Systematic review of management of incidental gallbladder cancer after cholecystectomy

K. Søreide1,3,4, R. V. Guest1, E. M. Harrison1, T. J. Kendall2, O. J. Garden1 and S. J. Wigmore1

1Clinical Surgery and 2Division of Pathology, Royal Infirmary of Edinburgh and University of Edinburgh, Edinburgh, UK, and 3Department of Gastrointestinal Surgery, Stavanger University Hospital, Stavanger, and 4Department of Clinical Medicine, University of Bergen, Bergen, Norway

Correspondence to: Professor K. Søreide, Department of Gastrointestinal Surgery, Stavanger University Hospital, PO Box 8100, N-4068 Stavanger, Norway (e-mail: ksoreide@mac.com)

Background: Gallbladder cancer is rare, but cancers detected incidentally after cholecystectomy are increasing. The aim of this study was to review the available data for current best practice for optimal management of incidental gallbladder cancer.

Methods: A systematic PubMed search of the English literature to May 2018 was conducted.

Results: The search identified 12 systematic reviews and meta-analyses, in addition to several consensus reports, multi-institutional series and national audits. Some 0.25–0.89 per cent of all cholecystectomy specimens had incidental gallbladder cancer on pathological examination. Most patients were staged with pT2 (about half) or pT1 (about one-third) cancers. Patients with cancers confined to the mucosa (T1a or less) had 5-year survival rates of up to 100 per cent after cholecystectomy alone. For cancers invading the muscle layer of the gallbladder wall (T1b or above), resection is recommended. The type, extent and timing of resection remain controversial. Observation time may be used for new cross-sectional imaging with CT and MRI. Perforation at initial surgery had a higher risk of disease dissemination. Gallbladder cancers are PET-avid, and PET may detect residual disease and thus prevent unnecessary surgery. Routine laparoscopic staging before resection is not warranted for all stages. Risk of peritoneal carcinomatosis increases with each T category. The incidence of port-site metastases is about 10 per cent. Routine resection of port sites has no effect on survival. Adjuvant chemotherapy is poorly documented and probably underused.

Conclusion: Management of incidental gallbladder cancer continues to evolve, with more refined suggestions for subgroups at risk and a selective approach to resection.

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Introduction

Gallbladder cancer has a dismal prognosis overall, with over one-third of patients presenting with distant metastasis at time of diagnosis1–3. By contrast, patients who present with early-stage disease have a more favourable outcome. As early gallbladder cancers do not have specific symptoms, they are most often discovered incidentally, usually at histopathological examination of the specimen after cholecystectomy performed for other indications.

Laparoscopic cholecystectomy has become one of the most frequently performed procedures in general surgery4,5. As it is most commonly performed for benign indications, such as biliary colic or inflammation, the need for routine histopathological investigation of the specimen has been questioned6–9. However, in recent series from Western countries 0.25–0.89 per cent of specimens demonstrated a gallbladder cancer as an incidental, unexpected finding6,8,10–12. The frequency of gallbladder cancer is even higher (up to 2 per cent) and age of presentation much younger (at 40 years) in endemic regions, such as Chile and India13. Notably, although gallbladder cancer usually presents in older people (age above 60 years) and has a low incidence in most Western countries, the majority (50–70 per cent) of gallbladder cancers are now detected as incidental findings after cholecystectomy14,15. The incidence of gallbladder cancer has increased in the past two decades, concurrent with the increase in cholecystectomy rates.

The incidental and unsuspected finding of gallbladder cancer may pose several dilemmas for further management. Incidental gallbladder cancers have a more favourable prognosis than cancers presenting with symptoms.
However, the role, timing and extent of further surgery, and the impact on outcome, remain controversial. Thus, the aim of this review was to explore currently available data for management of incidental gallbladder cancer after cholecystectomy.

Methods

A PubMed search was undertaken of the English literature up to May 2018 using the search words ‘gallbladder cancer’ AND ‘incidental’ and ‘surgery’, ‘laparoscopy’, ‘pathology’, ‘staging’, ‘CT/MRI/PET’ with ‘consensus’, ‘guideline’, ‘meta-analysis’, ‘systematic review’ alone or in combination. The main focus and aim of the systematic search was to identify consensus reports, guidelines, systematic reviews and meta-analyses that were published in the most recent 5 years (1 January 2013 to 30 May 2018). Aware of the predominant retrospective nature of the literature, data obtained from larger multicentre or collaborative work were sought in particular, including national reports or registry audits. Thus, small, retrospective or single-institution series were excluded, unless providing novel information. Where several reports were published from the same multicentre collaborative, registry or audit, the most relevant and updated reports were used for reference. Papers published before the most recent 5-year interval were included where no other data existed, or if they presented important reference to current knowledge or change in practice. Each identified and included study was searched for additional references to derive further reports or studies of interest.

Results

The literature search identified and included papers with direct (specific for incidental cases) or indirect (for example topics on gallbladder cancer in general) relation to the management of incidental gallbladder cancer. As data are sparse and few studies address incidental gallbladder cancer in isolation, papers were included when relevant data would have impact on management, such as studies on overall gallbladder cancer management. Thus, the identified studies included were 12 systematic reviews with or without meta-analysis\(^{10,16–26}\), seven consensus reports and guidelines\(^ {27–33}\), 15 multi-institutional series\(^ {14,15,34–46}\), and seven national series/audits or registries\(^ {47–51}\). References of the identified articles were further searched for additional studies or reports of interest.

Pathology and staging for incidental gallbladder cancer

As per the incidental nature of the diagnosis, pathological examination is important for appropriate staging and further management. The debate around routine pathological examination of all gallbladders, owing to the low risk of cancer, is influenced by several factors. These include competing workload in the pathology department, the routine practice of opening the gallbladder for inspection by the clinician (which varies between institutions) and with what accuracy an ‘abnormal’ gallbladder can be distinguished from a ‘normal’ gallbladder macroscopically (by either the surgeon or the pathologist) on the background of, for example, chronic inflammation, or even be suspected before surgery\(^ {52–55}\). In one review\(^ {23}\) of studies reporting on whether macroscopic features were suspicious (before the diagnosis was confirmed), a high rate (60–100 per cent) of prediagnostic suspicion was found. However, routine rather than selective histopathological investigation detects more incidental gallbladder cancers\(^ 6\). Variation in the use of routine or selective histopathology of the surgical specimen is reported, with arguments supporting either approach\(^ {6–8,51,56}\). It is important to recognize the risk of a potentially considerable time delay (several weeks) in the diagnosis of cancer, as routine assessment of ‘benign, routine gallbladders’ may not take high priority in most pathology departments.

When a diagnosis of gallbladder neoplasia is confirmed, it is essential to establish the correct pathological stage (Table 1) for planning of further management\(^ {37,58}\). Neoplasia contained within the mucosa (Tis or pT1a) is considered to have a very low risk of recurrence and essentially to be cured by cholecystectomy alone, whereas invasion into the gallbladder muscle wall (pT1b) is considered to require further surgery. For pT2 cancers, the location in the gallbladder is important (Fig. 1), as cancers located on the liver side (as opposed to the peritoneal side) have a worse prognosis\(^ {59,60}\). Location is important for further treatment decision-making, and is incorporated

| Stage | Tumour category | Node category\(^ *\) | Metastasis category | Estimated 5-year survival (%) |
|-------|----------------|----------------------|---------------------|-----------------------------|
| 0     | Tis            | N0                   | M0                  | 80–100                      |
| I     | T1a (lamina propria) | N0               | M0                  | 80–100                      |
| II    | T1b (muscularis)   | N0                   | M0                  | 80–100                      |
| IIA   | T2a (peritoneal side) | N0              | M0                  | 40–75                       |
| IIB   | T2b (hepatic side)  | N0                   | M0                  | 28–50                       |
| IIIA  | T3             | N0                   | M0                  | 8–28                        |
| IIIB  | T1–3           | N1                   | M0                  | 8                            |
| IVA   | T4             | N0–1                 | M0                  | 7                            |
| IVB   | Any T          | N2                   | M0                  | 4                            |
|      | Any T          | Any N                | M1                  | 0–2                          |

\(^*\)N1, one to three metastatic nodes; N2, more than three metastatic nodes.
in the staging system (Fig. 1 and Table 1). Furthermore, determination of node status is essential, as the presence of nodal metastasis (pN+) is considered an adverse prognostic factor with poor overall survival. Finally, the cystic duct margin should be reported as part of the resection margin, as involvement would suggest need for re-resection. Neoplasia in the cystic duct or isolated cystic duct cancers are extremely rare\textsuperscript{61–63} and not considered as part of gallbladder cancer management in this review.

Studies on the quality of pathology reporting in incidental gallbladder cancer are lacking. One small multicentre study from France\textsuperscript{46} found that pathology reports frequently had missing data for key prognostic factors, including tumour stage, size, grade and resection margins. Several histopathological factors beyond pT and pN category have been reported\textsuperscript{15,41} to be of prognostic relevance, such as grade, lymphovascular and perineural invasion, and should be obtained together with pT and node status.

**Intraoperative events at primary surgery**

For the surgeon, it is of importance to obtain knowledge of any intraoperative event that may influence further management. Based on data from the German Registry\textsuperscript{64}, intraoperative perforation of the gallbladder bears a higher risk of local recurrence, and this does not change if a bag is used for retrieval of a perforated gallbladder. Perforation or bile spillage may be associated with an almost universal risk of peritoneal carcinomatosis and a poor prognosis\textsuperscript{55,65,66}, and essentially precludes further attempts...
at surgical cure. It is uncertain what factors are associated with risk for perforation, but a ‘difficult’ gallbladder may be expected with increasing pT category and degree of inflammation. Severe inflammation is a risk factor for gallbladder perforation\textsuperscript{67}. Although increased preoperative inflammation and a high neutrophil-to-lymphocyte ratio are reported as poor prognostic factors in gallbladder cancer\textsuperscript{44,68}, this is not reported as part of perforation or risk thereof. Type of surgery (either laparoscopic, converted or open) has no influence on outcome\textsuperscript{16}.

### T category at presentation

In a systematic review of over 2000 incidental gallbladder cancers\textsuperscript{10}, the most frequent stage at presentation was pT2, followed by pT3 and pT1. Notably, the systematic review includes incidental cancers diagnosed during surgery, so a ‘true’ incidental postoperative distribution cannot be assumed from this study. For example, T4 cancers (involving major structures and vessels) would not be expected to be part of a truly incidental gallbladder cancer setting, but some studies have included the incidental perioperative finding of unsuspected gallbladder cancer that proceeded with resection. This obviously creates some heterogeneity in the definitions and some inconsistency in data between studies. However, although higher rates of T4 disease are seen in symptomatic and unresectable gallbladder cancers, the distribution of T2 (about half) and T1 (about one-third) status corroborates well with findings from other studies\textsuperscript{6,15,46,69}, and is presented in Fig. 2 as extrapolated numbers. When looking exclusively at incidental gallbladder cancers found on histopathological examination alone, the rate of T1 cancers increases to about two-thirds.

### Timing of reresection

The majority of cholecystectomies are performed by general surgeons with no or little experience in advanced hepatobiliary surgery. Thus, when an unexpected diagnosis of cancer is obtained, early contact with a hepatobiliary centre should be made\textsuperscript{70}. In one US study, increasing travel distance to a treating centre was associated with worse outcome, suggesting barriers to care\textsuperscript{71}. However, the time interval from index operation to reresection (or evaluation at a hepatobiliary centre) is not straightforward, with contradictory results reported between studies in relation to the importance of the time interval.

Overall, the time interval from index cholecystectomy to reresection is reported with considerable variation across studies, with a median usually at 2–3 months and range between 1 and 11 months\textsuperscript{69,72,74}. The unexpected finding of a cancer comes with a sense of urgency for both treating surgeon and patient, and, even from the side of the receiving centre of the referral, urgent or even emergency transfers may occur after the diagnosis is confirmed. However, there are few data to support a need for an emergency referral and immediate redo surgery if an incidental cancer is detected, although the timing of surgery remains debated\textsuperscript{35,74–76}. In several studies, the unresectability rate at restaging (before redo surgery) is as high as 50 per cent for incidental cancers\textsuperscript{70,74–77}, despite early referral. Indeed, in one study\textsuperscript{75} early referral was a strong predictor of unresectability. Together, this may suggest that biology, rather than time, is the most essential factor for progression of disease. In particular, if perforation occurred during first operation, a period of observation may be allowed, as perforation may be associated with higher risk of disease dissemination and poor survival.

Early surgery is not associated with an improved outcome if the cancer has spread beyond the resection planes of the initial surgery\textsuperscript{75}. In a large multicentre study\textsuperscript{35}, the investigators found inferior outcomes for patients treated within the first 4 weeks of the primary operation, and also for those treated more than 8 weeks after surgery; a 4–8-week window had the best outcome. However, there is potential bias in the retrospective observational design of these data accrued from several centres, and the plausibility of a 4–8-week window for resection has been questioned\textsuperscript{74}. Indeed, others\textsuperscript{72,73,75,77} have shown that it is primarily the pT category at first operation, rather than time interval, that determines risk of residual disease and operability at second operation. Residual disease was found in half of 22 patients with T1b/T2 cancers after redo surgery, with very poor prognosis in those with...
residual disease. Consequently, surgery may simply act as a staging procedure rather than change the natural history of the disease, and an argument could be made for a time window for observation and re-imaging for optimal clinical restaging before commencement of surgery based on this. ‘Urgent’ re-resection (at less than 4 weeks) may be associated with ongoing or not yet resolved inflammation from index surgery, and complicate further resection. The ‘test of time’ interval before further redo surgery should take into account the operative report at index surgery and the pathological assessment of the resected specimen (Fig. 3). At the very least, as some time may usually pass until diagnosis has been confirmed and restaging is completed, it should be noted by involved parties that time per se is not the determinant of outcome. Rather, proper staging, underlying tumour characteristics, previous gallbladder...
perforation with risk of tumour spillage and the risk of residual disease are what determine the long-term prognosis.

**Preoperative restaging before resection**

Cross-sectional imaging should be performed to exclude disseminated disease or obvious early recurrence. This may depend largely on the time since primary resection and pathological stage. Chest and abdominal CT should be a minimum requirement for restaging, but other imaging modalities may be considered for higher sensitivity and specificity.

As CT has limitations in detecting disseminated disease, the option to perform PET–CT may be considered, as this has a high sensitivity for disseminated disease in gallbladder cancer.\(^{81–85}\) Gallbladder cancer is a rather PET-avid malignancy and thus may be suitable for preoperative staging.\(^{12,78,80,82}\) Specific data on the management of incidental gallbladder cancer are somewhat limited and restricted to a few cohorts\(^{81–84}\) with heterogeneous reporting of data (Table 2). In one study\(^{81}\) of 108 patients undergoing PET before resection, there was useful signal take-up in patients with disseminated disease, particularly in those with T2 status. Another study\(^{85}\) found altered management in 22 per cent of patients based on PET results, with accuracy reaching 100 per cent for disseminated disease when used in a restaging setting. Although data are currently based on few series of incidental gallbladder cancer,\(^{81–85}\) these suggest that PET–CT has a role before resection in any T1b cancer and above for detection of disseminated disease,\(^{82}\) and for ruling out local residual disease in T1b cancers.\(^{81}\) One study\(^{81}\) advised against undertaking redo surgery in patients with T1b cancers if PET–CT findings were negative, as the likelihood of finding residual disease was very low.

Previous studies have investigated laparoscopic staging in incidental gallbladder cancer given the high rate of associated peritoneal metastasis. Staging laparoscopy may avoid a non-therapeutic laparotomy in about half of patients with disseminated disease, but has the lowest yield in early stages.\(^{86}\) Overall, the diagnostic yield is low, but may be considered in poorly differentiated and higher T categories (for example T3) with a greater risk of disseminated disease\(^{86,87}\).

**Type and extent of resection**

Considerable debate still exists over re-excision, aggressiveness of surgery and its influence on outcome in incidental gallbladder cancer.\(^{88,89}\) There is consensus that R0 resection represents the strongest prognostic factor for long-term outcome and chance for cure. The timing, type and extent of reoperation, and patient selection, however, continue to be debated\(^{45,90}\). Management of incidental gallbladder cancer must take several factors into account for decision-making (Fig. 3), despite evidence for best management being based on poor-quality data.\(^{17,19,21,89}\)

In stage T1a cancers, the 5-year survival rate approaches 100 per cent, with a less than 2 per cent risk of pN+ disease on resection; thus simple cholecystectomy is considered curative for these patients.\(^{81}\) This has reached consensus

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**Table 2** Studies of PET in incidental gallbladder cancer after cholecystectomy

| Reference       | Interval       | Country | Study design | n† | Interval‡ | SUV cut-off§ | PET-positive* | Residual disease* |
|-----------------|----------------|---------|--------------|----|-----------|--------------|---------------|------------------|
| Shukla et al.\(^{83}\) | 2006–2007 | R       | 80           | 51 (17–152) days | n.r. | n.r. (numbers combined with MDCT) | 7 of 24 resected |
| Butte et al.\(^{82}\) | 2006–2008 | Chile   | P, SC        | 32 | 6 (2–52) weeks | ≥ 2.5 | All: 19 of 32 (59) | n.r. |
| Goel et al.\(^{81}\) | 2008–2014 | India   | P, SC        | 108 | 42 (28–118) days | > 2.4 | All: 44 of 108 (40–77) | n.r. |
| Leung et al.\(^{84}\) | 2001–2013 | USA     | R, SC        | 64 | n.r. | > 2.0 | All: 22 of 64 (34) | n.r. |

*Values in parentheses are percentages. †Number of incidental gallbladder cancers reported in study as seen on PET. ‡Median (range) time from primary cholecystectomy to PET. §Standard uptake value (SUV) on PET for defining positive scan. ∥Values as reported by Goel et al.\(^{81}\) do not sum up to the total stated. R, retrospective; n.r., not reported; MDCT, multidetector CT; P, prospective, SC, single-centre.
in most guidelines. Current guidelines suggest that T1b cancers should undergo extended resection with lymphadenectomy, as about 10 per cent of these tumours will have pN+ status. However, although there is a difference in survival between T1a and T1b cancers, this does not appear to be influenced by simple cholecystectomy or extended lymphadenectomy. In a systematic review covering 29 studies and including 1266 patients with T1 incidental gallbladder cancer, 1-1 per cent of patients with T1a disease died from cancer, compared with 9-3 per cent of those with T1b disease. The authors concluded that there is no firm evidence that extended surgery confers a survival benefit in T1b cancers.

In stage T2, there is more consensus regarding extended lymphadenectomy at reoperation. However, with the recently introduced subdivision of T2 into pT2a and pT2b (Fig. 1), there appears to be new debate over the need for reoperation and extended surgery in all peritoneal-side T2 cancers. Although T2 sidedness is already included in the TNM system, it is based on a rather limited number of patients. One study included 157 patients with T2 cancers, of whom 33 had peritoneal-side cancer; no patient with peritoneal-side cancer who had a simple cholecystectomy died. Another study included 252 patients with T2 disease from four institutions and found that, compared with peritoneal-side tumours, hepatic-side T2 cancers had a higher risk of both liver recurrence (23 versus 3 per cent; \( P = 0.003 \)) and distant lymph node metastasis (16 versus 3 per cent; \( P = 0.019 \)), even after radical resection. In both studies, the presence of histopathological features such as lymphovascular invasion, perineural infiltration and poor differentiation grade were associated with poorer outcome. This may imply that biological features of the cancer, rather than extent of surgical resection, dictate the outcome of patients with early-stage incidental gallbladder cancer. These findings may be controversial in relation to current recommendations and previous findings, but on closer inspection of studies reporting on outcome in T2 cancers in the past and benefit of extended surgery, it is usually the presence of liver involvement or node metastasis that is related to poor survival. Indeed, previous extensive surgery reported from tertiary-centre series have not yielded an effect of improved survival after either excision of common bile ducts (CBDs) or multiple organ resections in gallbladder cancers as well as in redo surgery for incidental gallbladder cancers. In general, there are no clear adverse outcomes from laparoscopic resections compared with open operations, and the laparoscopic access route is increasingly entertained and promoted by specialists. One concern is that laparoscopic access has been associated with a reduced lymph node yield. Open or laparoscopic access for resection appears to have no effect on outcome in early gallbladder cancer, whereas data on the minimally invasive approach in more advanced cancers (T2 or above) are based on small series and not established as a standard approach.

### Effect of radical and extensive resection on outcome

The proportion of patients with unresectable advanced disease at reoperation varies, but the systematic review by Choi and colleagues reported an overall pooled rate of 23 per cent. Some recent studies from the UK suggest the unresectability rate is twice as high, at about 50 per cent.

Gallbladder cancer is prone to the development of peritoneal metastasis, and early reports after laparoscopic cholecystectomy reported high rates of port-site metastasis. However, a recent systematic review found that since the 1990s, compared with the 2000s era, the incidence of port-site metastasis in incidental gallbladder cancer has decreased from 18-6 (95 per cent c.i. 15-3 to 21-9) per cent before 2000 to 10-3 (7-9 to 12-7) per cent since then (\( P < 0.001 \)). The extraction site is at significantly higher risk than non-extraction sites, and the risk of port-site metastasis is associated with increased T category and the presence of poor histopathological features. Several studies, including a multicentre consortium study from the USA and a French registry study, reported no survival benefit from routine port-site excision, and this practice is largely obsolete in modern practice. The European Society for Medical Oncology guidelines suggest port-site excision if there is documented intraoperative perforation of the specimen, but this is not supported by available data.

Resection of the CBD is a further controversial area. In patients without involvement of the CBD (for instance, based on cystic duct evaluation), there was no benefit for extrahepatic bile duct resection over ‘radical cholecystectomy’ in terms of overall survival, lymph node yield and recurrence rate, but associated morbidity was higher when the CBD was resected. Recent studies further showed no improvement in lymph node retrieval with resection of the CBD, and overall survival was worse. When adjusting for disease stage, survival was similar in

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patients undergoing CBD resection and those having no resection\textsuperscript{10}, suggesting that it is disease stage that drives the biology and thus the outcome, rather than extent of surgery. Similar findings have been reported from Japan\textsuperscript{106}.

**Role of tumour markers**

There are currently no good biomarkers for gallbladder cancer. In incidental gallbladder cancer, tumour markers are usually not available from the preoperative assessment, and thus the prognostic role of frequently used tumour markers such as carbohydrate antigen (CA) 19-9 or carcinoembryonic antigen (CEA) is not known. For gallbladder cancer in general, a high preoperative CA 19-9 or CEA value is considered a poor prognostic sign\textsuperscript{107–112}, as it relates to tumour burden. In general, the prognostic accuracy of both CEA and CA 19-9 is rather low and non-specific for raised values\textsuperscript{110–112}, and the best information may be having a value within the normal range, which is usually associated with a good prognosis. Other tumour markers, such as CA 242\textsuperscript{112} and thymidine kinase\textsuperscript{111}, have been proposed as promising or better than CEA and CA 19-9, but are non-specific and require further validation. In patients considered for resection, with suspicious findings on CT or PET, an increased CA 19-9 level may suggest underlying occult disease and the need for an observational strategy rather than extended redo surgery. However, the role of tumour markers or other biomarkers needs to be assessed with prospective data in relation to optimal imaging to delineate further their role in decision-making.

**Outcome prediction and prognostic score**

A number of factors are associated with outcome in incidental gallbladder cancer. Among the most important is the ability to achieve an R0 resection, whereas both a higher T category and the presence of lymph node metastasis are strong predictors of poor survival\textsuperscript{40,113–115}. Several attempts at refining prognostication have been entertained, with a Gallbladder Cancer Predictive Risk (GBPR) score developed from a multicentre series of incidental gallbladder cancers\textsuperscript{41}. The GBPR score consists of four pathology-derived risk factors associated with either locoregional or disseminated disease according to risk groups (Table 3). In the original study, of the 262 patients with incidental gallbladder cancers, only 88 (33.6 per cent) had data on all four factors to allow for predictive use of the score. Even though the score helps to redistribute T1b cancers with higher risk based on additional poor prognostic factors, the validity of the score remains uncertain based on the low proportion of patients available for constructing the score. A single-centre study from Japan\textsuperscript{116} of 56 patients has validated the prognostic role of the GBPR score as being an independent factor for overall and recurrence-free survival. A valid and robust risk score may be useful in selecting patients for both redo surgery and adjuvant therapy.

**Adjuvant chemotherapy**

The role of adjuvant chemotherapy in gallbladder cancer is poorly documented, with data from series or trials grouping all types of biliary tract cancer together, based on large retrospective comparisons in registries or occasional multicentre experiences\textsuperscript{20,24–26,117–120}, as compiled in four meta-analyses\textsuperscript{20,24–26}. Overall, adjuvant chemotherapy seems to be associated with better survival for all biliary tract cancers\textsuperscript{20,25}, as well as in series of incidental gallbladder cancer\textsuperscript{15}, with gemcitabine being the drug of choice in the investigated studies. Since 2010, cisplatin and gemcitabine have been the preferred combination, based on results obtained in advanced biliary tract cancer\textsuperscript{121}. However, overall application is low (less than 30 per cent) and the overall treatment effect small\textsuperscript{122}. Application of adjuvant therapy has remained low in the population at risk, despite data suggesting a survival benefit\textsuperscript{123}. This may reflect a largely elderly and co-morbid population, but also reluctance to subject any patient with early-stage cancer (such as T1b or T2 with no node metastases) to chemotherapy when the effect is documented.

Table 3 Predictive risk score for gallbladder cancer

| Risk factor                  | Points |
|-----------------------------|--------|
| T category                  |        |
| Tis/T1a                     | 0      |
| T1b                         | 1      |
| T2                          | 2      |
| T3/T4                       | 3      |
| Grade (differentiation)     |        |
| G1 (well)                   | 1      |
| G2 (moderate)               | 2      |
| G3 (poor)                   | 3      |
| Lymphovascular infiltration |        |
| No                          | 1      |
| Yes                         | 2      |
| Perineural infiltration     |        |
| No                          | 1      |
| Yes                         | 2      |
| Residual disease (%)        |        |
| Low                         | 3–5    |
| Intermediate                | 6–7    |
| High                        | 8–10   |

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to be marginal. Thus, it will be paramount to define the appropriate risk groups who should be good candidates with the greatest benefits for receiving adjuvant therapy.

In a registry study, with patients matched for characteristics, median survival was longer for extended cholecystectomy with adjuvant therapy (23-3 months) than for simple cholecystectomy with adjuvant therapy (16-4 months), and was significantly longer than either simple (12-4 months) or extended (10-7 months) cholecystectomy alone. Notably, in the registry only about one-third of patients ever received chemotherapy, and almost 90 per cent of resections were simple cholecystectomies. The authors proposed that adjuvant chemotherapy could be considered rather than extended resection in some patients. However, there is a bias towards chemotherapy in younger, more fit patients with higher likelihood of both T3 and node-positive cancers, and having extended resections.

Of note, adjuvant chemoradiotherapy was not associated with improved survival in a collective review, but had higher toxicity. A registry series proposed better survival for all patients with reresected cancers who received adjuvant radiotherapy, but not for patients who had chemotherapy alone. Another study could not confirm a benefit for radiotherapy. Radiotherapy is controversial as it is performed (and, thus, considered) only in some centres. There are no randomized trials for radiotherapy as adjuvant therapy. A systematic review reported favourable survival for patients who had radiotherapy after radical surgery, whereas receiving radiotherapy was a negative prognostic factor in another registry study.

The heterogeneity in the data should be noted: the mix of symptomatic and incidental cancers; gallbladder and other extrahaepatic cholangiocarcinomas, studies also including intrahepatic cholangiocarcinomas; the type and duration of chemotherapy used in various time intervals; and a selection bias for both surgery and adjuvant therapy in most of the reports. As the concept of neoadjuvant therapy is not possible, by definition, in incidental gallbladder cancers, and symptomatic cancers may have a different inherent biology, findings from the present data would need to be extrapolated. Consequently, guidelines and consensus statements are vague, but recommend adjuvant chemotherapy for most patients after resection, in particular those with any T2 disease and above with N1 disease, given the high risk of recurrence and nodal dissemination. A French multicentre study found no difference in recurrence-free survival between GEMOX (gemcitabine–oxaliplatin) and observation alone in biliary tract cancers, based on data presented in abstract form only. The randomized BILCAP trial demonstrated better survival for capecitabine after radical surgery of biliary tract cancer, but has so far been presented only in abstract form (ASCO 2017). Gallbladder cancers made up but a subset of the BILCAP population (about one-third of all biliary tract cancers), and published results are awaited from this trial. Based on the preliminary reported results from BILCAP, another ongoing European trial (ACTICCA-1130), which compares cisplatin–gemcitabine combination with observation alone after radical surgery, may possibly change the trial protocol to test that combination of cisplatin–gemcitabine versus capecitabine, rather than a simple ‘observational’ arm. The optimal regimen or selection of subgroups for adjuvant chemotherapy is currently not known based on available data. It is hoped that more targeted therapy based on genetic aberrations may improve both patient selection and treatment effect in the future.

**Discussion**

The present review of management of incidental gallbladder cancer highlights the contemporary lack of good data on which to base current decision-making and planning for the individual patient. A predominant belief in resection for most, if not all, patients seems to be based on a mechanistic approach that contributes to staging, but with poor data to suggest effect on survival. An increasing body of data, as well as the current TNM staging system, increasingly emphasizes biology as the determinant of survival. Thus, defining the biology of gallbladder cancer from improved clinical, imaging and biomarker definitions should lead to better clinical decision-making in the future. A limitation of this review is evident in the lack of high-quality data. Although large registry data point to trends, these bear the risk of resembling outdated or selective practice and not using contemporary staging standards. Thus, there is a need for improved data quality from prospective observational cohorts, imaging studies, oncogenomic profiling studies and novel therapeutics.

With a relatively low incidence and overall poor outcome in muscle-invasive stages, collaborative efforts are needed to increase numbers and speed of recruitment of patients to studies, and thus come to meaningful results and increase knowledge in incidental gallbladder cancers. Networks across regional or national registries and larger international trials are needed to answer several treatment questions in incidental gallbladder cancer. Specifically, the timing and extent of resection in subgroups need to be defined better. The role and timing of imaging in directing surgery or sparing patients from intervention must also be addressed, particularly with more widespread
availability of PET scanners. The role of adjuvant therapy also needs to be investigated in better detail and for sub-groups. As the molecular mechanisms are explored and new targets become available, these may help improve stratified medicine approaches and the prognosis of patients with gallbladder cancer.

Disclosure
The authors declare no conflict of interest.

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