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REVIEW ARTICLE

Timing of revision surgery for incidental gallbladder cancer: a systematic review and individual patient data meta-analysis

B. Selvakumar[1,#], Shraddha Patkar[2,#], Phani K. Nekarakanti[3], Muhammed A. Shamim[4], Shaleen Agarwal[5], Paleswan J. Lakhey[6], Orlando Jorge M. Torres[7], Mahesh Goel[9] & Vinay K. Kapoor[8]

[1]Department of Surgical Gastroenterology, All India Institute of Medical Sciences (AIIMS), Jodhpur, India, [2]Department of GI & HPB Surgical Oncology, Tata Memorial Hospital (TMH), Mumbai, India and Homi Bhabha National Institute (HBNI), Mumbai, India, [3]Department of Surgical Gastroenterology, Nizams Institute of Medical Sciences (NIMS), Hyderabad, India, [4]Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Jodhpur, India, [5]Liver Transplant and HPB Services, Amrita Hospital, Faridabad, India, [6]Department of Surgical Gastroenterology, Maharajgunj Medical Campus, Tribhuvan University Teaching Hospital (TUTH), Institute of Medicine, Kathmandu, Nepal, [7]Department of Hepatopancreatobiliary and Transplant Surgery, Federal University of Maranhão, São Luís, Brazil, [8]Mahatma Gandhi Medical College and Hospital (MGMCH), Jaipur, India and Mahatma Gandhi University of Medical Sciences & Technology (MGUMST), Jaipur, India, and [9]Department of GI & HPB Surgical Oncology, Tata Memorial Hospital (TMH), Mumbai, India

Abstract

Aims: We conducted this systematic review to answer the questions: a. what are the timing categories for revision surgery (RS) in incidental gallbladder cancer (iGBC)? b. which RS timing achieves better oncological outcomes?

Methods: We performed literature search in 4 databases (PubMed, Scopus, Google Scholar and Cochrane Reviews) till 10th October 2025 and included studies which reported patient outcomes based on RS timing. Study characteristics, timing category definitions and RS outcomes were collected. (Study protocol PROSPERO ID CRD42023453990).

Results: Twelve retrospective studies were included, with 2067 iGBC patients (566 males and 1346 females). On the 'Joanna Briggs Institute' (JBI) tool, most studies scored a 'Yes' to 7–8 out of 10 questions. There was no consensus on the definitions of 'early', 'intermediate' and 'delayed' timings for RS. Successful RS, perioperative morbidity, R0 resection were similar. On individual patient data meta-analysis, there was no difference in overall survival between RS at '</ = 4 weeks' and '>4 weeks' [hazard ratio: 1.29, 95 % CI: 0.79–2.10].

Conclusion: There was no consensus on the definitions of timing categories and optimum timing for RS in iGBC. Definitions of timing categories need to be standardised and future studies based on these categories may identify the ideal timing of RS in iGBC.

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Correspondence

Vinay K Kapoor, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India. E-mail: vkkapoor.india@gmail.com

Introduction

Gallbladder cancer (GBC) is the commonest biliary tract cancer (BTC) worldwide.[1] GBC carries one of the most dismal prognoses among the abdominal visceral cancers. The prognosis depends on various factors such as tumour (T) stage, nodal (N) stage and margin status. GBC can be suspected either preoperatively or diagnosed incidentally on histopathological examination of the GB specimen removed by simple cholecystectomy performed for benign pathology such as gall stone disease - this is incidental GBC (iGBC). Revision surgery (RS), in the form of completion extended (radical) cholecystectomy (CEC), is recommended for all iGBC with stage pT1b-T4 disease in the absence of metastasis, but the timing of RS after the index simple cholecystectomy remains controversial.[2–4] The controversy lies in the identification of the appropriate time for RS by

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Joint first authors.

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balancing two factors - avoidance of acute postoperative inflammation and tumor biology to facilitate the conduct of a safe and successful RS.

Our aim to conduct this systematic review was to standardize the timing categories of RS in order to achieve optimum outcomes in iGBC as well as have uniformity in future research where outcomes in each category can be compared to get a fair idea as to which timing category of RS achieves optimal oncological outcomes. This may aid in clinical decision-making for a given iGBC patient and improve overall patient management. Hence, we conducted this systematic review of the published English literature and intended to answer the following two research questions:

a. what are the timing categories for RS?
b. which timing category of RS achieves better oncological outcomes?

Methods

Search strategy and selection criteria

This is a systematic review and meta-analysis with intent to include all clinical studies on iGBC that categorized patients based on the timing of RS and reported patient outcomes between the various timing categories of conduct of RS. Randomised controlled trials, original observational case—control or cohort studies and case series with more than 10 cases in English language were included while narrative reviews, systematic reviews, invited commentaries, case reports, case series with less than 10 patients and book chapters were excluded.

A literature search was performed in 4 databases (PubMed, Scopus, Google Scholar and Cochrane Reviews) for clinical studies published till 10th October 2025. The search terms included 'incidental gallbladder cancer', 'reoperation' or 're-resection', 'revision surgery', and 'time' or 'timing' (detailed syntax and search strategy in Supplementary data). The reference list of published articles concerning RS and timing was manually searched for further relevant publications. The search was limited to English language and was performed by two authors (PKN and BS) independently with any controversies resolved through a consensus-based approach with other authors (SA, PJL, OJMT and MG). This systematic review was reported in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2020 and the MOOSE guidelines[5,6,7]. The study protocol was registered with the international prospective register of systematic reviews (PROSPERO) vide registration number CRD42023453990 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=453990).

Data analysis

The included studies were assessed for outcomes of interest as per the patients/population, intervention, comparator/reference standard, outcomes and timeline (PICOT) framework (details in Supplementary data). Studies were included irrespective of the method of RS — open, laparoscopic or robotic and the use of

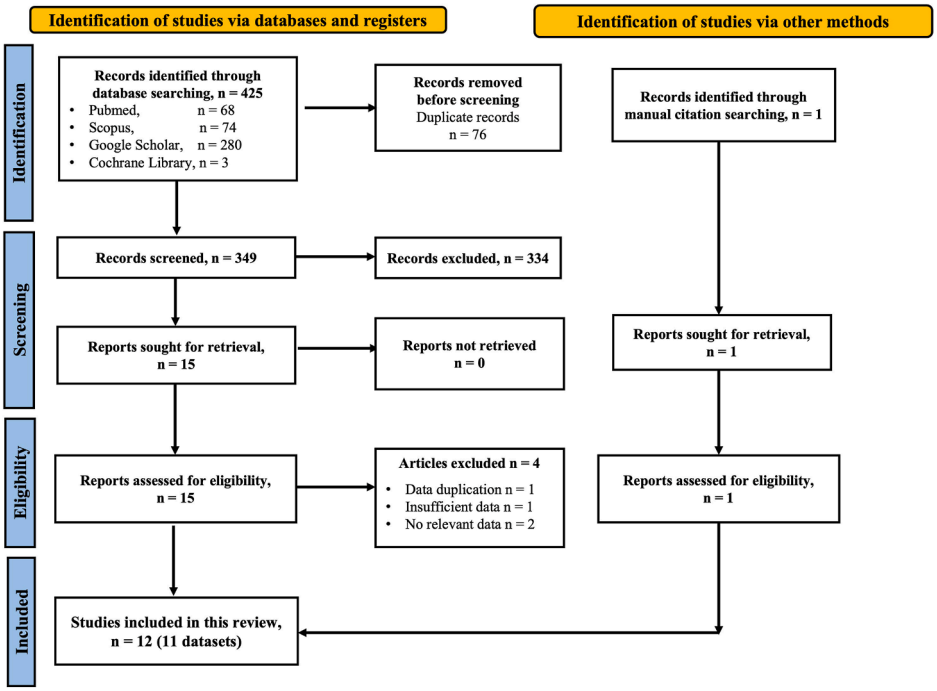

Figure 1 PRISMA chart for this review.

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Table 1 Definitions of timing of revision surgery (RS) for iGBC

Sl. No.	Author, Year, Country (Ref)	Study type	Sample size	Age and M:F ratio[a]	T-stage	Timing Categories	Conclusions/Remarks by authors
East Asian studies							
1	Toyonaga T 2003 Japan [14]	Retrospective	43	63 (47–76) 16:27	T2 - 43	I: <2 weeks II: ≥2 weeks	No difference in OS[a] between both timing categories
2	Du J 2018 China [17]	Retrospective	80	NR[a] 27:53	T1/T2 – 61 T3/T4 - 19	A: <2 weeks B: 2–4 weeks C: >4 weeks	Operative morbidity similar between all groups A had better 1-, 3- and 5-yearr OS than other two groups. B and C had similar OS
3	He S 2020 China [19]	Retrospective	89	59 (39–76)[b] 6:35	T1b – 1[b] T2 - 33 T3 - 7	Simultaneous: Intra-operative radical resection after frozen section + ve iGBC Salvage: re-resection A: <2 weeks B: 2–4 weeks C: >4 weeks	Salvage B group had superior OS; all other groups had similar OS
4	Peng DZ 2022 China [23]	Retrospective	65	NR 23:42	T1b – 10 T2 - 42 T3 - 13	A: <2 weeks B: 2–4 weeks C: >4 weeks	Similar OS, DFS[a] in the 3 groups
5	Cao J 2023 China [24]	Retrospective	49	NR 16:33	T1b – 5 T2 - 44	Time to treatment (TTT): Short: <7 days Long: ≥7 days	No difference in perioperative outcomes or OS, DFS
South Asian studies							
6	Rahul R 2021, 22 India [20,22]	Retrospective Cohort	91	53 (30–77) 24:67	T1b – 10 T2 - 55 T3 - 26	Early: <4 weeks Intermediate: 4–12 weeks Late: >12 weeks	Late – less curative resection. Early and intermediate - similar curative resection Early – non-significant trend towards better survival
7	Patkar S 2021 India [21]	Retrospective	382	NR 103:279	T1b - 56 T2 – 274 T3 - 32	A: <6 weeks B: 6–10 weeks C: 10–14 weeks D: >14 weeks	After matching for T-stage - C had best OS, DFS
Western studies							
8	Ausania F 2013 UK [15]	Retrospective	49	64 (48–85) 20:29	T2 – 38 T3 - 11	Delayed: 12 weeks	Re-staging/re-surgery >12 weeks – selects good biology iGBC for revisional surgery Median OS – 20.4 months
9	Ethun CG 2017 USA [16]	Retrospective cohort	207	NR 77:130	T1b – 16[b] T2 - 96 T3/T4 - 70	Early: <4 weeks Intermediate: 4–8 weeks Late: >8 weeks	Intermediate group had better OS than other groups
10	Vega EA 2019 Multi-center [18]	Retrospective	118	60 (32–81) 32:82	T2 - 118	I: <60 days II: >/ = 60 days	Similar morbidity and recurrence rates

(*continued on next page*)

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Table 1 (*continued*)

Sl. No.	Author, Year, Country (Ref)	Study type	Sample size	Age and M:F ratio[a]	T-stage	Timing Categories	Conclusions/Remarks by authors
11	Shah S 2023 USA [25]	National cancer DataBase (NCDB) Retrospective	791 T1b-T3	NR 222:569	T1b – 53 T2 – 373 T3 – 265 Tx - 100	I: 0–4 weeks II: 5–8 weeks III: 9–12 weeks IV: >12 weeks	Re-resection after 4 weeks is of benefit.
Total			2067	30–85 M:F 566:1346 (1:2.4)	T1b – 151 (8 %) T2 -1116 (60 %) T1/T2 – 61 (3 %) T3 – 354 (19 %) T3/T4 – 89 (5 %) Tx – 100 (5 %)		

[a] Age in years expressed as median (range); DFS – disease free survival; M:F – male:female ratio; NR – not reported; OS – overall survival; RS revision surgery.
[b] Details provided for only those patients who underwent curative resection at RS.

neoadjuvant therapy (NAT), if any, prior to RS. Data including author, country, year, study design, study duration, sample size, patient demography and the pathological tumor (pT) stage of the iGBC before RS was collected from the included studies. For the first research question — details about the different categories used for the conduct of RS and the remarks by the respective authors justifying the categories were noted. For the second research question, the following outcomes between the different time categories of RS were noted — number of patients in each time category, number who underwent successful RS, peri-operative morbidity, patients with residual disease and margin-negative (R0) resection status in the final histopathology after RS, median overall survival (OS) and median disease-free survival (DFS). 'Successful RS' in this study was defined as the number of patients who were operated with a curative intent and successfully underwent a radical RS (without metastases). In case a few outcomes were missing in the included studies, the corresponding authors were contacted via email and if they responded, the additional data was recorded. Data from studies was collected independently by two authors (BS and PKN) and verified by a third author (SP).

The qualitative assessment of the included studies was done with the 'Joanna Briggs Institute' (JBI) critical appraisal tool.[8] This tool assesses the risk of bias using a set of 8—10 questions about definition of the condition, patient selection, reporting of data, follow-up and use of appropriate statistical tests. For a given study, each question is graded as 'Yes', 'No', 'Unclear' or 'Not applicable'. It does not provide a summary score for the studies, as each question looks at a specific aspect of methodology and the individual questions can't be taken to have equal weightage. Studies which have 'Yes' to most questions are considered to be of 'high quality' and those which have 'No' to most questions are considered to be of 'Low quality'. The qualitative assessment of the included studies was done independently by two authors (BS and PKN) and any discrepancies were resolved through consensus with the senior authors (SP and VKK).

We summarized our findings regarding peri-operative and survival outcomes for the various timing categories of RS in iGBC. We did a one-stage individual patient data meta-analysis (IPDMA) as it adjusts for both in-trial and between-trial heterogeneity and is considered superior.[9,10] We used median hazard ratio (MHR) for multi-level survival analysis (time-to-event), as different studies from different settings exhibit heterogeneity due to varying baseline hazards and unmeasured covariates.[11] In the context of this study, MHR gives an idea of median change of HR for OS in iGBC timing categories due to early resection (compared to later resection), which may be different in the included studies. We also estimated the restricted mean survival time difference (RMSTD) which expresses the gain or loss of event-free survival at varying lengths of follow-up in one group as compared to another. As compared to HR, RMSTD is considered to give a more clinically intuitive interpretation with higher statistical reliability for time-dependent effect estimation.[12,13] The R software was used for meta-analysis (https://www.r-project.org).

Results

Our search strategy yielded 425 records with one additional record identified through a manual citation search. After removing 76 duplicate records, a further 334 records were found irrelevant based on title and abstract screening and were excluded. Thus, 16 studies fulfilled the eligibility criteria and were sought for retrieval, out of which four studies were excluded and twelve full papers[14—25] were included in this review as these met our PICOT criteria (see Supplementary data). Two papers reported on different outcomes from the same dataset and hence were combined as a single study for this review[20,22] (see PRISMA Diagram in Fig. 1). The study characteristics are summarized according to our research questions, in Tables 1 and 2.

Of the twelve studies, four studies were from China, three from India, two from the United States of America (USA), one

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Table 2 Outcome of revision surgery (RS) in iGBC based on timing

Sl No	Author, Year, Country (Ref)	Sample size	iGBC[b] Timing Categories – Break-up	Successful RS	Morbidity	R0 resection status[b]	Locoregional residual disease	Median OS[b] (months)	Median DFS[b] (months)
East Asian studies									
1	Toyonaga T 2003 [14]	43	I: <2 weeks II: >/ = 2 weeks	Overall 18 (42 %)	NR	NR	NR	5 year OS −57 % 5 year OS - 24 %	NR
2	Du J[a] 2018 [17]	80	<2 weeks - 37 2–4 weeks - 26 >4 weeks - 17	37 (100 %) 26 (100 %) 17 (100 %)	NR	NR	NR	86.1 26.0 27.4	NR
3	He S 2020 [19]	89	A < 2 weeks - 11 B 2–4 weeks - 19 C > 4 weeks–11	Overall 42 (47 %)	NR	41 (98 %)	NR	B Had better OS	NR
4	Peng[a] 2022 [23]	65	<2 weeks - 22 2–4 weeks - 24 >4 weeks–19	22 (100 %) 24 (100 %) 19 (100 %)	NR	NR	6 (27 %) 9 (38 %) 9 (47 %)	Similar	Similar
5	Cao J[a] 2023 [24]	49	<7 d - 28 >/ = 7 d - 21	28 (100 %) 21 (100 %)	NR	NR	28 (100 %) 21 (100 %)	Similar	Similar
South Asian studies									
6	Rahul R 2021& 2022 [20,22]	91	<4 weeks–22 4–12 weeks - 48 >12 weeks - 21	11 (50 %) 31 (65 %) 6 (29 %)	1 (9 %)[b] 2 (7 %) 0 (0 %)	11 (100 %) 29 (94 %) 5 (83 %)	5 (46 %) 12 (39 %) 3 (50 %)	104.5 84.7 75.4	101.9 82.5 73.5
7	Patkar S 2021 [21]	382	<6 weeks - 76 6–10 weeks -127 10–14 weeks - 86 >14 weeks - 93	60 (79 %) 107 (84 %) 73 (85 %) 74 (80 %)	NR	59 (98 %) 106 (99 %) 69 (95 %) 72 (97 %)	Overall 82 (26 %)	Not reached 58 Not reached 66	21 22 Not reached 42
Western studies									
8	Ausania F 2013 [15]	49	>12 weeks–49 (100 %)	24 (49 %)	5 (21 %)	18 (75 %)	10/24 (42 %)	20.4	NR
9	Ethun CG 2017 [16]	207	<4 weeks–25 (12 %) 4–8 weeks – 91 (44 %) >8 weeks–91 (44 %)	22 (88 %) 74 (81 %) 72 (79 %)	3 (13 %) 8 (9 %) 16 (18 %)	19 (76 %) 72 (79 %) 69 (76 %)	14/25 (56 %) 42/91 (46 %) 42/91 (46 %)	17.4 40.4 22.4	NR
10	Vega EA[a] 2019 [18]	118	<60 days - 50 >/ = 60 days - 68	50 (100 %) 68 (100 %)	10 (20 %) 9 (13 %)	45 (90 %) 62 (91 %)	NR	NR	NR
11	Shah S 2023 [25]	791	0–4 weeks - NR 5–8 weeks - NR 9–12 weeks - NR >12 weeks - NR	NR	NR	NR	NR	22.7 44.1 44.3 51.1	NR

[a] These studies included only those iGBC patients who had undergone successful RS with curative intent.
[b] DFS – disease-free survival, iGBC – incidental gallbladder cancer, NR – not reported; OS – overall survival, RS – revisional surgery, R0 – margin negative resection.

from the United Kingdom (UK), one from Japan and one was a multi-center study involving Chile and USA. Overall, there were five studies from East Asia (China and Japan), four from the West (Chile, UK and USA) and three studies from South Asia (India). All the included studies were retrospective in nature, with majority being case series. There was a total of 2067 iGBC patients from T1b to T4 stages, who were considered for or successfully underwent RS. The age of these patients ranged from 30 to 85 years with a male:female ratio of 1:2.4. The T stage of majority of iGBC cases who underwent RS in the included studies was T2 (60 %) followed by T3 (19 %).

The qualitative assessment of the included studies, by the JBI critical appraisal tool, is presented in Fig. 2. Only one dataset scored 'Yes' to all the questions[20,22] while one study scored 'Yes' to only 4 questions.[25] Majority of the studies scored 'Yes' to about 7—8 questions.

Timing categories and RS

Early timing for RS

East Asian studies considered <2 weeks as early timing for RS[14,17,19,23]; one study even considered <7 days as early timing for RS.[24] Indian and Western studies considered <4 weeks[16,20,22,25] or up to 6 weeks as early timing for RS.[21] Thus, the definition of 'early' timing to RS varied from less than 1 week to 6 weeks among the published studies.

Intermediate timing for RS

While East Asian studies used 2—4 weeks' time for this category,[16,18,22] Indian studies used 4—12 weeks or 6—14 weeks[20—22]

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Study	*Joanna Briggs Institute critical appraisal tool*										No. of questions answered 'Yes'
	Q1*	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	
Toyonaga 2003 (14)	+	+	?	+	+	+	+	?	+	+	8
Ausania 2013 (15)	+	+	+	+	?	-	?	+	+	+	7
Ethun 2017 (16)	+	?	+	+	+	+	+	+	+	+	9
Du 2018 (17)	+	+	+	+	-	+	+	?	+	+	8
Vega 2019 (18)	+	+	+	+	-	+	+	+	+	+	9
He 2020 (19)	+	+	+	+	-	-	-	+	+	+	7
Rahul 2021 (20)	+	+	+	+	+	+	+	+	+	+	10
Patkar 2021 (21)	+	+	?	?	-	+	+	+	+	+	7
Rahul 2022 (22)	+	+	+	+	+	+	+	+	+	+	10
Peng 2022 (23)	+	+	+	?	-	+	+	+	+	+	7
Cao 2023 (24)	+	?	?	+	-	+	+	+	+	+	7
Shah 2023 (25)	?	-	-	+	+	-	-	+	-	+	4

+ Yes - No ? Unclear *Q - Question

Figure 2 Qualitative assessment of the included studies.

while Western studies used 4–8 weeks or 5–12 weeks' time for this category.[16,25] Thus, intermediate timing category had the most variation, ranging from 2 to 14 weeks. Also, irrespective of the geographical differences, this was the category where the majority (356/724, 49 %)[16,17,20–23] of iGBC patients underwent RS.

Delayed timing for RS

While most East Asian studies considered >4 weeks' time for RS as delayed,[17,19,23] others considered even a delay of 1 week as 'late/delayed'.[24] Indian studies considered >12–14 weeks as 'delayed',[20–22] while Western studies considered > 8–12 weeks as delayed timing for RS.[15,16,18,25]

Thus, there was no consensus on the definitions of 'early', 'intermediate' and 'delayed' timings for RS in the published studies. However, there was a trend towards early RS in East Asian centers as most (158/194, 81 %)[17,23,24] patients were operated <4 weeks of index cholecystectomy/referral. In India and the West, there was a trend for RS in 'intermediate' or 'delayed' timing categories. The included studies had variable reporting of the various perioperative outcomes of interest as seen from Table 2. Regarding oncological outcomes, we pooled data from studies which reported survival outcomes at a '4-week cut-off', as this was the cut-off described in most studies across East and West.[16,17,19,20,22,23,25]

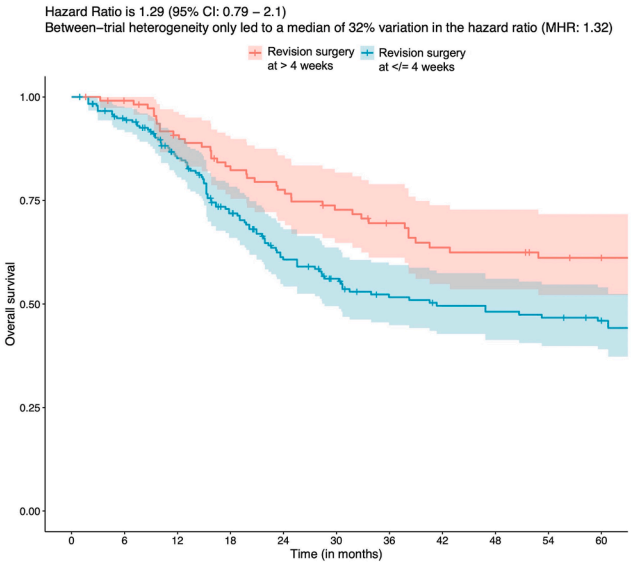

Figure 3 Individual patient data meta-analysis (IPDMA) of overall survival (OS) in incidental gallbladder cancer (iGBC) based on timing of revision surgery (RS).

Timing of RS and outcomes

Successful RS

There was variability in the percentage of iGBC patients undergoing successful RS. One Indian study reported 29–65 % iGBC patients undergoing RS with a lower rate of successful RS in those operated >12 weeks.[20,22] However, others reported RS rates between 79 and 88 % with similar successful RS rates in all timing categories.[16,21] Three other studies reported overall 42–49 % rate of successful RS; however, the RS rates in the various timing categories were not reported.[14,15,19] Four studies included only those iGBC patients who underwent successful RS,[17,18,23,24] hence overall RS rates could not be calculated (Table 2).

Perioperative outcomes

Perioperative morbidity of successful RS was between 0 and 21 % with R0 resection rates of 76–100 % and locoregional residual disease rates between 26 and 56 %. Perioperative morbidity, R0 resection rates and percentage of patients with

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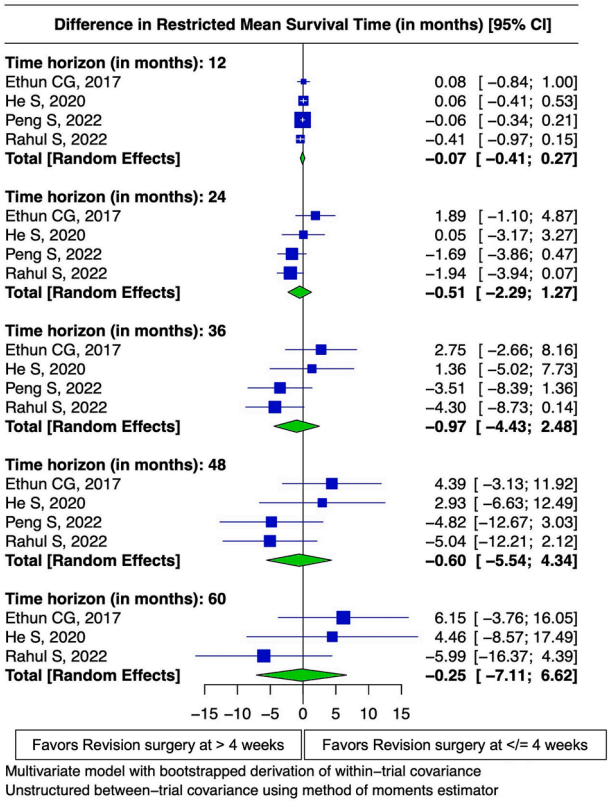

Figure 4 Forrest plot of overall survival (OS) by restricted mean survival time difference (RMSTD) analysis.

locoregional residual disease were reported similar between various timing categories (Table 2).

Long−term outcomes

Regarding long-term oncological outcomes of RS for iGBC, there was controversy among the conclusions in the published studies. Three studies (two from China, one from India) reported similar OS and DFS after RS in iGBC in various timing categories.[20,22−24] Three East Asian studies reported better OS for RS < 2 weeks or 2−4 weeks and thus recommended early RS.[14,17,19] Western studies reported better OS for RS > 4 weeks or 4−8 weeks and thus recommended RS after 4 weeks.[16,25] One Western study, which followed delayed RS > 12 weeks as a policy, reported a low OS of 20.4 months but argued that this approach selects good biology patients for RS.[15] Assessment of OS and DFS in the various timing categories was affected by many confounders. A varying proportion of iGBC patients, especially those who had a delay in RS or those with residual disease detected on imaging, were given neoadjuvant chemotherapy in the studies. A varying proportion of others, after successful RS, received adjuvant chemotherapy with or without radiotherapy. Both neoadjuvant and adjuvant treatments affect both OS and DFS, the extent of which was not uniformly reported in the studies and hence could not be assessed in this review.

As very few studies had reported DFS (see Table 2), we conducted an IPDMA only for OS at a 4-week cut-off. We excluded studies which did not use this cut-off[14,15,18,21,24] or which did not provide the number of participants in the Kaplan−Meier curve.[17,25] Overall, this yielded 404 iGBC patients who underwent RS with 123 patients at '</ = 4 weeks (early)' vs 281 patients at '> 4 weeks (intermediate/delayed)' timing categories from 4 datasets.[16,19,20,22,23] We limited the duration till 60 months, as there were very few events after this time. Although the OS curves visually showed consistent separation favoring the '> 4 weeks (intermediate/delayed)' timing category, it was not statistically better with an HR of 1.29 (95 % confidence interval, CI − 0.79−2.10) and an MHR of 1.32 (Fig. 3). In the RMSTD analysis, the actual survival gained in the '> 4 weeks (intermediate/delayed)' timing category at 2, 3 and 5 years was about 0.5, 1.0 and 0.25 months respectively, which was also not statistically significant and is unlikely to be clinically relevant (Fig. 4).

There were many lacunae in the included studies while assessing long-term oncological outcomes. Many important prognostic factors determine the long-term survival in iGBC like perforation of GB and bile spill during index cholecystectomy, whether the index cholecystectomy was open or laparoscopic, whether the GB specimen was retrieved in an endobag, whether port-sites were excised during RS etc. Almost all studies failed to report these factors based on the various timing categories of RS, thus confounding our interpretation of survival outcomes in the various RS timing categories.

Discussion

GBC is an aggressive malignancy with poor prognosis. Another reason for poor outcomes is its non-specific presenting symptoms which may lead to low clinical suspicion, delayed referral and diagnosis at an advanced stage. Thus, about half of the GBCs are mis-diagnosed at initial presentation as benign conditions affecting the GB like gallstone disease, acute cholecystitis, GB polyp, Mirizzi syndrome or xantho-granulomatous cholecystitis (XGC).[2,26] These patients undergo simple cholecystectomy usually by general surgeons at peripheral centers, without surgical awareness about oncological principles and GB perforation with bile spill and/or a potential tumor capsule breach, and then are diagnosed as iGBC on histopathological examination of the GB specimen. Despite this, iGBC tends to be diagnosed at earlier stages and has a better prognosis than non-iGBC.[26,27] For iGBC stages above pT1a, there is a need for RS in the form of CEC which entails sampling of inter aorto-caval lymph nodes, resection of GB liver bed with an intent to achieve negative margins, regional lymphadenectomy, and excision of the cystic duct stump with optional addition of extrahepatic biliary excision if the stump is positive for cancer on frozen section.[2,28−31] RS is necessary for various reasons − radical clearance of the residual loco-regional disease in,

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accurate disease staging and for prognosis. A significant proportion of iGBC patients may have occult metastases in form of peritoneal or omental metastases or metastases in non-regional lymph nodes such as interaortocaval/paraaortic regions, which while undetected on preoperative imaging, becomes evident during RS and changes the intent of treatment from curative to palliative. That is why in most studies in this review, the proportion of patients who underwent successful RS is <100 %.

While the need and indications of RS are well established and accepted, the timing of RS varies widely across the globe and depends on various factors — awareness of the primary surgeon regarding GBC, timing of referral to a hepato-biliary or oncology center, complications of the index simple cholecystectomy like bile leak, sepsis etc, and patient load/waitlist at the referral center performing RS. In this systematic review, we found that there was no consensus about the definitions of different timing categories of RS in the published literature and there was a difference in perceptions of 'early' and 'delayed' timing between the East and the West. Individual authors have chosen the timing categories of RS arbitrarily without a clear justification for the cut-offs. Hence, we could not do any meaningful meta-analysis to determine which timing of RS achieves superior post-operative outcomes and/or long-term survival in iGBC patients.

To overcome this, we propose the following definitions for the various timing categories of RS —

A. 'Early'— RS within 4 weeks of the index simple cholecystectomy, likely in post-operative inflammed bed, possibly with immature adhesions, bleeding and increased surgical difficulty.
B. 'Intermediate'— RS done from 5 to 12 weeks of the index simple cholecystectomy, after healing of the post-operative bed with mature adhesions but not very late. This window is probably the most practicable timing globally, given the logistics in many centers.
C 'Delayed'— RS done beyond 12 weeks of the index simple cholecystectomy; GBC being an aggressive disease, would be expected to progress by 12 weeks. Successful RS in this timing may indicate good tumor biology even if residual disease is found in the final specimen.

These definitions for the timing categories for RS should be validated by a Delphi consensus among the experts from high-volume centers treating GBC globally. Once validated, future studies should report the timing of RS using these definitions; this would help in standardization and comparability of survival outcomes after RS for iGBC across the world.

In this review, we also found that there was no consensus regarding the recommended ideal timing for RS. Practically, if the cholecystectomy is done at a peripheral center, it usually takes about 4 weeks' time for the biopsy of the index simple cholecystectomy specimen to be processed, reviewed by the primary surgeon, referral and the patient to reach a higher center for RS. We found that East Asian centers tend to do RS early (within 4 weeks), based on their national guidelines[32–34] while the Western centers tend to do RS in a delayed fashion (beyond 8 weeks). The central controversy regarding the ideal timing of RS for iGBC is a debate between extirpation of the residual disease, if any, at the earliest in order to achieve R0 resection status (early surgery) versus assessment of the tumor biology and offering surgery to only selected patients with favorable biology who would benefit from it (delayed surgery). Logically, operating too early may lead to a difficult surgery in an inflamed post-operative field while operating late may lead to progression of the disease to incurable (locally unresectable or metastatic) stages. However, the current review found no differences in the post-operative morbidity among patients who underwent RS in the various timing categories. Although it sounds intuitive to intervene as early as possible, there is no strong evidence to support this argument as evident by heterogeneity of the results in studies dealing with this issue.[16,19,21,25,28,35] The IPDMA done in the current study also showed no difference in OS in iGBC for RS performed between '</ = 4 weeks (early)' and '> 4 weeks (intermediate/delayed) timing after index cholecystectomy.

Not only the of timing of referral and execution of RS, but intraoperative events of the index simple cholecystectomy and tumor biology based on the histopathological examination of the GB specimen also must be taken into consideration to appropriately select the optimum timing of RS. Perforation of the GB and bile spill during the index simple cholecystectomy is another important poor prognostic factor and rushing with early surgery in this setting may not improve outcomes.[36,37] Residual disease, either in the liver bed or in the loco-regional lymph nodes either at imaging or at the time of RS adversely impacts long term outcomes in iGBC.[31,38] Higher T-stage (T2b-T4) is another adverse factor in iGBC due to the high chances of tumor capsule breach and tumor spill during the index simple cholecystectomy.[39,40] Buying more time before RS helps in accurate restaging using imaging in a field free of post-operative edema/fluid and allows for identification of residual disease and potentially unresectable/metastatic patients avoiding a futile second surgery.

Another debatable issue is the use of some form of neoadjuvant therapy (NAT), either chemotherapy or chemoradiotherapy, between the index simple cholecystectomy and RS in iGBC. Many retrospective studies have reported benefit of NAT in T2—T4 and N + GBC patients,[41–44] although there are no studies specifically on iGBC. While some authors say it is too early to recommend NAT in GBC,[45,46] others recommend a selective approach for using NAT in young good performance status iGBC patients with high risk features (>T2b, N+, residual disease on imaging, poor differentiation, bile spillage).[47] A recent systematic review proposes 3 or 4 cycles of preoperative neoadjuvant chemotherapy (using a gemcitabine-based regimen) after the index cholecystectomy and before RS in

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patients with iGBC who are at high risk of recurrence e.g. those who had intraoperative GB perforation and bile spill during the index simple cholecystectomy, those with advanced T stage (T3 or T4), node-positive disease, higher differentiation grade, or other histopathological features including perineural invasion, lymphovascular invasion, pericapsular invasion, or tumor budding. RS should be advised if there is no progression of the disease; those exhibiting disease progression may instead continue with definitive chemotherapy, without RS.[48] Thus for any iGBC patient receiving NAT, a waiting period of 12 weeks (for 3—4 cycles of chemotherapy followed by re-staging imaging) before RS may be prudent.

This systematic review has many limitations. All the included studies were retrospective case series with selection and reporting bias. There was lot of heterogeneity regarding the definitions of various timing categories for RS after the index simple cholecystectomy with wide practice variations between East and West. An international Delphi consensus among high-volume expert hepatobiliary centers treating GBC is required for the definitions of various timing categories of RS proposed by us. Based on the current evidence, it is still unclear which timing for RS is better for optimum long-term outcomes in iGBC. Ongoing phase III trials on NAT may throw further light regarding the appropriate regimen and benefits of NAT in iGBC.[49,50] A prospective international iGBC registry encompassing East Asian, South Asian and Western centers should be established with periodic analysis of the outcomes, to study geographic differences in iGBC management and establish the optimum timing for RS in iGBC for improved patient outcomes.

Conclusion

There is no consensus on the definitions of timing categories of RS among the published studies. Also, the current literature doesn't guide us regarding the optimum timing for RS in iGBC following index simple cholecystectomy. The definitions of timing categories of RS need to be standardised by international expert consensus for future studies. More prospective data, probably from an international registry, based on these standardised categories may identify the ideal timing of RS for achieving best outcomes in iGBC.

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Data sharing

All the data collected during this study is available with the corresponding author, upon reasonable request.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2025.12.017.

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