ONLINE FIRST

Risk and Cost-effectiveness of Surveillance Followed by Cholecystectomy for Gallbladder Polyps

Vaux Cairns, MBChB; Christopher P. Neal, MD, MRCS; Ashely R. Dennison, MD, FRCS; Giuseppe Garcea, MD, FRCS

Objective: To ascertain the best management options for patients presenting with gallbladder polyps.

Design: Retrospective case-note analysis.

Setting: Tertiary referral teaching hospital practice.

Patients: Patients with ultrasonography-detected gallbladder polyps.

Interventions: Ultrasonography surveillance or surgery.

Main Outcome Measures: Demographic data and size and number of polyps were recorded as well as size increase and histological findings. Detection rates for potentially neoplastic and frankly neoplastic polyps were recorded and compared with complication rates from cholecystectomy. Cost-effectiveness of ultrasonography surveillance was examined.

Results: Nine hundred eighty-six patients were identified and 467 patients underwent further follow-up. Only 6.6% of polyps exhibited an increase in size over the surveillance period. Polyps that subsequently progressed in size on surveillance had a significantly greater diameter at first presentation than those polyps that remained static (7 mm vs 5 mm, respectively) ($P<.05$). Only 3.7% of resected polyps had malignant or potentially malignant histology. Size greater than 10 mm and increase in size during surveillance predicted neoplastic potential.

Conclusions: A surveillance with or without selective surgery policy could potentially detect and prevent 5.4 gallbladder cancers per 1000 individuals per year with a cost saving of more than £130 000 (US $201 676) per year. Cancer prevention benefits would exceed the risk ratios from cholecystectomy complications. Polyps greater than 10 mm should be resected; those between 5 and 10 mm should be under ultrasonography surveillance.

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ANY ELEVATION OF THE MUcosal surface of the gallbladder may be interpreted as a polyp on ultrasonography (USS). A number of varying pathologies may be responsible for this appearance. Many will turn out to be stones accreted against the gallbladder wall and hence appearing as a mucosal abnormality rather than cholelithiasis on USS. True mucosal lesions are generally benign, the most common being cholesterol polyps, which occur because of focal or generalized cholesterol deposits within the gallbladder wall.[1] Adenomyomatosis is another common cause for gallbladder wall thickening and is secondary to proliferation of the gallbladder wall.[1] Benign causes for gallbladder polyps account for up to 95% of lesions seen on USS. Certain polyps may carry neoplastic potential, in particular adenomas of the gallbladder. Although these represent the minority of gallbladder polyps, the exceptionally poor survival from gallbladder cancer mandates their removal. Unfortunately, since most putative gallbladder polyps are benign, there is considerable ambiguity in how to best manage gallbladder polyps, which polyps to survey and which to resect. This study examines one of the largest series of sonographically detected gallbladder polyps in an attempt to determine the indications for cholecystectomy, surveillance, or no follow-up. This study also attempts to determine, for the first time in the literature to our knowledge, whether surveillance of polyps is cost-effective.

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Author Affiliations: Department of Hepatobiliary and Pancreatic Surgery, University Hospitals of Leicester, Leicester, England.

METHODS

All patients coded with gallbladder polyps on radiological records were captured from a computerized database from 2000 to 2011. These patients had all presented to a single tertiary referral hepatobiliary unit. Case notes were retrieved and demographic details, recorded. Number of scans, scan interval, size of polyps, number of polyps, and progression of these parameters over further follow-up were also recorded. Data from patients undergoing cholecystectomy for gallbladder polyps were also examined and the final histological findings, recorded.

Receiver operator curves, *t* test, and χ^2 test were used to analyze data using MedCalc (version 11.6.10; MedCalc Software). Rates of detection of potentially neoplastic or neoplastic polyps were then extrapolated per 1000 population using the data from this study. These data were modeled against previously published mortality rates from laparoscopic cholecystectomy,[2,3] rates of common bile duct injury,[3-9] and rates of incidental gallbladder cancer.[10-15] Extrapolated costs of surveillance were then compared against previously published data regarding costs of treatment of cancer in the United Kingdom.

RESULTS

Nine hundred eighty-six patients were identified from medical records with a median follow-up of 39.3 months (range, 1-143 months). Median age was 57.1 years (range, 35-74 years) and 54.9% of patients were female (**Table 1**). Approximately half of all polyps were detected from USS undertaken for upper abdominal pain (suggestive of gallstones); the majority of the remainder were purely incidental findings (Table 1). The number of polyps detected demonstrated a bimodal distribution, with a single polyp being the most frequently encountered (62.0%) followed by more than 3 polyps (24.4%) (Table 1). The majority of polyps were less than 5 mm (69.0%) and polyps greater than 20 or 30 mm were very rare (0.5% and 0.1%, respectively).

Polyps were rarely discussed at a specialist hepatobiliary multidisciplinary meeting and 49.6% of all patients diagnosed with gallbladder polyps were not followed up any further (Table 1). The majority of polyps under surveillance showed no increase in either size or number (67.7% and 58.0%, respectively). An increase in the number of polyps between scans was not uncommon (22.7%) and some polyps also exhibited a decrease in either size or number (25.7% and 19.3%, respectively). Only 6.6% of polyps exhibited an increase in size over the surveillance period (Table 1). Polyps that subsequently progressed in size on surveillance had a significantly greater diameter at first presentation than those polyps that remained static (7 mm vs 5 mm, respectively) ($P < .05$). There were no significant differences in age and polyp size between patients undergoing surveillance and those not selected for a surveillance program. However, a significantly greater proportion of patients undergoing surveillance were seen by a hepatobiliary consultant (**Figure 1**).

The most common indication for surgery was pain or a polyp greater than 10 mm (**Table 2**). Nearly half of all gallbladders examined histologically demonstrated no other abnormality other than cholesterolosis or cholesterol polyps (Table 2). Stone disease formed a significant number of all final diagnoses on histological analysis (16.4%). The overwhelming majority of gallbladders removed demonstrated benign pathology (96.4%), with only 3.7% having frankly malignant or potentially malignant conditions (Table 2). Only 1 gallbladder specimen displayed a polyp with malignant change. There were no complications or mortality in cholecystotomies undertaken for nonstone disease, with the only complication (1 bile leak) occurring in a patient who had gallstones as the final pathology (Table 2).

Size progression, absolute size, and duration of follow-up were significantly different between patients with benign disease at cholecystectomy and those with potentially malignant or malignant disease (**Table 3**). Gallbladder specimens containing malignant or potentially malignant pathology had a median size of 10 mm, with a median follow-up before surgery of 21.4 months; all of them had exhibited an increase in size during the surveillance period (Table 3).

Table 1. Age and Number and Size of Polyps and Progression Over the Follow-up Period

	No. (%)
Age, y, median (range)	57.1 (35-74)
Sex	
M	445 (45.1)
F	541 (54.9)
Symptoms	
Upper abdominal pain	474 (48.1)
Vomiting	31 (3.1)
Bloating	38 (3.9)
Flatulence	23 (2.3)
Incidental	447 (45.3)
No. of polyps	
1	612 (62.0)
2	105 (10.6)
3	28 (2.8)
>3	241 (24.4)
Size, mm	
<5	681 (69.0)
5-9	259 (26.2)
10-19	40 (4.1)
20-29	5 (0.5)
30-39	1 (0.1)
Follow-up, mo, median (range)	39.3 (1-143)
Discussed at HPB MDT meeting	
Yes	53 (5.4)
No	933 (94.5)
Outcome	
Nothing	519 (51.6)
Surveillance ± surgery	467 (47.3)
No. of polyps over time	
No change	210 (58.0)
Decrease	70 (19.3)
Increase	82 (22.7)
Polyp size	
No change	245 (67.7)
Decrease	93 (25.7)
Increase	24 (6.6)
Polyps that increased in size, median (range)	7 (3-18)[a]
Polyps that showed no increase, median (range)	5 (2-8)

Abbreviations: HPB, hepatobiliary; MDT, multidisciplinary team.
[a] $P < .05$.

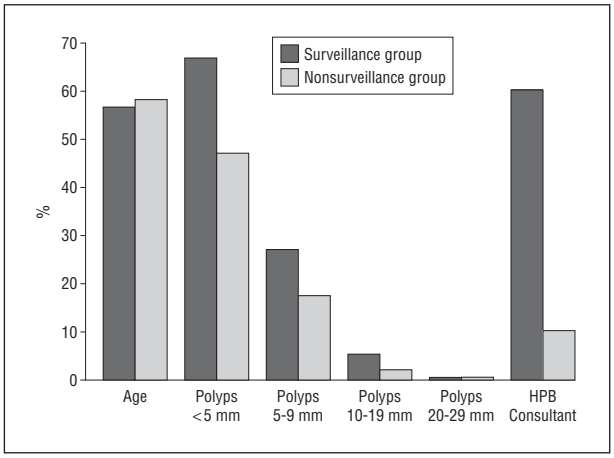

Figure 1. Demographic differences and polyp size between patients undergoing surveillance and those not submitted to surveillance. HPB indicates hepatobiliary.

COMMENT

The difficulty in deciding on an appropriate management algorithm for gallbladder polyps reflects their relative rarity and the lack of knowledge regarding their natural history and hence the actual risk of malignancy from a putative true polyp within the gallbladder. Because of the difficulties in accurately imaging the gallbladder wall, many polyps (up to 20% in this study) turn out to be stones accreted to the gallbladder wall instead of true polyps. In addition, many polyps are not true polyps at all on final histological analysis. Finally, even true gallbladder polyps with malignant potential may never progress to malignancies within the subject's life span. The adenoma-carcinoma sequence for gallbladder polyps may not be similar to that observed in colorectal polyps. For example, in a series of 1600 resected gallbladders, 18 adenomas were found, with around 40% containing cancer; however, 79 incidental gallbladder cancers were found, with only 20% containing residual adenomatous tissue.[16] Therefore, a significant number of gallbladder cancers would appear to arise via an alternative oncogenic pathway. These considerations render any discussions of gallbladder polyp management problematic.

SELECTIVE SURGERY VS NONSELECTIVE SURGERY

Within the cohort of patients in this study, the incidence of true polyps with malignant potential was 5 of 134 patients undergoing surgery (3.7%), with an invasive cancer observed in 1 polyp specimen (0.75%). Of the original 986 patients with gallbladder polyps, only 467 were followed up further with either treatment or surveillance. While none of the 490 patients originally identified but not offered surveillance had a gallbladder malignancy in the cancer network's database, it cannot be assumed that all of these patients could not develop gallbladder cancer in the future as a consequence of an unsurveyed polyp. To gain a perspective into the efficacy of surveillance and surgery in the management of gallbladder polyps, a range of detection rates need to be used (**Figure 2**), ie, detection rates per number of resected specimens, per number of followed-up patients, and per total number within the cohort. Incidences of cancer detection rates per 1000 patients (assuming 100% progression of all potentially malignant pathology found on histological analysis) can then be compared with published rates of mortality, common bile duct injury, and incidence of gallbladder cancer in nonselected patients (Figure 2).

Figure 2 clearly shows that if all potentially malignant gallbladder polyps are assumed to become malignant over time, there is a strong argument for appropriate follow-up incorporating either immediate surgery or surveillance followed by surgery because the pick-up rate for potentially malignant and frankly malignant gallbladder polyps exceeds mortality and complication rates from laparoscopic cholecystectomy (cohort 1). If all patients who underwent surveillance were to have prophylactic cholecystectomy (cohort 2), then the potential benefits of removing frankly neoplastic polyps are less clear since bile duct injury rates (1-6 per 1000) and mortality rates (1-7 per 1000) exceed the detection rate of neoplastic polyps (2.1 patients per 1000). This observation relies on an important assumption that the surveillance method has been 100% accurate in detecting all gallbladder polyps requiring removal, and hence, some caution must be applied in its interpretation. If this rationale is extrapolated to all patients initially identified with gallbladder polyps (cohort 3), then the benefits of prophylactic cholecystectomy for all patients are even less significant.

Table 2. Indications for Surgery and Final Histological Findings for Patients Undergoing Laparoscopic Cholecystectomy

	No. (%)
Indications for surgery	
Pain	41 (30.6)
Increase in size	24 (17.9)
>10 mm at Presentation	40 (29.9)
Patient request	15 (11.2)
Multiple polyps	14 (10.4)
Histological findings	
Stone disease	22 (16.4)
Cholesterol polyp and adenomyomatosis	55 (41.0)
Chronic cholecystitis[a]	23 (17.2)
Associated chronic cholecystitis	75 (56.0)
Other benign	29 (21.6)
Papilloma	1 (0.7)
Adenoma	3 (2.2)
Dysplasia	0
Malignancy	1 (0.7)
All operations	
Mortality	0
Morbidity[b]	1 (0.7)
Operations with gallstones found at final histological analysis	
Mortality	0
Morbidity	1 (4.5)
Operations for nonstone gallbladders	
Mortality	0
Morbidity	0

[a] Chronic cholecystitis as the only finding.
[b] One bile leak.

Table 3. Predictors of Benign vs Neoplastic/Potentially Neoplastic Polyps

	Median (Range)			
	Benign	Potentially Malignant/Malignant	Area Under Curve	*P* Value
Size of polyps, mm	5 (2-22)	10 (6-13)	0.81	<.001
Follow-up, mo	8.7 (0.1-188.5)	21.4 (7.5-62.3)	0.79	.001
No. of polyps	1 (1-4)	1 (1-4)	0.59	.98
Age, y	53.6 (22-89)	62.6 (44-76)	0.63	.34
	No. %			
	Benign	Potentially Malignant/Malignant	*P* Value	
Size progression	19 (14.7)	100	<.001	
Multiple	13 (10.1)	1 (20.0)	.23	
Female	78 (60.5)	3 (60.0)	.87	

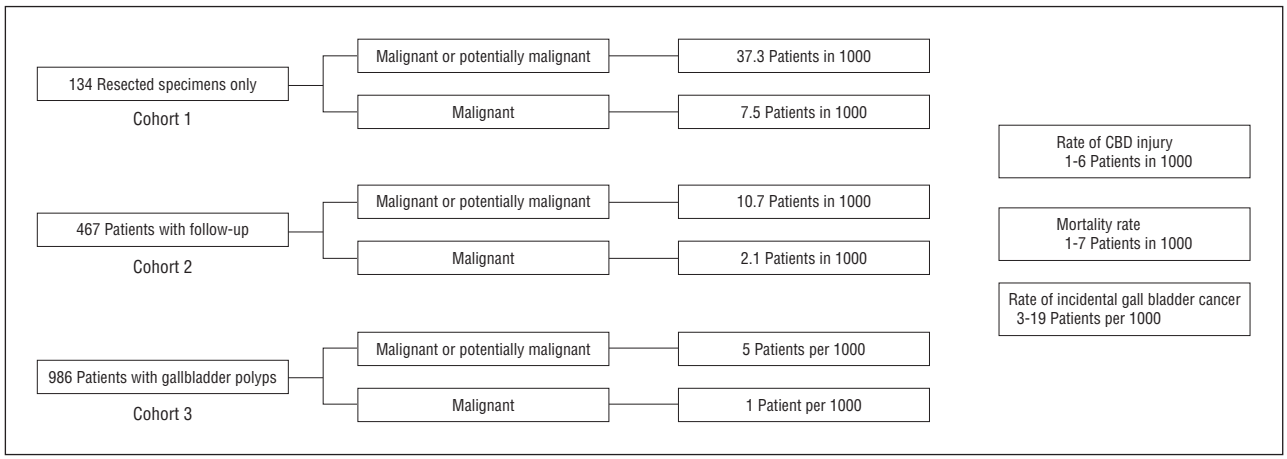

Figure 2. Detection rates for potentially neoplastic/neoplastic polyps compared with risk of surgery for all resected patients (cohort 1), all patients undergoing surveillance (cohort 2), and patients initially identified in the study (cohort 3). CBD indicates common bile duct.

COST OF SURVEILLANCE

Applying blanket surveillance to all gallbladder polyps would usually involve routine USS. Over an individual's lifetime, this could represent a significant cost to the health care system. The cost of cancer to the United Kingdom (including National Health Service costs, hospice costs, and loss in productivity) has been estimated at £18.3 billion (US $28.4 billion) in 2008 in the gray literature, with National Health Service costs of £5 billion (US $8 billion).[17] The incidence of all cancers has been recorded as 309 500 patients in the United Kingdom[18] and the prevalence of cancer survivors has been estimated at 2 million people in the United Kingdom.[19] The majority of the estimated financial outlay probably relates to patients with newly diagnosed cancers undergoing treatment; a broad cost value per individual with newly diagnosed cancer can be estimated as almost £60 000 (US $94 069) per individual.

The incidence of gallbladder cancer in the United Kingdom has been recorded as 1.4 cases per 100 000 on a background cancer incidence of 504 cases per 100 000 people.[19,20] Gallbladder cancer, therefore, is a rare entity probably accounting for 840 new cases diagnosed per year. A broad estimate of the socioeconomic burden from gallbladder cancer can therefore be approximated at £50 million (US $78 million) per year. Given the poor survival and late presentation of gallbladder cancers, for some patients the costs will undoubtedly be lower. However, for fit patients with resectable disease, the complex surgical procedures involved with intense use of high-dependency and specialist services probably makes this a fair approximate.

The median age of all patients diagnosed with gallbladder polyps was 57 years, and with an assumed 20-year survival at presentation and biannual USS surveillance, this would accrue a financial cost of £30 000 (US $47 036) per year (assuming a cost of £150 [US $235] per USS performed) and £6 million (US $9.4 million) over 20 years if all patients initially identified with polyps underwent surveillance. Assuming a minimum pick-up rate of 10.7 patients per every 1000 (Figure 2, cohort 2) every 2 years (median follow-up from presentation to surgery was found to be 21.3 months) (Table 1), this would result in 5.4 lives saved every year, again assuming that all neoplastic polyps would become malignant. From the

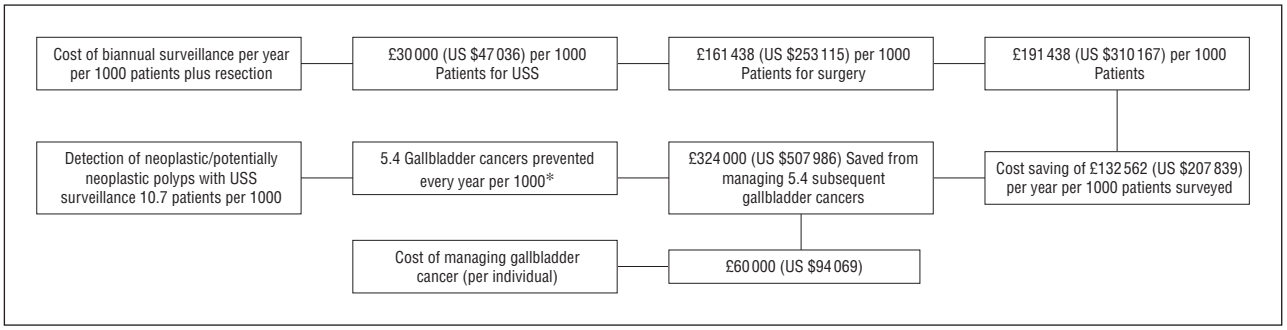

Figure 3. Cost analysis of ultrasonography (USS) surveillance for all polyps detected against cost savings from prevented gallbladder cancer. *Assuming a detection rate of 5:1000 every 2 years.

series of patients identified in this study, 134 in 467 (approximately 30%) underwent surgery within the 40-month median follow-up of their initial USS. If these figures are extrapolated over 1000 patients, then 287 patients would undergo surgery within a surveillance with or without resection program over a 40-month period. The typical tariff for an elective laparoscopic cholecystectomy is £1875 (US $2941),[21] incurring costs of £538 135 (US $844 113) in surgical treatment over 40 months and a per annum cost of £161 438 (US $253 115). This combined with the cost of biannual USS surveillance of £30 000 (US $47 036) gives a surveillance cost of £191 438 (US $310 167) per 1000 patients per annum (**Figure 3**).

Having argued that gallbladder cancer has an associated cost of £60 000 (US $94 069) per individual, surveillance with or without resection would prevent 5.4 incidences every year, with an associated saving of £324 000 (US $507 986). Hence, even with surveillance costs being considered, surveillance would result in a net saving of £132 562 (US $207 839) per annum (Figure 3). This financial saving applies with an absolute minimum detection rate for gallbladder polyps and could, in theory, be considerably higher. Equally, adopting a US surveillance model of 12-monthly USS scans could further reduce costs and, hence, cost-effectiveness.

TARGETED SURVEILLANCE

Initial polyp size of greater than 10 mm and increase in size were found to be predictors of potentially neoplastic polyps on definitive histological analysis. The median starting size for polyps that demonstrated subsequent size progression was 7 mm vs 5 mm ($P < .05$) (Table 1). Hence, the cost savings discussed earlier could be further improved by only surveying polyps greater than 5 mm at initial presentation.

CAVEATS

To our knowledge, this is the first attempt to determine the cost-effectiveness of surveillance or surgery for gallbladder polyps. Several important assumptions have been made that have been discussed earlier and any conclusions drawn must be tentative. In general, the findings of this study agree with those of previous reports, in particular the observation that initial size greater than 10 mm and subsequent growth on interval scanning predicts neoplastic or potentially neoplastic polyps.[22-26] In addition, the results are in accordance with other observations regarding the very low rate of true polyps and malignant polyps in patients with sonographic mucosal abnormalities consistent with possible polyps[22-26]; further refinements have attempted to correlate the rate of growth with neoplastic potential.[27] The relatively small number of patients (n = 134) who underwent surgery also requires consideration when interpreting the validity of the results.

The difficult polyp group remains those between 5 and 10 mm in diameter. Characterization of these lesions with USS is poor[28,29] and this has not improved significantly even with the advent of endoscopic USS[30,31] or cross-sectional imaging.[32] Furthermore, long-term follow-up studies have shown that given a long enough period, even these polyps may exhibit malignancy.[33] This study has demonstrated that even a blanket surveillance policy may still be cost-effective in preventing gallbladder cancer. In addition, this could be further enhanced by surveillance only of polyps greater than 5 mm in diameter; as yet, no study to our knowledge has shown that these very small polyps progress to malignancy. In a 7-year follow-up of more than 2000 patients with a median polyp diameter of 5 mm, no evidence of malignant disease was found.[34]

Other considerations relate to the population in which the clinician practices. The incidence of gallbladder cancer varies considerably across the world and equally the risk of neoplasia within gallbladder polyps (as well as their prevalence).[35] Certain subgroups may exhibit a risk ratio higher than that of the base population; for example, increased malignant potential has been observed in patients with sclerosing cholangitis[20,36,37] and the Asian population.[38] Any policy regarding gallbladder polyp management must be tailored to the surrounding demographics.

A perhaps alarming finding of this study was that up to 50% of patients received no further follow-up among the surveyed group and this probably relates to the investigation having been organized by a non-hepatobiliary surgeon unaware of the need for further surveillance or surgery. The median follow-up was around 40 months in spite of the database capturing all USS performed within the last 10 years. This suggests that some patients are escaping regular surveillance. In the very young, an argument may, therefore, be made for prophylactic cholecystectomy even with polyps less than 10 mm because the long protracted follow-up involved would be impractical and probably unsustainable.

CONCLUSIONS

The incidence of true neoplastic polyps is low. Polyps less than 5 mm can probably be ignored, although regular USS surveillance is still likely to be cost-effective in this group. Polyps between 5 and 10 mm should be under USS surveillance. Special considerations for early cholecystectomy could be made for the young or high-risk groups. Polyps greater than 10 mm or exhibiting an increase in size should be removed. All gallbladder polyps represent potentially premalignant disease and require discussion at a hepatobiliary multidisciplinary team meeting because this would enhance and standardize the management of this condition.

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Correspondence: Giuseppe Garcea, MD, FRCS, Department of Hepatobiliary and Pancreatic Surgery, University Hospitals of Leicester, Gwendolen Road, Leicester LE5 4PW, England (gg43@le.ac.uk).
Author Contributions: *Study concept and design:* Dennison and Garcea. *Acquisition of data:* Cairns and Neal. *Analysis and interpretation of data:* Garcea. *Drafting of the manuscript:* Cairns, Neal, and Garcea. *Critical revision of the manuscript for important intellectual content:* Dennison and Garcea. *Statistical analysis:* Neal and Garcea. *Administrative, technical, and material support:* Cairns. *Study supervision:* Dennison.
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