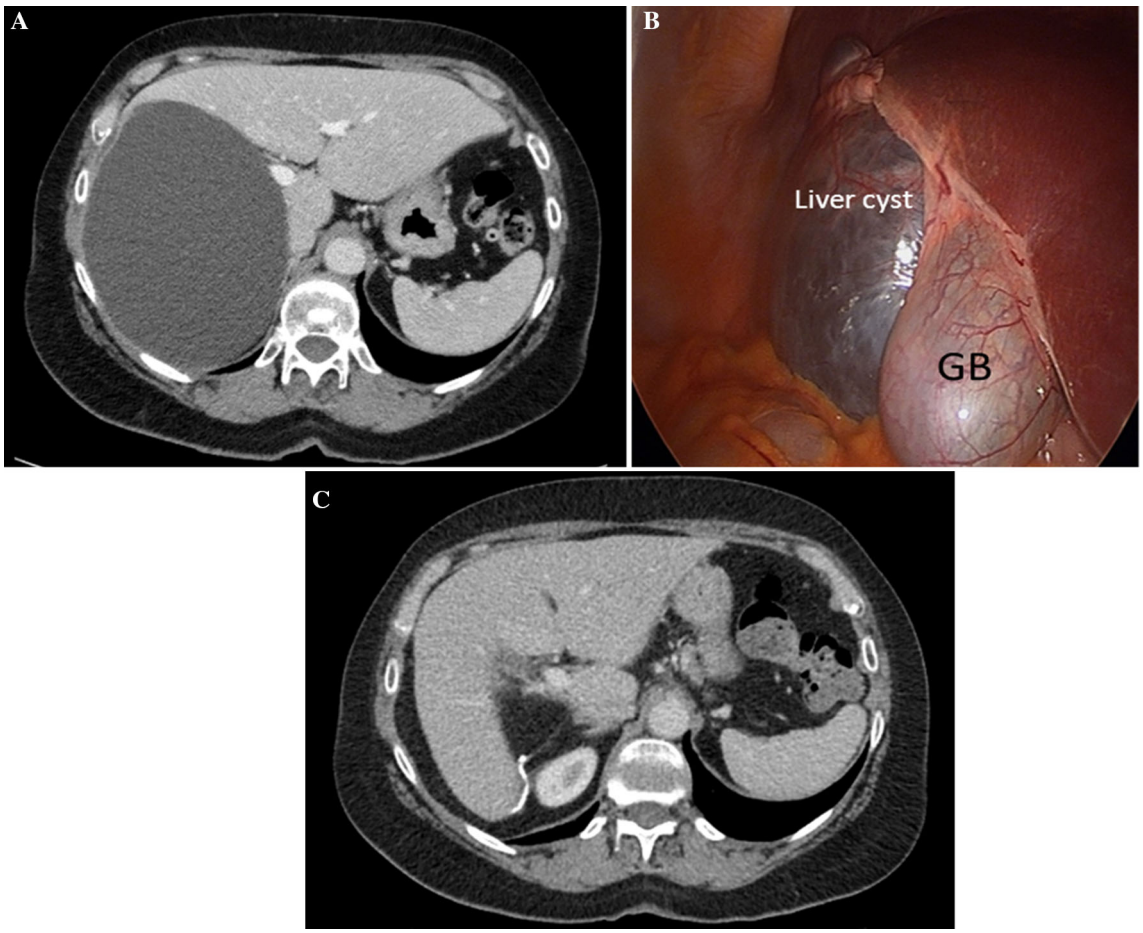

Fig. 3 **A** Pre-operative CT scan of a dominant cyst in S5/6. **B** Laparoscopic view prior to puncture and stapled excision. **C** CT scan 49 months post operatively

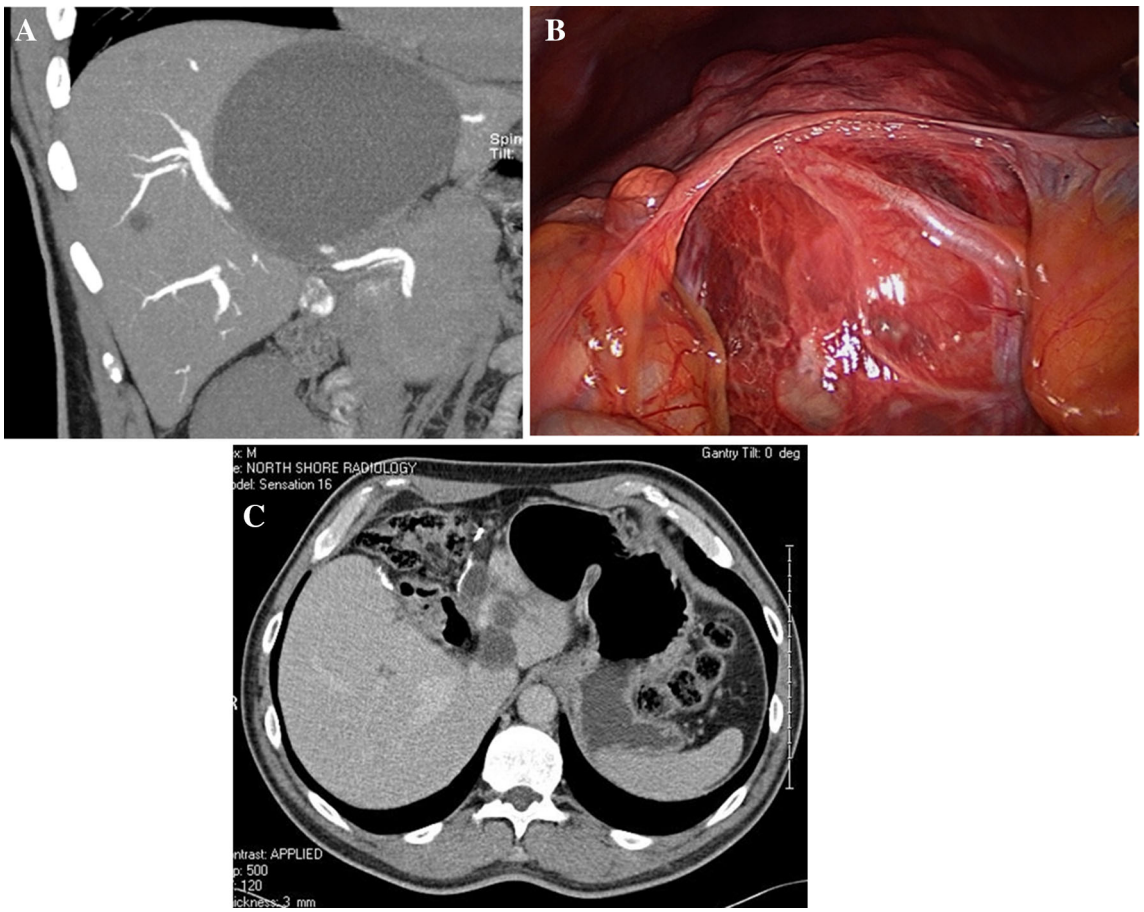

Fig. 4 **A** Pre-operative CT scan of a dominant cyst in S4a/4b. **B** Laparoscopic view prior to puncture and stapled excision

exclude a functional gallbladder problem. Although not done in the present series, trial percutaneous aspiration of a large cyst may be helpful in this group of patients prior to surgical intervention. Certainly, good results have been reported in symptomatic patients using up-front aspiration and injection of a range of sclerosant agents including tetracycline, ethanol and ethanolamine [27–30]. However, there are ongoing concerns about high recurrence rates with this approach as well as the potential for biliary complications.

At long-term follow-up, >91% of patients in our cohort were satisfied with the treatment or advice provided in relation to their liver cysts. Interestingly, even though there was a relatively high rate of residual symptoms in the conservative group at long-term follow-up many of these patients were also happy with their treatment. In part, this may be because a proportion of these patients had pathology unrelated to the liver cysts diagnosed and treated at the time of presentation.

This study has several limits. Firstly, baseline quality of life data were not available in our patients. Prospective data assessment on quality of life would make longitudinal analysis possible and outcomes more reliable. Secondly, QoL was only assessed at a single moment after a variable interval since the diagnosis of the liver cyst(s). However, the analysis did not show significant variation in outcome over time (data not shown) indicating that this interval did not affect the present findings. Finally, the control group consisted of data from a healthy Australian population. Although it is plausible that QoL in these patients is different from those in the present study (referred from Sydney and surrounds), the real impact of these geographical differences between cases and controls is unknown.

In conclusion, laparoscopic stapled excision of non-parasitic simple liver cysts is a safe and reliable procedure with low morbidity. Patient selection for surgical treatment is based on patient characteristics, symptomatology and occasionally on the success of a primary percutaneous intervention. Results from the present study show low long-term recurrence rates and good long-term patient-reported outcomes and quality of life after surgical intervention. Similarly, for those with asymptomatic liver cysts or atypical symptoms, a conservative approach results in good long-term outcomes for most patients. However, at long-term follow-up, a proportion of this latter group have

ongoing symptoms that may or may not be related to the liver cysts.

Compliance with ethical standards

Disclosures Dr Philip De Reuver, Dr Izak van der Walt, Ms. Maria Albania, Dr Jaswinder S. Samra and Dr Thomas J. Hugh have no conflicts of interest or financial ties to disclose.

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