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ORIGINAL ARTICLE

Radical resection for T1b gallbladder cancer: a decision analysis

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Abstract

Background: Gallbladder cancer is the most common malignancy of the biliary tract. Radical surgery (including liver resection and regional lymphadenectomy) is applied for some gallbladder cancers, but the benefits of these procedures are unproven. For patients with T1b cancers discovered incidentally on cholecystectomy specimens, the utility of radical surgery remains debated.

Methods: A decision analytic Markov model was created to estimate and compare life expectancy associated with management strategies for a simulated cohort of patients with incidentally discovered T1b gallbladder cancer after routine cholecystectomy. In one strategy, patients were treated with no additional surgery; in another, patients were treated with radical resection. The primary (base-case) analysis was calculated based on a cohort of 71-year-old females and incorporated best available input estimates of survival and surgical mortality from the literature. Sensitivity analysis was performed to assess the effects of model uncertainty on outcomes.

Results: In the base-case analysis, radical resection was favoured over no further surgical resection, providing a survival benefit of 3.43 years for patients undergoing radical resection vs. simple cholecystectomy alone. Sensitivity analysis on the age at diagnosis demonstrated that the greatest benefit in gained life-years was achieved for the youngest ages having radical resection, with this benefit gradually decreasing with increasing age of the patient. High peri-operative mortality rates (≥36%) led to a change in the preferred strategy to simple cholecystectomy alone.

Conclusions: Decision analysis demonstrates that radical resection is associated with increased survival for most patients with T1b gallbladder cancer.

Keywords

gallbladder cancer, T1b, decision analysis, surgery

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Introduction

Gallbladder cancer is the most common malignancy of the biliary tract.[1] Curative surgical resection remains the best method for achieving long-term survival. There is considerable debate as to whether T1b gallbladder cancers (tumour invading into, but not through, the muscularis propria) are best treated by simple cholecystectomy alone or by radical resection (including liver resection and regional lymphadenectomy).[2,3] Although some authors suggest that simple cholecystectomy is sufficient,[1,4–9] others advocate radical resection.[3,10–17]

Because of the low incidence of gallbladder cancer, it is unlikely that controlled clinical trials that would resolve this debate will ever be conducted.

Decision analysis provides an ideal method for assessing treatment paradigms for the management of T1b gallbladder cancer, enabling incorporation of risks and benefits of each strategy. In this study, the survival benefit of radical gallbladder resection was evaluated using decision-analytic techniques. A decision-analytic

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Markov model was developed to estimate life expectancy associated with each intervention for a simulated cohort of patients with incidentally discovered T1b gallbladder cancer found on gallbladder specimens. One group had no additional surgery and patients were observed. In the second group, patients were treated with radical resection. The stability of results to changes in key parameters were evaluated in sensitivity analysis.

Material and methods

Decision tree

A decision-analytic Markov model was developed to estimate life expectancy for 71-year-old women with T1b gallbladder cancer (Fig. 1). The primary (base-case) analysis incorporated specified best available model input estimates. Stability of results over changes in model estimates was evaluated in secondary (sensitivity) analysis. The age of 71 was used, as it was the mean age of diagnosis reported in a recently published study of over 4000 patients with early-stage gallbladder cancers in the Surveillance, Epidemiology, and End Results (SEER) tumour registry.[18] In this same study, women comprised the majority of patients with early gallbladder cancer.[18] The model decision tree was constructed and analysed using software (TreeAge Pro, 2007; TreeAge Software, Williamstown, MA, USA).

Primary tumour (T)

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*
T1	Tumour invades lamina propria or muscle layer
T1a	Tumour invades lamina propria
T1b	Tumour invades the muscle layer
T2	Tumour invades perimuscular connective tissue; no extension beyond serosa or into the liver
T3	Tumour perforates the serosa (visceral perioneum) or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, or pancreas, omentum or extrahepatic bile ducts
T4	Tumour invades main portal vein or hepatic artery or invades multiple extrahepatic organs or structures

Gallbladder. In: American Joint Committee on Cancer.: AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer, 2002, pp 139–44.

Figure 1 Gall bladder cancer T-stage as described in: American Joint Committee on Cancer.: *AJCC Cancer Staging Manual*. 6th ed. New York, NY: Springer, 2002, pp 139–144

Markov model

The cohorts' post-treatment life-time course was estimated using a Markov model with a 1-year cycle length. We constructed this model in keeping with widely accepted methods for Markov modelling in medicine.[19]

Patients entered the model after incidental discovery of T1b gallbladder cancer after or during simple cholecystectomy. Some patients had no additional surgery, whereas the others were treated with radical gallbladder resection in a second operation. Patients in the 'radical resection' group were faced with an initial risk of peri-operative death. Patients in both groups faced potential cancer-specific mortality each year after diagnosis. Patients in both groups were also subject to non-cancer mortality.

Model data and data sources

For data collection of probabilities, an initial systematic Medline search was conducted using the keyword search terms 'gallbladder cancer and survival and surgery' to identify survival data for patients undergoing surgical treatment for T1b gallbladder cancer. Upon detailed review of the selected articles and corresponding references, additional articles were subsequently identified that

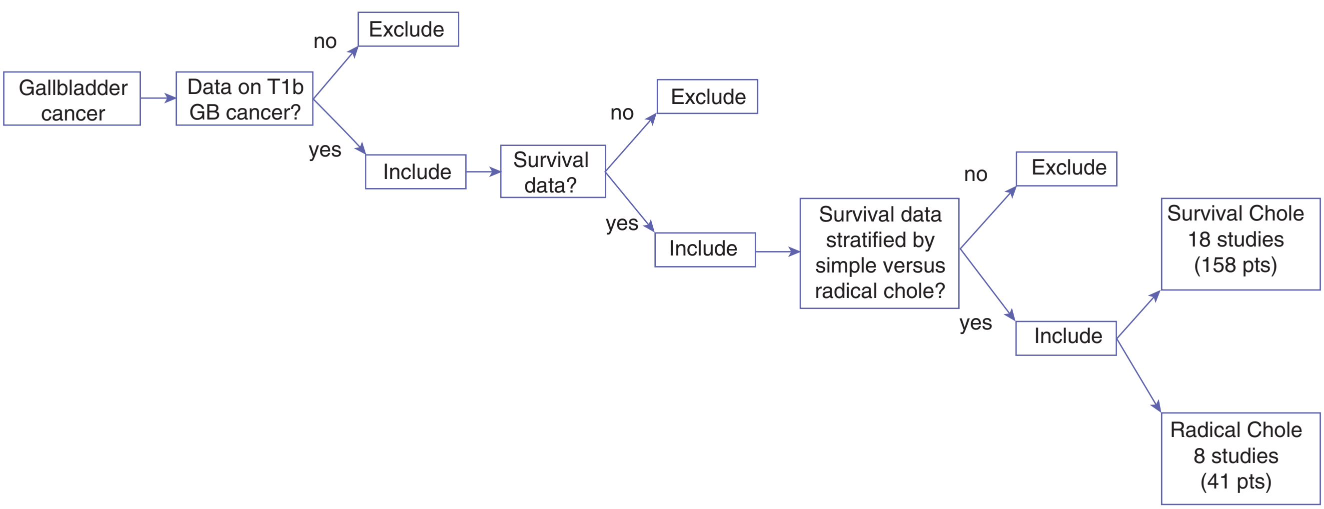

Figure 2 Algorithm illustrating criteria used for inclusion and exclusion of literature reporting 5-year survival for T1b gallbladder cancer patients treated with simple cholecystectomy or radical resection

Table 1 Published studies reporting 5-year survival for patients with T1b gallbladder cancers treated with simple cholecystectomy alone

Author	Institution	Patients	5-year survival
Wagholikar *et al.*[13]	Sanjay Gandhi, India	7	57
Cangemi *et al.*[12]	University of Rome, Italy	8	37.5
Mizumoto *et al.*[29]	Mie University, Japan	9	100
Kim *et al.*[30]	Catholic University, Korea	3	100
Wakai *et al.*[9]	Niigata University, Japan	13	100
Ouchi *et al.*[31]	Miyagi Cancer Cent, Japan	2	50
Principe *et al.*[15]	University of Bologna, Italy	1	0
Kwon *et al.*[2]	Kansai University, Japan	2	100
Yagi *et al.*[32]	Keio University, Japan	1	100
Foster *et al.*[33]	Roswell Park, Buffalo, USA	2	50
Cucinotta *et al.*[14]	University of Messina, Italy	6	0
Sun *et al.*[8]	Yonsei University, Japan	5	100
Nevin *et al.*[34]	M.C.V. & Memorial Hosp, USA	5	100
Benoist *et al.*[35]	French Cooperative Group	23	74
Shibata *et al.*[36]	Oita University, Japan	1	100
Yamamoto *et al.*[37]	Kobe University, Japan	15	93[a]
Goetze *et al.*[23]	Multiple centers, Germany	49	45[a]
Puhalla *et al.*[38]	University of Vienna, Austria	5	44[a]

[a]Calculated cancer-specific mortality.

Table 2 Published studies reporting 5-year survival for patients with T1b gallbladder cancers treated with radical cholecystectomy

Author	Institution	Patients	5-year survival
Cangemi *et al.*[12]	University of Rome, Italy	3	100
Mizumoto *et al.*[29]	Mie University, Japan	3	100
Kim *et al.*[30]	Catholic University, Korea	2	100
Wakai *et al.*[9]	Niigata University, Japan	7	92
Ouchi *et al.*[31]	Miyagi Cancer Cent., Japan	1	100
Shibata *et al.*[36]	Oita University, Japan	1	0
Goetze *et al.*[23]	Multiple centers, Germany	23	85[a]

[a]Calculated cancer-specific mortality.

met inclusion criteria. Critical appraisal of each study was performed and studies were selected on the basis of the inclusion criteria used for this analysis (See Fig. 2).

For the purposes of this study, reviewed publications were excluded from our analysis if: (i) the number of patients undergoing surgical resection; or (ii) 5-year survival data for those patients were unavailable.

A second search was conducted using the keywords 'gallbladder cancer and perioperative mortality and radical cholecystectomy' in order to obtain peri-operative mortality statistics. Representative studies containing peri-operative mortality for patients undergoing radical resection (not just those for T1b cancers) were included.

Letters, reviews without original data, animal studies, studies without survival data and overlapping studies were also excluded from our analysis.

For survival data in the simple cholecystectomy alone group, data were included regardless if the procedure was performed by laparoscopic or open technique. In the radical resection group, survival data were included if the procedure was completed during the initial operation (cancer discovered intraoperatively) or if a simple cholecystectomy was performed on the initial operation and followed at a later date with a more extended resection (e.g. discovered on pathology reports post-operatively followed by radical resection). For the radical resection group, we initially attempted to include only those patients undergoing at least a wedge resection of the liver bed and regional lymphadenectomy. However, in a few studies survival data include a few patients who had undergone less extensive procedures (only a lymphadenectomy and cholecystectomy) or slightly more extensive procedures (cholecystectomy, liver resection, bile duct resection).

Table 3 Published studies reporting peri-operative mortality associated with radical resection for gallbladder cancer

Author	Institution	Patients	Periop mortality
Cubertafond *et al.*[39]	French Surgical Association	724	22
Tsukada *et al.*[40]	First Department of Surgery, Japan	106	0.9
Todoroki *et al.*[41]	Institute of Clinical Medicine, Japan	135	3.7
Bartlett *et al.*[42]	Memorial Sloan, USA	23	0
Ouchi *et al.*[31]	Miyagi Cancer Cent., Japan	4	0
Shirai *et al.*[43]	Niigata University, Japan	14	7.1
Fong *et al.*[44]	Memorial Sloan, USA	19	5.3
Todoroki *et al.*[41]	University of Tsukuba, Japan	135	3.7
Muratore *et al.*[10]	Umberto I Mauriziano Hospital, Italy	33	3
Yoshida *et al.*[45]	Oita Medical University, Japan	35	0
Suzuki *et al.*[46]	Fujimnomiya City General Hospital, Japan	12	0
Mondragon-Sanchez *et al.*[47]	Instituto Nacional de Cancerologia, Mexico	20	10
Frena *et al.*[48]	Regional Hospital of Bolzano, Italy	20	0
Yamaguchi *et al.*	Kyushu University, Japan	4	0
Onoyama *et al.*[49]	Saiseikai Nakatsu Hospital, Japan	32	0
Puhalla *et al.*[38]	University of Vienna, Austria	32	6.3
Behari *et al.*[50]	Sanjay Gandhi, India	42	4.8
Toyonaga *et al.*[7]	Kyushu University, Japan	21	0
Taner *et al.*[51]	Mayo Clinic, USA	60	1.7
Yildirim *et al.*[52]	Ankara, Turkey	28	0
Foster *et al.*[33]	Roswell Park, USA	13	0
Yagi *et al.*[32]	Keio University, Japan	47	0
Chan *et al.*[53]	University of Hong Kong, China	12	0
Principe *et al.*[15]	University of Bologna, Italy	29	0
Benoist *et al.*[35]	Hopital Henri-Mondor, France	21	4.8
Schauer *et al.*[5]	Ludwig-Maximilian University, Germany	23	0
Cangemi *et al.*[12]	Peitro Valdoni, Italy	3	0
Wagholikar *et al.*[13]	Sanjay Gandhi, India	2	0
Reddy *et al.*[54]	Duke University, USA	22	4.5
Shih *et al.*[28]	Johns Hopkins, USA	50	4
Ito *et al.*[55]	Brigham and Women's, USA	8	0

Table 4 Study variables

Variable	Weighted average (%)	Range (%)
5-year survival (simple cholecystectomy)	61.3	0–100
5-year survival (radical cholecystectomy)	87.5	0–100
Perioperative mortality	2	0–6

In studies that did not explicitly state survival time periods in the text, we have estimated the survival based on the data given in tables, text, or presented Kaplan–Meier survival curves.

Peri-operative mortality was defined as death within 30 days of the surgery. However, in-hospital or operative mortality (procedure-related) was used as a substitute for peri-operative mortality when death within 30 days of surgery was not reported.

Non-cancer-related mortalities were incorporated into the model using data from the United States Year 2000 Life-Tables.[20]

Decision analysis models and calculations

Weighted means were calculated for the: (i) 5-year survival for those patients undergoing simple cholecystectomy; (ii) 5-year survival for those patients undergoing radical cholecystectomy; and (iii) peri-operative mortality associated with a radical cholecys-

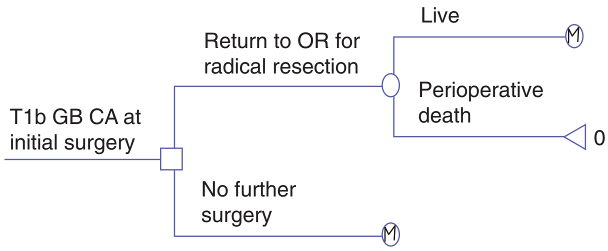

Figure 3 Decision tree for treatment of patients with incidentally discovered T1b gallbladder cancer after routine cholecystectomy. Therapeutic strategies are shown after decision node (to right of □). Probabilistic outcome is shown after chance node (to the right of ○). Terminal nodes signify death (Δ) or that Markov model defines ensuing pathway (M). OR, operating room

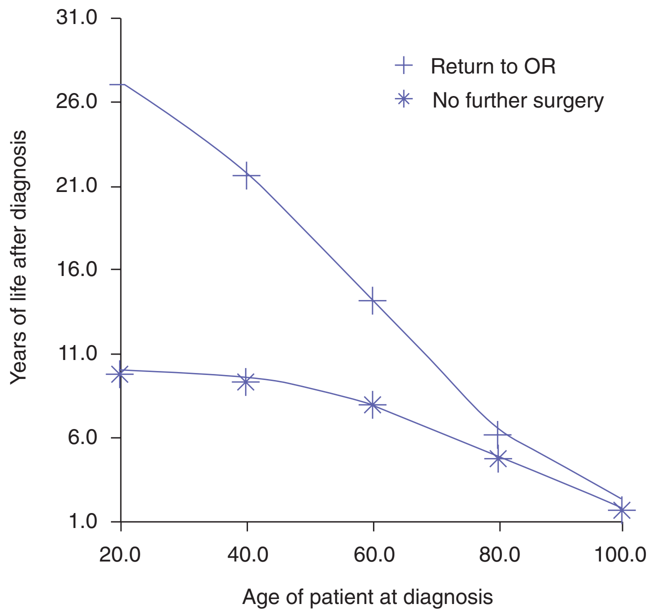

Figure 4 One-way sensitivity analysis varying the age at diagnosis from 20 to 100 years. The greatest benefit in terms of gained life-years was achieved for the youngest ages having radical resection, with this benefit gradually decreasing with increasing age of the patient subset. OR, operating room

tectomy. Weighted means were considered baseline estimates and were weighted based on the number of patients contributing to the particular mean.

Calculated 5-year cancer-specific survival probabilities were converted to 1-year cancer-specific mortality probabilities for use in the decision-analytic Markov model, using the standard assumption of an exponential relationship between an event probability (p) and hazard rate (r) over a specified time period (t), which can be expressed as $p = 1 - e^{-rt}$.[21,22]

For those studies reporting overall (not cancer specific-) survival, we calculated an adjusted cancer-specific mortality rate utilizing data of female, age-based mortality rates from the United States Life Tables, 2000.[20]

Sensitivity analysis

Sensitivity analysis was performed to evaluate the effects of model assumptions and parameters on results. Specifically, sensitivity analysis was performed for the peri-operative mortality rate, age of diagnosis and gender. A threshold value was calculated in cases for which a change in the preferred strategy was traversed.

Results

Studies used in the analysis are shown in Tables 1 and 2 for the group undergoing simple cholecystectomy alone and the group undergoing radical cholecystectomy, respectively. Overall, a total of 18 studies including 157 patients and 7 studies including 40 patients were used to calculate baseline probabilities for the simple- and radical cholecystectomy groups, respectively. For the simple cholecystectomy alone group, we calculated a weighted mean 5-year cancer-specific survival of 61.3%. For those patients undergoing radical resection we obtained a mean 5-year survival of 87.5% (Table 4). Weighted peri-operative mortality was slightly less than 2% (Tables 3 and 4). For those 40 patients having a radical cholecystectomy, we calculated a weighted probability of lymph node metastases to be 2.5%.

Our Markov model (shown in Fig. 3) demonstrates the two potential treatment arms: radical resection vs. no additional surgery. Patients in the radical resection group were faced with an initial potential for a peri-operative death. Patients in both groups faced potential cancer-specific mortality each year after diagnosis. And finally, patients in both groups were subject to non-cancer-related mortalities.

For our cohort of patients, the base-case decision analysis favoured radical resection over simple cholecystectomy without additional surgery. Life-expectancy after simple cholecystectomy alone was 6.42 years after diagnosis. In contrast, radical resection improved life-expectancy to 9.85 years after diagnosis, providing an additional 3.43 years survival benefit over simple cholecystectomy alone.

Sensitivity analysis

One-way sensitivity analyses in which the age-at-diagnosis was varied is shown in Fig. 4. Varying the age from 20 to 100 years at the time of diagnosis demonstrated that the greatest benefit from radical resection in terms of gained life-years was achieved when the diagnosis was made at a young age.

For all ages, men had a slightly decreased survival benefit compared with females, likely secondary to their slightly shorter overall life expectancy (Table 5).

The decision to perform a radical resection for T1b gallbladder cancer over a simple cholecystectomy is sensitive to the perioperative mortality rate. When the probability of peri-operative

Table 5 Age at diagnosis, gender and outcomes

Age at diagnosis	Gender	Procedure	Life expectancy(years)
35	Male	Simple cholecystectomy	9
		Radical cholecystectomy	19
35	Female	Simple cholecystectomy	9
		Radical cholecystectomy	20
65	Male	Simple cholecystectomy	7
		Radical cholecystectomy	11
65	Female	Simple cholecystectomy	7
		Radical cholecystectomy	12

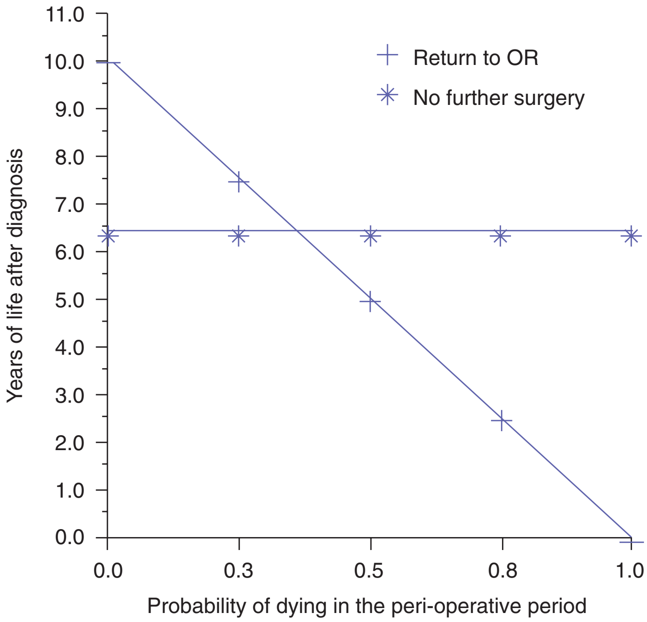

Figure 5 One-way sensitivity analysis varying probability of peri-operative mortality. The decision to treat with radical cholecystectomy vs. simple cholecystectomy is sensitive to varying the peri-operative mortality. Once peri-operative mortality reaches a threshold of ≥36% (intersection of the two lines in the graph) the analysis favours no further surgery over radical resection. OR, operating room

mortality is ≥36% (intersection of the lines in Fig. 5) the analysis favours treatment with simple cholecystectomy alone over radical resection.

Discussion

Radical gallbladder resection in the management of T1b gallbladder cancers is controversial. Despite the fact that radical resection for these patients is recommended by many hepatobiliary surgeons, a recently published administrative database study suggests that less than 5% of patients with T1b gallbladder cancer in the United States currently undergo radical resection.[18]

In our analysis, we demonstrated increased long-term survival for patients with T1b gallbladder cancer who undergo radical resection vs. those treated with simple cholecystectomy alone. This finding is robust (note the high threshold value for peri-operative mortality rate on sensitivity analysis) and valid over a wide range of patient age at which gallbladder cancer is diagnosed.

Prior analysis of outcomes associated with T1b gallbladder cancer have been limited to small single institution series.[9,23] Two analyses of the Surveillance, Epidemiology, and End Results (SEER) registry database for gallbladder cancer have been reported; however, in neither report were outcomes associated with simple cholecystectomy vs. radical resection compared specifically for patients with T1b lesions.[18,24]

A decision analysis study, such as ours, is not without potential limitations, which we enumerate here. In addition to the limited number of published studies that met inclusion criteria for our analysis (as noted above), we are using published data from multiple different authors and institutions which has lead to variability in the pooled data. For example, there were variations in the specific surgical procedures performed between (and even within) studies. In the simple cholecystectomy group, some patients had open cholecystecomy performed whereas others had laparoscopic procedures. However, we do not believe this variability adversely affects our results to a great extent as data from previously published studies indicates no survival difference between treatment with conventional open procedure vs. laparoscopic surgery for those patients with early gallbladder cancer.[25–27] Ouchi *et al.*, for example, found little difference upon comparing outcomes data from 498 patients with gallbladder cancer treated laparoscopically to their survival data from standard open procedures.[27] They determined that laparoscopic cholecystectomy did not have any adverse effects on the long-term outcomes of these patients.[27]

Similarly, in the radical cholecystectomy group, some patients were treated with radical cholecystectomy during the initial operation whereas others were 're-resected' at a later date after an initial simple cholecystectomy. Again, we do not believe this issue affects our findings. Shih *et al.* determined that there was no difference in survival between patients who were discovered to have gallbladder cancer incidentally on laparoscopic cholecystectomy and immediately converted to an open resection and those who had a completed laparoscopic cholecystectomy and were re-explored at a later point when found to have gallbladder cancer by subsequent pathology.[28]

Additional shortcoming of our analysis include an inability (because of a lack of published data) to stratify survival data based on resection margin status, lymph node involvement and adjuvant therapy. Furthermore, the findings from this study, while useful on a population basis, do not take into account individual patient characteristics (e.g. co-morbidities, medications, family history), nor individual patient wishes for treatment. It must be reiterated, as such, that decisions to treat with one modality vs. another need to be made on a case-by-case basis taking into account all relevant factors.

In conclusion, decision analysis based on data available for the subset of patients with T1b gallbladder cancer demonstrates that radical cholecystectomy is associated with improved survival for most patients with T1b gallbladder cancer.

Conflicts of interest

None declared.

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