





# Cost-effectiveness of gallbladder histopathology after cholecystectomy for benign disease

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**Background:** The prevalence of incidental gallbladder cancer is low when performing cholecystectomy for benign disease. The performance of routine or selective histological examination of the gallbladder is still a subject for discussion. The aim of this study was to assess the cost-effectiveness of these different approaches.

**Methods:** Four management strategies were evaluated using decision-analytical modelling: no histology, current selective histology as practised in Sweden, macroscopic selective histology, and routine histology. Healthcare costs and life-years were estimated for a lifetime perspective and combined into incremental cost-effectiveness ratios (ICERs) to assess the additional cost of achieving an additional life-year for each management strategy.

**Results:** In the analysis of the four strategies, current selective histology was ruled out due to a higher ICER compared with macroscopic selective histology, which showed better health outcomes (extended dominance). Comparison of routine histology with macroscopic selective histology resulted in a gain of 12 life-years and an incremental healthcare cost of approximately €1 000 000 in a cohort of 10 000 patients, yielding an estimated ICER of €76 508. When comparing a macroscopic selective strategy with no histological assessment, 50 life-years would be saved and the ICER was estimated to be €20 708 in a cohort of 10 000 patients undergoing cholecystectomy.

**Conclusion:** A macroscopic selective strategy appears to be the most cost-effective approach.

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## Introduction

Cholecystectomy is one of the most common surgical procedures performed. Despite this, there is still debate regarding to perform routine or selective histological analysis of the gallbladder specimen, and large differences are seen within and between healthcare systems<sup>1,2</sup>. The rationale behind histological analysis when performing cholecystectomy for benign disease is to detect incidental gallbladder cancer, which is present in 0.19–1.05 per cent of all cholecystectomies according to published data<sup>2–4</sup>. Global epidemiological trends show an increasing incidence of gallbladder cancer, with the highest burden in Asia, followed by Europe and Latin America<sup>5</sup>.

The main argument for routine submission of the gallbladder specimen is that not all incidental gallbladder cancers have visible macroscopic abnormalities and

patients with undiagnosed disease will be deprived of additional treatment<sup>1,6,7</sup>. To improve survival, current evidence<sup>8,9</sup> supports resection, including liver resection and lymph node dissection for T1b, T2 and T3 gallbladder cancer. For patients with Tis and T1a incidental cancers, cholecystectomy appears to suffice<sup>10–12</sup>. In addition, a desire for diagnostic completeness and fear of litigation may contribute to the routine examination of gallbladder specimens. A previous study<sup>2</sup> from the present authors' institution indicated that routine histological assessment of the gallbladder specimen may detect more incidental gallbladder cancers and that a selective approach may exclude patients, even when based on predictive factors for gallbladder cancer.

Several studies<sup>13–17</sup> have suggested selective assessment of the gallbladder specimen, on the basis that incidental

gallbladder cancer is unusual in the macroscopically normal gallbladder, and because of an increasing workload and cost. The extent to which the proposed cost-savings, in terms of decreasing the amount of histological analysis, are offset by costs accruing elsewhere in the healthcare systems, as a result of managing missed gallbladder cancers, is not known.

The aim of this study was to compare healthcare costs and health outcomes of the current selective approach of histological analysis of gallbladder specimens, as well as selective histology based on macroscopic appearance of the gallbladder and routine assessment of histology, by employing a decision-analytical modelling approach using data from previous studies of incidental gallbladder cancer in the Swedish population.

## Methods

The study population was patients undergoing cholecystectomy for benign disease in Sweden. Four distinct management strategies for these patients were evaluated: histological analysis not performed in any patients (no histology); selective histological analysis based on current practice in Sweden, where the surgeon responsible for cholecystectomy decides whether the gallbladder specimen should be submitted for histopathological examination or not (current selective histology); histological analysis performed by macroscopic evaluation of the gallbladder as a presumed standardized regimen in the context of normal or abnormal appearance (macroscopic selective histology); and histological analysis performed in all patients (routine histology). As there is no standard regimen for submitting the gallbladder, and the proportion submitted for histopathological examination varies widely between hospitals in Sweden<sup>2</sup>, in this study current selective histology refers to the diagnostic performance of the mean (44.3 per cent) proportion of gallbladders submitted for histopathology in Sweden between 2007 and 2014. Macroscopic selective histology is based on registration of the macroscopic appearance of the gallbladder specimen at cholecystectomy. Registration is done by the surgeon in charge and documented in a national quality register. The register does not specify what constitutes a normal gallbladder, but is the surgeon's subjective evaluation.

## Cost-effectiveness analysis

A decision-analytical modelling approach<sup>18</sup> was used to synthesize evidence to estimate healthcare costs and health outcomes in terms of life-years for the four management strategies. Estimated costs and life-years were combined

into incremental cost-effectiveness ratios (ICERs) to assess the additional cost of achieving an additional life-year for each management strategy.

Costs are reported in 2018 euros (€) and were converted from Swedish krona (SEK) to euros based on the 2018 average exchange rate from the Central Bank of Sweden<sup>19</sup> of 100 SEK being equivalent to €10.26.

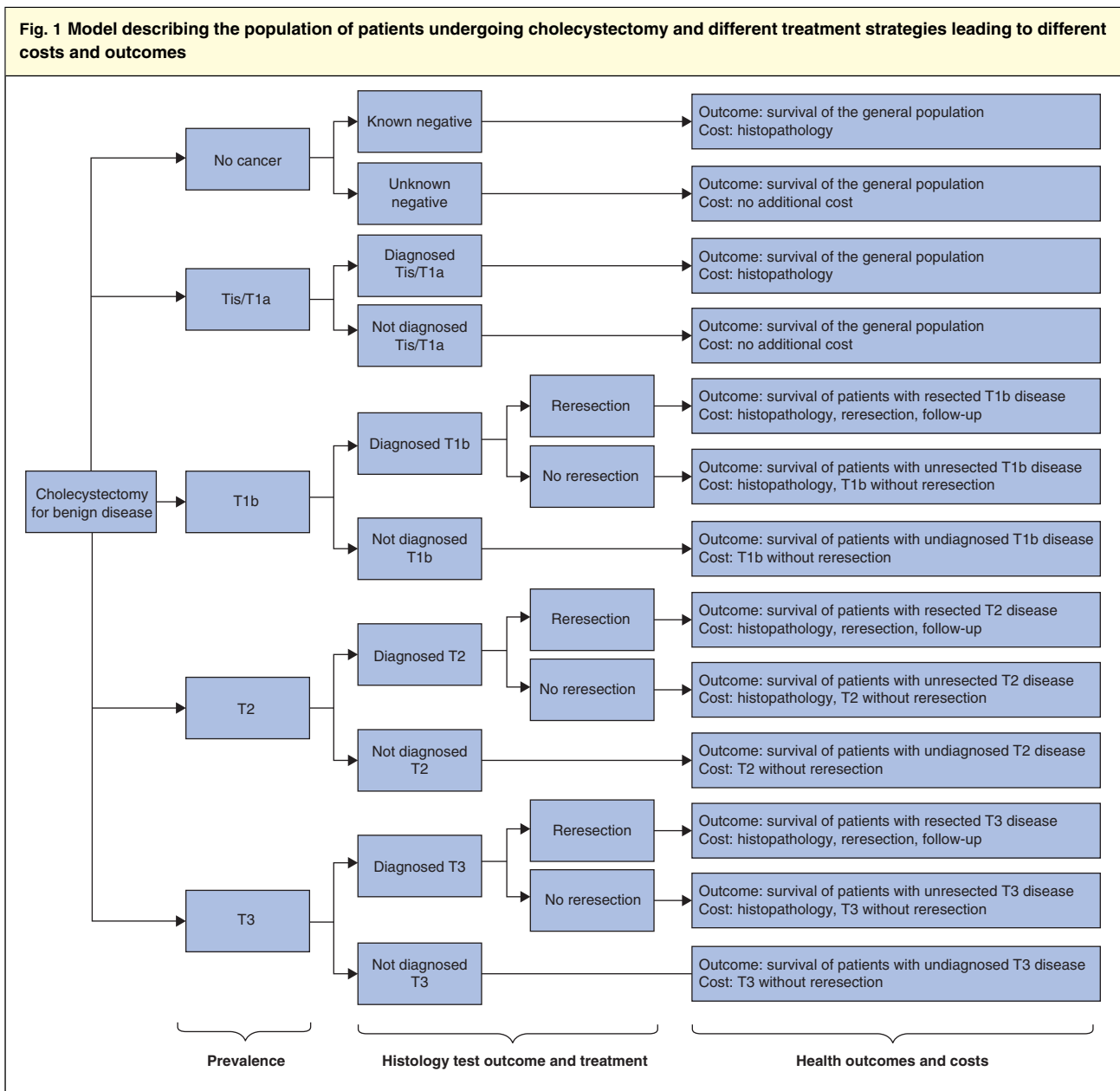
## Model

A decision-tree structure was used for the analytical model in an attempt to prioritize clarity and a general understanding of the conceptual issues over complexity (*Fig. 1*). For this reason, undiscounted costs and health outcomes are reported. To the left of the tree, the patient population of cholecystectomies and the prevalence of cancer, by stage, is depicted. In a sequence of chance nodes, diagnostic accuracy and treatment patterns are described. In the strategy with 100 per cent of gallbladders sent for histological examination, all patients with cancer will be identified with the disease and with the correct disease stage. A proportion of these patients will then undergo treatment. To the right of the tree, the consequences of each end node are described. The estimated consequences include the survival prognosis associated with a particular pathway, as well as the estimated healthcare costs. Key parameters estimated include: the prevalence of cancer; the proportion of patients detected with cancer with the clinical practice strategy (100 per cent for the case where all gallbladder specimens are sent for histological assessment, and 0 per cent for the strategy where histological examination is not performed); the proportion of patients treated with resection if detected with cancer; and survival prognosis and healthcare costs conditional on cancer stage and treatment.

In the analysis of the model, the cohort size was set at 10 000 patients, corresponding approximately to the number of cholecystectomies performed for benign disease annually in Sweden. The starting point for age in the model was set to 70 years, representing the mean age of patients with incidental gallbladder cancer in Sweden<sup>2</sup>. Only those diagnosed with incidental gallbladder cancer were subjected to intervention in the model, and therefore the model was not affected by the age of patients undergoing cholecystectomy with benign histopathology.

## Data sources

The primary data source for populating the model was cholecystectomies registered in GallRiks (the Swedish Registry of gallstone surgery and endoscopic retrograde cholangiopancreatography (ERCP))<sup>20</sup> between January



2007 and September 2014. The selection process and descriptive data have been presented previously<sup>2</sup>. The GallRiks registry is web-based and validated continuously<sup>21</sup>. Variables are standardized, and include baseline characteristics, indication for surgery, macroscopic evaluation of the gallbladder, whether histological analysis was performed, and an abbreviated version of the histology report. Patients were excluded if the indication for surgery was polyps or suspected malignancy, or the cholecystectomy was subordinate to another abdominal operation.

Additional data required to populate the model were retrieved from published sources and administrative databases.

In the follow-up of the Swedish cohort of patients with incidental gallbladder cancers<sup>8</sup>, histology reports were examined in detail. This meant that some patients with pT4 disease were excluded owing to other primary diagnosis of cancer, and some were restaged. As only six patients with pT4 disease remained, they were excluded in the analyses and no separate pT4 stage was modelled.

## Prevalence

Hospitals submitting at least 90 per cent of gallbladder specimens were analysed to estimate the expected prevalence of incidental gallbladder cancer during the study period. The eight hospitals with a frequency of histological assessment of 90 per cent or more were assumed to contribute accurate prevalence estimates as almost all gallbladders were sent for histopathological assessment.

## Proportion of expected incidental gallbladder cancers diagnosed

With routine histology, all cancers were assumed to be diagnosed, assuming 100 per cent sensitivity and specificity. With the no histology strategy, no cancers would be diagnosed as no gallbladder specimens were analysed.

The expected frequency of cancers to be found per pT category with routine histology was retrieved and compared with the actual frequency of cancers found by the current selective setting and the selective strategy based on macroscopic abnormality.

For the macroscopic selective strategy, the variable of peroperative macroscopic assessment in GallRiks was utilized. Gallbladder specimens registered as 'normal' were expected to have been discarded, and all other specimens were expected to have been analysed (listed as 'acute cholecystitis', 'chronic cholecystitis', 'polyp', 'suspected malignancy', 'spontaneously perforated gallbladder' and 'other deviating findings').

## Proportion resected

A proportion of patients diagnosed with pT1b, pT2 and pT3 status will undergo resection. The proportion of patients resected per pT category was estimated from a previous study<sup>8</sup> of a Swedish national cohort of patients with incidental gallbladder cancer (*Table 1*). No patient with pTis or pT1a disease was resected. The different proportions of patients undergoing resection were incorporated in the model to determine life expectancy and healthcare costs.

## Probability of recurrence

The rate of recurrence for each pT category was estimated from previous data<sup>8</sup>. Recurrence was defined as a radiological finding of local recurrence or distant metastasis in staging radiology or macroscopic finding of metastases at planned resection. The rate of recurrence according to pT category and treatment are shown in *Table 1*.

<b>Overall prevalence of incidental gallbladder cancer</b>	34.3 per 10 000
<b>Estimated proportion with recurrence by pT category and treatment</b>	
pTis/pT1a	0.00
pT1b resected	0.19
pT1b not resected	0.53
pT2 resected	0.42
pT2 not resected	0.67
pT3 resected	0.67
pT3 not resected	0.86
<b>Proportion of diagnosed cancers resected by pT category</b>	
pTis/pT1a	0.00
pT1b	0.52
pT2	0.47
pT3	0.18
<b>Years of life expectancy by pT category and treatment</b>	
No cancer	16.2
pTis/pT1a	16.2
pT1b resected	11.7
pT1b not resected	8.3
pT2 resected	9.4
pT2 not resected	3.5
pT3 resected	3.4
pT3 not resected	0.9

Recurrence was incorporated in the model to determine life expectancy and healthcare costs.

## Life expectancy

Survival data for patients with incidental gallbladder cancer according to pT category were estimated from previous data<sup>8</sup>. The 5-year disease-specific survival rate for each pT category was included in the model.

For the proportion of patients surviving more than 5 years, further life expectancy was anticipated to be the same as survival in the general population. For the proportion of patients who did not survive for 5 years, mean survival was calculated per pT category from the incidental gallbladder cancer cohort presented in previous data<sup>8</sup> (*Table 2*). For patients without incidental gallbladder cancer and for those with pTis/T1a incidental gallbladder cancer, survival was expected to be the same as that for the general population. Years of life expectancy were calculated from life expectancy in the general population for the proportion of patients surviving more than 5 years, and using the mean survival for patients not surviving to 5 years according to pT category and treatment (*Table 1*).

**Table 2** Five-year disease-specific and mean survival of patients with incidental gallbladder cancer

Treatment	No. of patients*	5-year disease-specific survival (%)	Mean survival (months)†
<b>pT1b category</b>			
Cholecystectomy	15	43	27.9
Reresection	21	64	43.4
<b>pT2 category</b>			
Cholecystectomy	49	16	12.5
Reresection	55	48	36.7
<b>pT3 category</b>			
Cholecystectomy	64	0	11.4
Reresection	15	13	17.7

Data are from a previous study<sup>8</sup> of 249 patients with incidental gallbladder cancer. \*Patients evaluated for 5-year disease-specific survival; †patients who did not survive to 5 years after diagnosis of incidental gallbladder cancer were evaluated separately.

**Costs**

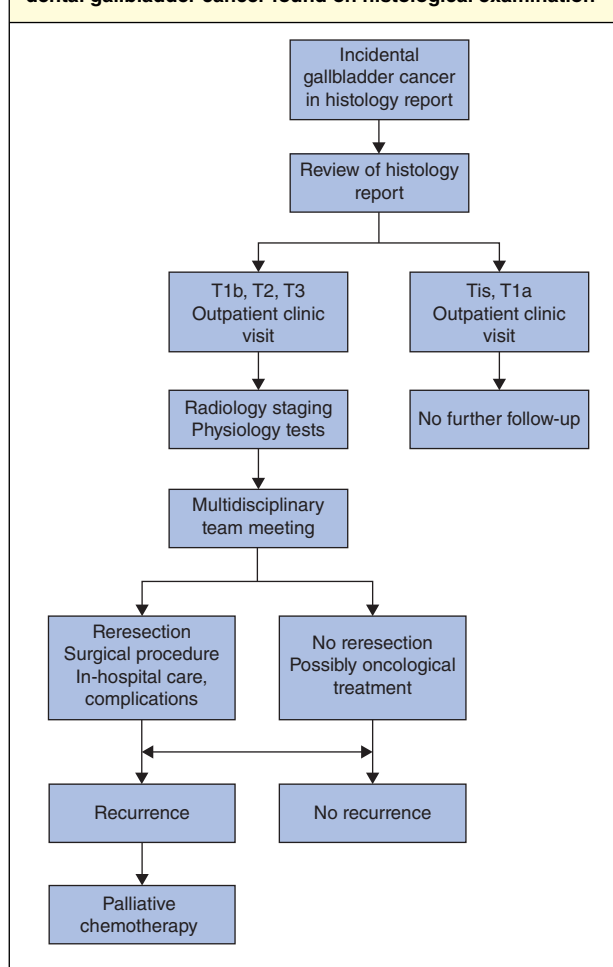
Healthcare costs were those associated with histopathological assessment and other costs related to diagnosis, as well as the treatment of patients with incidental gallbladder cancer, according to the process and management on discovery of incidental gallbladder cancer in the histology report (Fig. 2). All costs used in the model were adjusted to 2018 values.

Six main cost categories were considered: histopathology, outpatient visit, multidisciplinary meeting, in-hospital care including treatment of complications, oncology, and palliative care. Unit costs for all procedures were retrieved from regional debit price lists in Östergötland Region<sup>22,23</sup>. Costs are listed in Table 3.

In Sweden, histological analysis of the gallbladder specimen is usually performed by a standard method, resulting in a written histology report within approximately 2–3 weeks. If malignancy is suspected during surgery, the specimen is submitted with high priority, with expected histology report within five working days. Using previous data<sup>2</sup>, it was found that 28.2 per cent of the patients were suspected during surgery to have gallbladder malignancy, including the presence of gallbladder polyps. Thus, 71.8 per cent of the total cost of histological analysis was based on the cost for the standard regimen, and 28.2 per cent on the cost of high priority for histological analysis.

As review of the gallbladder specimen is recommended when unexpected gallbladder cancer is found, an additional cost for reviewing the specimen was added for the proportion of patients with a positive finding on histopathological examination.

**Fig. 2** Flow diagram of the management of patients with incidental gallbladder cancer found on histological examination



Patients diagnosed with pTis and pT1a incidental gallbladder cancer were assumed to have had an outpatient visit for information, but no further follow-up. Patients diagnosed with pT1b, pT2 and pT3 disease were expected to have had extended investigation, including radiological staging and, in some cases, physiology tests, as a basis for deciding on further surgery. Costs for these preoperative investigations were added to the outpatient clinic visit according to the regional debit price list in Östergötland Region<sup>23</sup>.

The cost of a multidisciplinary team (MDT) meeting was retrieved from a recently published Swedish observational study<sup>24</sup>. The cost estimate for an MDT meeting for upper gastrointestinal cancer was used in the model.

Calculations of costs regarding reresection included surgical facilities and instrumentation, wages, and in-hospital care. The cost of wages was based on standard wages

Table 3 Healthcare costs	
	Cost per patient (€)
<b>Histological analysis</b>	183.4
<b>Review of histological analysis</b>	87.0
<b>Outpatient visit after cholecystectomy</b>	
pTis/pT1a	292.4
pT1b–pT3	682.3
<b>Multidisciplinary conference</b>	444.2
<b>Reresection</b>	
Preparation	1508
Facilities	3070
Bed-days on surgical ward	3509
Ultrasound aspirator and instruments	395
Wages of surgeons	441
Postoperative facilities	624
Total	9547
<b>Treatment of complications after reresection</b>	24.8
<b>Palliative oncological treatment</b>	
Outpatient visit to oncologist	786
Gemcitabine/oxaliplatin (per treatment)	538
<b>Palliative home care by pT category</b>	
No cancer	0
pTisp/T1a	0
pT1b resected	1005
pT1b not resected	2819
pT2 resected	2168
pT2 not resected	3527
pT3 resected	3527
pT3 not resected	4532

from Statistics Sweden<sup>25</sup>, with monthly wages of €7732 for physicians. Social security costs and payroll taxes were added to salary costs. A reresection was expected to involve the employment of two surgeons for 3 h each. Monthly salaries were converted to salary per hour by dividing by 160, as this represents standard monthly working hours in Sweden.

The length of hospital stay and presence of complications for reresected patients were obtained from previous data relating to the Swedish national cohort of incidental gallbladder cancer<sup>8</sup>. Median length of stay for patients resected with curative intent was 8 (range 3–64) days. The unit cost per bed-day in a surgical ward was retrieved from regional debit price lists.

Costs of complications for reresected patients were based on the observed proportion of complications using previous data<sup>8</sup> for bile leakage (7.6 per cent) and infections (4.3 per cent). Unit costs for percutaneous drainage were retrieved from regional debit price lists<sup>23</sup>. The cost of antibiotic treatment was based on a regimen of 3 days of intravenous piperacillin–tazobactam and 7 days of oral

antibiotics as a combination of ciprofloxacin and metronidazole.

Adjuvant oncological treatment has not been standard in Sweden for gallbladder cancer and was therefore not included in the model. Palliative oncological treatment costs included outpatient oncology department visits and chemotherapy using a combination of gemcitabine and oxaliplatin. From the national prospective internet-based Swedish Registry for cancer in the biliary tract and liver, SweLiv<sup>26</sup>, the proportion of patients with incidental gallbladder cancer who received palliative chemotherapy was retrieved. Between 2012 and 2018, approximately 36 per cent were registered for palliative chemotherapy. Using these data, the length of palliative chemotherapy treatment was estimated to be 3 months.

Palliative care in Sweden is based mostly on domiciliary services with an interdisciplinary team approach; the cost was assessed from an Israeli study of patients having oncological palliative treatment at home<sup>27</sup>. The mean healthcare cost per patient during the last year of life was estimated as €5486. This was compared to a recently published study in Sweden that analysed the cost-effectiveness of palliative advanced home care for patients with severe heart failure disease<sup>28</sup>, where the total cost was estimated as €4232 per patient over a period of 6 months, adjusted to 2018 values. For the present study, the total cost of palliative home care of patients with gallbladder cancer was estimated to be €4873. The cost was calculated for each pT category in relation to the proportion of patients with recurrence (*Table 3*).

### Ethical approval

Approval of previous data analysis for input data to the decision analysis model in this study was obtained from the Regional Ethical Committee in Linköping, Sweden (Dnr 2014/39-31 and 2016/408-32).

### Results

A total of 68 hospitals and 81 349 cholecystectomies were registered in GallRiks. Overall, 44.3 per cent of gallbladder specimens were sent for histological assessment; this proportion was used as the current selective approach for submitting gallbladder specimens in the model. A total of 213 incidental gallbladder cancers (0.3 per cent) were diagnosed.

In the estimation of the prevalence of gallbladder cancer, a total of 7293 (mean 912, range 623–1447) cholecystectomies were registered at the eight included hospitals; the mean frequency of histopathological assessment was 95.5

**Table 4** Estimated prevalence of incidental gallbladder cancer in a cohort of 10 000 patient undergoing cholecystectomy for benign disease, and outcome data from a decision-analytical model analysis of healthcare costs and expected life-years

	Management strategy			
	No histology	Current selective histology	Macroscopic selective histology	Routine histology
<b>Size of cohort</b>	10 000	10 000	10 000	10 000
<b>Prevalence and no. of gallbladders submitted for histological examination</b>				
No cancer	9965.7	9965.7	9965.7	9965.7
Histology	0.0	4426.6	5082.5	9965.7
No histology	9965.7	5539.1	4883.2	0.0
pTis/T1a category	5.5	5.5	5.5	5.5
Histology	0.0	2.6	4.1	5.5
No histology	5.5	2.9	1.4	0.0
pT1b category	1.4	1.4	1.4	1.4
Histology	0.0	1.4	1.4	1.4
No histology	1.4	0.0	0.0	0.0
pT2 category	20.6	20.6	20.6	20.6
Histology	0.0	10.7	16.5	20.6
No histology	20.6	9.9	4.1	0.0
pT3 category	6.9	6.9	6.9	6.9
Histology	0.0	6.9	5.5	6.9
No histology	6.9	0.0	1.4	0.0
<b>No. of resections performed</b>	0.0	6.9	9.4	11.6
<b>Healthcare costs per cohort (€)</b>				
Histological assessment	0	831 236	957 018	1 858 049
Resection-related costs	0	74 959	100 566	123 919
Other costs	107 554	98 210	94 765	91 882
Total	107 554	1 004 405	1 152 349	2 073 850
<b>Life-years per cohort</b>	161 623	161 658	161 673	161 685
<b>Incremental life-years per cohort</b>				
		35*	15†	12‡
<b>Cost-effectiveness results (per patient means)</b>				
Total healthcare costs (€)	11	100	115	207
Life-years	16.162	16.166	16.167	16.169
Incremental costs (€)		90*	15†	92‡
Incremental life-years		0.0035*	0.0015†	0.0012‡
ICER per life-year gained (€)		25 593*	9600†	76 508‡

\*Current selective histology *versus* no histology; †macroscopic selective histology *versus* current selective histology; ‡routine histology *versus* macroscopic selective histology.

(range 90.0–99.5) per cent. A total of 25 incidental gallbladder cancers were discovered, corresponding to 34.3 patients with incidental gallbladder cancer in a cohort of 10 000 patients undergoing cholecystectomy. The proportion with each pT category is shown in *Table 4*.

Compared with the current selective strategy, the observed frequency of diagnosed pT1b and pT3 disease was higher than expected. It was assumed that 100 per cent (1.00 of the proportion expected) of pT1b and pT3 cancers would be diagnosed by the current selective histology strategy. However, for pTis/pT1a and pT2, 47 and 53 per cent of patients respectively (0.47 and 0.53 of the proportions expected) were estimated to be diagnosed

(*Table 4*). Specimens evaluated as macroscopically abnormal constituted 51.0 per cent of all specimens. When comparing findings for macroscopic selective histology with the expected number, all patients with pT1b disease were diagnosed (1.00 of the proportion expected), and 75 per cent of patients with pTis/pT1a disease and 80 per cent for both pT2 and pT3 (0.75 and 0.80 of the proportion expected respectively).

**Base case results**

Base case results are shown in *Table 4*. Comparing current clinical practice in Sweden (selective strategy) with no

**Table 5 Outcome data from a decision-analytical model of healthcare costs and expected life-years for a cohort of 10 000 patients undergoing cholecystectomy for benign disease**

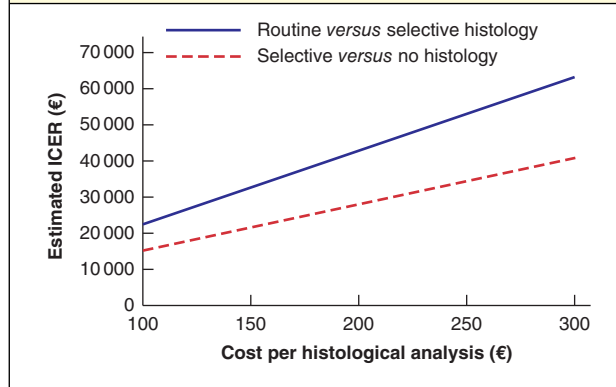
	Management strategy		
	No histology	Macroscopic selective histology	Routine histology
<b>Cost-effectiveness results (per cohort)</b>			
Healthcare costs (€)	107 554	1 152 349	2 073 850
Life-years	161 623	161 673	161 685
Incremental costs (€)		104 480	92 150
Incremental life-years		50	12
<b>Cost-effectiveness results (per patient means)</b>			
Healthcare costs (€)	11	115	207
Life-years	16.162	16.167	16.169
Incremental costs (€)		10*	92†
Incremental life-years		0.0050*	0.0012†
ICER per life-year gained (€)		20 708*	76 508†

\*Macroscopic selective histology *versus* no histology; †routine histology *versus* macroscopic selective histology.

histology resulted in an estimated 35 life-years gained and an incremental cost of approximately €1 000 000 for a hypothetical cohort of 10 000 patients, yielding an estimated ICER of €25 593. Comparing the macroscopic selective strategy with current selective strategy resulted in improved health outcomes and another 15 life-years gained at a slightly increased cost, yielding an estimated ICER of €9600. When routine histology was compared with macroscopic selective histology, this resulted in a gain of 12 life-years and an incremental healthcare cost of approximately €900 000 for a cohort of 10 000 patients, yielding an estimated ICER of €76 508 (the difference in total costs comparing macroscopic selective histology and routine histology is calculated by 2 073 850 – 1 152 349 = 921 501). The fact that the current selective strategy had a higher ICER than the macroscopic selective strategy indicates 'extended dominance', which can be explained by the fact that an ICER for a given alternative is higher than that of the next, more effective, alternative.

The current selective strategy was then eliminated from the model, which was then analysed including no histology, macroscopic selective histology and routine histology (Table 5). Comparing macroscopic selective histology with no histology resulted in a gain of 50 life-years and an incremental cost of approximately €1 000 000 for a hypothetical cohort of 10 000 patients, yielding an estimated ICER of €20 708. Excluding the current selective strategy did not impact the ICER of the routine histology strategy.

**Fig. 3 Sensitivity analysis of how the cost of histological analysis affects the incremental cost-effectiveness ratio**



ICER, incremental cost-effectiveness ratio.

The sensitivity of submitting only macroscopic abnormal gallbladder specimens would be 93.9 per cent (200 of 213) and the specificity would be 52.0 per cent (42 211 of 81 136).

## Sensitivity scenarios

### Cost of histology analysis

The relationship between the cost of the histology analysis and the ICER is shown in Fig. 3. If the cost of a single histology analysis should increase, this would have an important impact on the ICER.

### Costs of outpatient visits and multidisciplinary team meetings

Increasing the cost of outpatient visits for patients with pT1s/pT1b or pT1b–pT3 disease did not affect the results in any substantial way; neither did the cost of MDT meetings (results not shown).

### Costs of resection

The costs of resection had little impact on the results (results not shown).

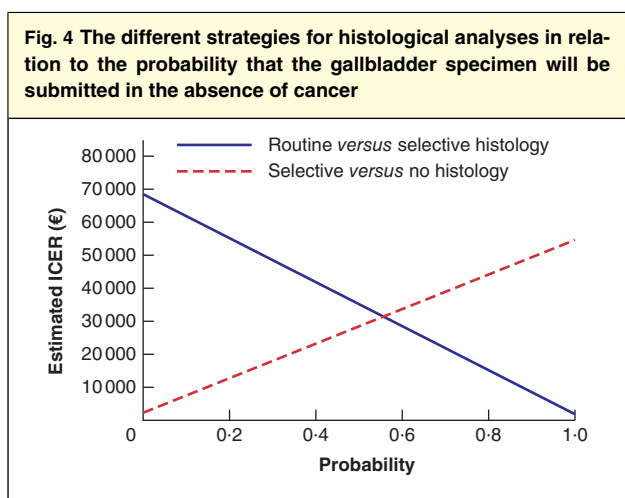
### Probability of recurrence

The recurrence rate of pT1b and pT2 disease also had only a minor impact on the findings (results not shown).

### Life-years gained from resection

The number of life-years gained following resection in patients with pT2 disease was, as expected, of importance for the results of the model, illustrating the fact that finding further cancers becomes more valuable the better the treatment outcome of those cancers (results not shown).





To the left of the diagram the specificity is increased, with few specimens submitted without cancer. To the right of the diagram, the specificity is decreased. ICER, incremental cost-effectiveness ratio.

#### *Probability of histology if no cancer present*

The impact on the results of the probability that the gallbladder specimen is submitted in the absence of cancer is illustrated in Fig. 4. To the left of the graph, the specificity of submitting gallbladders is increased, meaning that the probability of submitting a specimen without cancer is low. To the right of the diagram, the specificity is decreased. The results clearly illustrate that the specificity of submitting gallbladder specimens is likely to be important for interpretation of the results, and in the determination of an optimal management strategy.

## Discussion

This study evaluated a selective approach to histological examination of gallbladder specimens after benign cholecystectomy compared with routine assessment, with respect to healthcare costs and health outcomes related to finding incidental gallbladder cancer, from a national perspective. The current selective approach in Sweden of submitting about 44 per cent of all gallbladder specimens for histological examination, with no standard regimen, was eliminated as an extendedly dominated strategy. When comparing a macroscopic selective strategy with no histological assessment, 50 life-years would be saved and the ICER was estimated to be €20 708 in a cohort of 10 000 patients undergoing cholecystectomy. Choosing routine histology instead of the macroscopic strategy would lead to a gain of 12 life-years, at an ICER of €76 508 in a cohort of 10 000. Thus, few lives would be saved at high cost if a macroscopic strategy were to be switched to routine histology.

Several sensitivity analyses were performed in this study to understand the importance of individual parameters, and their potential impact, on the results. The cost of the histology analysis had an obvious impact on the ICER, most likely due to the ratio of a large number of cholecystectomies annually to the health outcome of few incidental gallbladder cancers found. Increasing the cost of outpatient visits or MDT meetings did not affect the ICER. Even with a doubling of the reresection costs, there was only a slight increase in the ICER, again indicating that the costs for histological analyses had the greatest impact on the ICER.

The subject of routine or selective histology at benign cholecystectomy has been studied several times previously. A retrospective study from India<sup>7</sup> analysed 170 patients and compared patients who had early diagnosis from the gallbladder histology report with patients with cancer that was missed at cholecystectomy and who presented with late symptoms. Early detection of incidental gallbladder cancer resulted in an increased reresection rate (69.9 per cent), compared with a decreased rate (7.8 per cent) for late detection. The authors<sup>7</sup> therefore recommended routine histology of gallbladder specimens. Several other studies<sup>6,29–33</sup> recommend routine histology, based on the fact that cancer in the gallbladder may be present without macroscopic abnormalities, although a review<sup>15</sup> concluded that supporters of routine histology more often come from areas with an increased prevalence of gallbladder cancer and that a selective approach could be proposed only for areas of very low prevalence.

Two of the key factors in the argument for a selective approach are to reduce costs and ensure that no incidental gallbladder cancers are detected in a normal gallbladder specimen<sup>13,14,34–37</sup>. The cost analyses in these studies are based mostly on direct costs of the histological analysis and the savings that could be made if fewer gallbladder specimens were submitted. A proposition that histological examination should be carried out only in cases of unexpected appearance of the gallbladder suggested an overall saving of £10 875 (€12 205, exchange rate 1 September 2020) over a 5-year period from 2000 to 2005<sup>36</sup>. In a study<sup>13</sup> from China, involving 14 369 routine histological analyses of gallbladder specimens, 44 of 46 patients with incidental gallbladder cancer had macroscopic abnormalities, and the two patients with a normal gallbladder were diagnosed as having pTis and pT1a disease.

When evaluated from an age perspective, of 3041 cholecystectomies with routine histology, eight patients (0.3 per cent) with incidental gallbladder cancer were found<sup>37</sup>. A cut-off value of 51 years was calculated from the receiver operating characteristic (ROC) curve, with 100 per cent

sensitivity and 45 per cent specificity of identifying incidental gallbladder cancer<sup>37</sup>. Applying this selection, £15 225–21 960 (€17 087–24 645, exchange rate 1 September 2020) would have been spared between March 2004 and December 2012.

In a study from the Netherlands<sup>38</sup>, it appeared that national guidelines regarding histological assessment of gallbladder specimens had been revised in 2014, with a recommendation of selective histology based on divergent macroscopic appearance of the gallbladder or abnormal finding on preoperative radiology. A slight decline in the proportion of histological analyses has been seen in recent years. It is estimated that the revised guidelines could save around €1 600 000 annually in the Netherlands, based on 27 550 cholecystectomies performed in 2015.

This study has several limitations. The estimated prevalence of incidental gallbladder cancer is based on the prevalence from only eight hospitals with a routine procedure of submitting gallbladder specimens. This gives uncertainty to the figures used in the present model, because of the low disease prevalence. The best starting point would have been a larger sample of routine histological analyses in cholecystectomies nationwide. When estimating the expected frequency of patients with incidental gallbladder cancer with pT1b and pT3 status for the current selective histology strategy, the observed frequency was higher than expected. The calculations in the model therefore assumed that all cancer cases for T1b and T3 were found in current selective histology. For pT3 this may be accurate, as this stage of gallbladder cancer represents tumour growth through the serosa and should be identifiable macroscopically. Therefore, it was surprising that 80 per cent of pT3 was found only when analysing the macroscopic selective histology strategy. This can probably be explained by estimating prevalence from a relatively small cohort, where the macroscopic appearance of the gallbladder specimen from one patient with pT3 disease was registered as normal, affecting the proportion of patients discovered with pT3 gallbladder cancer in a macroscopic selective setting. It does not seem reasonable to believe that a pT3 gallbladder cancer would have a normal appearance and, therefore, this may account for registration errors. In the model, only patients with pT1b–pT3 cancer have been appropriate for extended resection, an accepted treatment for incidental gallbladder cancer<sup>8</sup>. In analysis of the data, patients with pTis, pT1a and pT4 incidental gallbladder cancer were judged to have no further survival benefit from resection.

A further limitation relates to the term ‘normal gallbladder’, as there is no uniform description. Some may call the gallbladder normal despite ongoing inflammation, whereas others would use the term abnormal if the

gallbladder wall were above a particular thickness. For example, Tayeb and colleagues<sup>39</sup> referred to a normal gallbladder specimen when there was ‘no mucosal ulceration/irregularity, mass, polyp, localized or generalized wall thickness’, whereas Bazoua and co-workers<sup>40</sup> designated the gallbladder as normal if the gallbladder wall was less than 3 mm in thickness. In the present study, the specimen was evaluated as normal by the surgeon in charge at the cholecystectomy and not by predefined criteria, which is of course a limitation of the study.

The analyses may lack costs associated with palliative treatment, for example ERCP in patients with jaundice. Adjuvant chemotherapy after resection of incidental gallbladder cancer has not been the standard regimen in Sweden, and neither the cost of adjuvant treatment nor the health outcome of adjuvant treatment has been considered in the model.

Even though all hospitals submitting all gallbladder specimens were analysed, patients are selected for cholecystectomy in the first place. Knowing that incidental gallbladder cancer is more common in older patients, women and those with chronic cholecystitis<sup>41</sup> could affect the frequency of its discovery, if selection of patients differs between hospitals.

The strength of the present study is the large sample of nationally registered data in facilitating the estimation of health-related costs and survival data. On the basis of these results, a change to routine histological analysis of gallbladder specimens in Sweden would mean increased costs with minimal improved health outcomes. Instead, a standard approach to histological assessment of gallbladder specimens based on a macroscopic selective strategy seems desirable.

## Disclosure

The authors declare no conflict of interest.

## References

- 1 Jayasundara JASB, de Silva WMM. Histological assessment of cholecystectomy specimens performed for symptomatic cholelithiasis: routine or selective? *Ann R Coll Surg Engl* 2013; **95**: 317–322.
- 2 Lundgren L, Muszynska C, Ros A, Persson G, Gimm O, Valter L *et al*. Are incidental gallbladder cancers missed with a selective approach of gallbladder histology at cholecystectomy? *World J Surg* 2018; **42**: 1092–1099.
- 3 Pitt SC, Jin LX, Hall BL, Strasberg SM, Pitt HA. Incidental gallbladder cancer at cholecystectomy: when should the surgeon be suspicious? *Ann Surg* 2014; **260**: 128–133.
- 4 Choi SB, Han HJ, Kim CY, Kim WB, Song T-J, Suh SO *et al*. Incidental gallbladder cancer diagnosed following

- laparoscopic cholecystectomy. *World J Surg* 2009; **33**: 2657–2663.
- 5 Are C, Ahmad H, Ravipati A, Croo D, Clarey D, Smith L *et al*. Global epidemiological trends and variations in the burden of gallbladder cancer. *J Surg Oncol* 2017; **115**: 580–590.
  - 6 Lohsiriwat V, Vongjirad A, Lohsiriwat D. Value of routine histopathologic examination of three common surgical specimens: appendix, gallbladder, and hemorrhoid. *World J Surg* 2009; **33**: 2189–2193.
  - 7 Agarwal AK, Kalayarasan R, Singh S, Javed A, Sakhuja P. All cholecystectomy specimens must be sent for histopathology to detect inapparent gallbladder cancer. *HPB (Oxford)* 2012; **14**: 269–273.
  - 8 Lundgren L, Muszynska C, Ros A, Persson G, Gimm O, Andersson B *et al*. Management of incidental gallbladder cancer in a national cohort. *Br J Surg* 2019; **106**: 1216–1227.
  - 9 Goetze TO, Paolucci V. Immediate re-resection of T1 incidental gallbladder carcinomas: a survival analysis of the German Registry. *Surg Endosc* 2008; **22**: 2462–2465.
  - 10 Aloia TA, Jarufe N, Javle M, Maithel SK, Roa JC, Adsay V *et al*. Gallbladder cancer: expert consensus statement. *HPB (Oxford)* 2015; **17**: 681–690.
  - 11 Zaidi MY, Maithel SK. Updates on gallbladder cancer management. *Curr Oncol Rep* 2018; **20**: 21.
  - 12 Sternby Eilard M, Lundgren L, Cahlin C, Strandell A, Svanberg T, Sandström P. Surgical treatment for gallbladder cancer – a systematic literature review. *Scand J Gastroenterol* 2017; **52**: 505–514.
  - 13 Deng Y-L, Xiong X-Z, Zhou Y, Shrestha A, Li F-Y, Cheng N-S. Selective histology of cholecystectomy specimens – is it justified? *J Surg Res* 2015; **193**: 196–201.
  - 14 Emmett CD, Barrett P, Gilliam AD, Mitchell AI. Routine *versus* selective histological examination after cholecystectomy to exclude incidental gallbladder carcinoma. *Ann R Coll Surg Engl* 2015; **97**: 526–529.
  - 15 Jamal K, Ratansingham K, Siddique M, Nehra D. Routine histological analysis of a macroscopically normal gallbladder – a review of the literature. *Int J Surg* 2014; **12**: 958–962.
  - 16 Matthyssens LE, Ziol M, Barrat C, Champault GG. Routine surgical pathology in general surgery. *Br J Surg* 2006; **93**: 362–368.
  - 17 Koppatz H, Nordin A, Scheinin T, Sallinen V. The risk of incidental gallbladder cancer is negligible in macroscopically normal cholecystectomy specimens. *HPB (Oxford)* 2018; **20**: 456–461.
  - 18 Briggs A, Claxton K, Sculpher MJ. *Decision Modelling for Health Economic Evaluation*. Oxford University Press: Oxford, 2006.
  - 19 The Riksbank. *Annual Average Exchange Rates*. <https://www.riksbank.se/en-gb/statistics/search-interest--exchange-rates/annual-average-exchange-rates/> [accessed 19 March 2019].
  - 20 GallRiks. [Annual reports.] <https://www.ucr.uu.se/gallriks/fou/arsrapporter> [accessed 4 March 2019].
  - 21 Rystedt J, Montgomery A, Persson G. Completeness and correctness of cholecystectomy data in a national register – GallRiks. *Scand J Surg* 2014; **103**: 237–244.
  - 22 Östergötland Region. [Internal Debit Price List for Laboratory Medicine.] <https://vardgivarwebb.regionostergotland.se/Startsida/Verksamheter/DC/Laboratoriemedicin/Prislista-LMC/> [accessed 6 March 2019].
  - 23 Östergötland Region. [Regional Debit Price list for Radiology.] <https://vardgivarwebb.regionostergotland.se/Startsida/Verksamheter/DC/Rontgenklinikerna-i-Ostergotland/Atagande-och-prislista-for-undersokningar/> [accessed 6 March 2019].
  - 24 Alexandersson N, Rosell L, Wihl J, Ohlsson B, Steen Carlsson K, Nilbert M. Determinants of variable resource use for multidisciplinary team meetings in cancer care. *Acta Oncol* 2018; **57**: 675–680.
  - 25 Statistics Sweden. [Database Wages]. <https://www.scb.se> [accessed 6 March 2019].
  - 26 SweLiv. [Annual Report.] <https://statistik.incanet.se/SweLiv/> [accessed 4 March 2019].
  - 27 Tamir O, Singer Y, Shvartzman P. Taking care of terminally-ill patients at home – the economic perspective revisited. *Palliat Med* 2007; **21**: 537–541.
  - 28 Sahlen K-G, Boman K, Brännström M. A cost-effectiveness study of person-centered integrated heart failure and palliative home care: based on a randomized controlled trial. *Palliat Med* 2016; **30**: 296–302.
  - 29 Siddiqui FG, Memon AA, Abro AH, Sasoli NA, Ahmad L. Routine histopathology of gallbladder after elective cholecystectomy for gallstones: waste of resources or a justified act? *BMC Surg* 2013; **13**: 26.
  - 30 Behari A, Kapoor VK. Does gallbladder cancer divide India? *Indian J Gastroenterol* 2010; **29**: 3–7.
  - 31 Dincel O, Goksu M, Hatipoglu HS. Importance of routine histopathological examination of a gallbladder surgical specimen: unexpected gallbladder cancer. *J Cancer Res Ther* 2018; **14**: 1325–1329.
  - 32 Kalita D, Pant L, Singh S, Jain G, Kudesia M, Gupta K *et al*. Impact of routine histopathological examination of gall bladder specimens on early detection of malignancy – a study of 4115 cholecystectomy specimens. *Asian Pac J Cancer Prev* 2013; **14**: 3315–3318.
  - 33 Patel K, Dajani K, Iype S, Chatzizacharias NA, Vickramarajah S, Singh P *et al*. Incidental non-benign gallbladder histopathology after cholecystectomy in an United Kingdom population: need for routine histological analysis? *World J Gastrointest Surg* 2016; **8**: 685–692.
  - 34 van Vliet JLP, van Gulik TM, Verbeek PCM. Is it necessary to send gallbladder specimens for routine histopathological examination after cholecystectomy? The use of macroscopic examination. *Dig Surg* 2013; **30**: 472–475.
  - 35 Mittal R, Jesudason MR, Nayak S. Selective histopathology in cholecystectomy for gallstone disease. *Indian J Gastroenterol* 2010; **29**: 26–30.
  - 36 Darmas B, Mahmud S, Abbas A, Baker AL. Is there any justification for the routine histological examination of

- straightforward cholecystectomy specimens? *Ann R Coll Surg Engl* 2007; **89**: 238–241.
- 37 Elshaer M, Gravante G, Yang Y, Hudson S, Thomas K, Sorge R *et al.* Routine *versus* selective histologic analysis of gallbladder specimens for the detection of incidental gallbladder cancers. A retrospective review over 9 years of activity with a special focus on patients' age. *Am J Surg* 2014; **208**: 444–449.
- 38 Olthof PB, Metman MJH, de Krijger RR, Scheepers JJ, Roos D, Dekker JWT. Routine pathology and postoperative follow-up are not cost-effective in cholecystectomy for benign gallbladder disease. *World J Surg* 2018; **42**: 3165–3170.
- 39 Tayeb M, Rauf F, Ahmad K, Khan FM. Is it necessary to submit grossly normal looking gall bladder specimens for histopathological examination? *Asian Pac J Cancer Prev* 2015; **16**: 1535–1538.
- 40 Bazoua G, Hamza N, Lazim T. Do we need histology for a normal-looking gallbladder? *J Hepatobiliary Pancreat Surg* 2007; **14**: 564–568.
- 41 Muszynska C, Lundgren L, Lindell G, Andersson R, Nilsson J, Sandström P *et al.* Predictors of incidental gallbladder cancer in patients undergoing cholecystectomy for benign gallbladder disease: results from a population-based gallstone surgery registry. *Surgery* 2017; **162**: 256–263.