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Review Article

Prognostic influence of multiple hepatic lesions in resectable intrahepatic cholangiocarcinoma: A systematic review and meta-analysis

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ABSTRACT

Background: Presence of multiple hepatic lesions in intrahepatic cholangiocarcinoma (iCCA) is included in staging as a negative prognostic factor, but both prognostic value and therapeutic implications remain debated. The aim of this study was to systematically review the prognostic influence of multiple lesions on survival after resection for iCCA, with stratification for distribution and number of lesions.
Methods: Medline and Embase were systematically searched to identify records (2010–2021) reporting survival for patients undergoing primary resection for iCCA. Included were original articles reporting overall survival, with data on multiple lesions including tumour distribution (satellites/other multiple lesions) and/or number. For meta-analysis, the random effects model and inverse variance method were used. PRISMA 2020 guidelines were followed.
Results: Thirty-one studies were included for review. For meta-analysis, nine studies reporting data on the prognostic influence of satellite lesions (2737 patients) and six studies reporting data on multiple lesions other than satellites (1589 patients) were included. Satellite lesions (hazard ratio 1.89, 95% confidence interval 1.67–2.13) and multiple lesions other than satellites (hazard ratio 2.41, 95% confidence interval 1.72–3.37) were significant negative prognostic factors. Data stratified for tumour number, while limited, indicated increased risk per additional lesion.
Conclusion: Satellite lesions, as well as multiple lesions other than satellites, was a negative prognostic factor in resectable iCCA. Considering the prognostic impact, both tumour distribution and number of lesions should be evaluated together with other risk factors to allow risk stratification for iCCA patients with multiple lesions, rather than precluding resection for the entire patient group.

1. Introduction

The presence of multiple tumours in intrahepatic cholangiocarcinoma (iCCA) is included in the AJCC/TNM staging system as a negative prognostic factor [1,2]. However, the precise prognostic value of multiple hepatic lesions, and the implications for therapy decisions, remain debated [3–5].

While multiple iCCA has been considered a relative contraindication to surgery [6], long-term survival after resection of two or three lesions has been presented in large multicenter series [7,8]. In trials of locoregional oncological therapy, multiple hepatic lesions has been considered as an unresectability criteria [9–11]. With regard to oncological therapy in iCCA, advances have been made in immunotherapy as well as systemic and regional oncological therapy, but with a majority of studies in patients with advanced disease and with evidence from randomized controlled-trials for neoadjuvant therapy still lacking [12,13].

Recently, multiple lesions was proposed to represent a metastatic "M1a stage" of iCCA [3], this analysis however did not take into account number or distribution of lesions, nor did it stratify for other factors including nodal and resection status [4,5,14,15]. Other

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Abbreviations

AJCC	American Joint Committee on Cancer
AT	adjuvant therapy
AUS	Australia
BR	Brazil
CHI	China
CI	confidence interval
CIR	cirrhosis
CT	computerized tomography
df	degrees of freedom
ENSCCA	European Network for the Study of Cholangiocarcinoma
EUR	Europe
FR	France
FU	follow-up;
GER	Germany
G3	grade 3 (low differentiation)
HBV	hepatitis B virus
HCV	hepatitis C virus
hep,	hepatectomy
HR	hazard ratio
iCCA	intrahepatic cholangiocarcinoma
IV	inverse variance
IT	Italy
KOR	Korea
LND	lymph node dissection
md	median
MeSH	medical subject headings
MF	mass-forming
mm	millimeter
MRI	magnetic resonance imaging
mult	multiple
N1	lymph node metastasis
N.AM	North America
NAT	neoadjuvant therapy
No	number
NS	reported not significant
PAT	histopathology
Pts	patients
RAD	radiology
R1	microscopically tumour positive resection margin
R2	macroscopically tumour positive resection margin
Ref	reference
SE	standard error
SEER	Surveillance, Epidemiology, and End Results Program
TNM	TNM Classification of Malignant Tumours
TWN	Taiwan
US	United States
vs	versus

authors have proposed multiple lesions to represent a T4 tumour extension [16].

According to the College of American Pathologists and the 8th edition of the AJCC/TNM staging system, the term multiple lesions comprises tumours with satellite nodules as well as multiple separate lesions (intrahepatic metastases and/or multifocal primary cholangiocarcinomas) [1,17]. Discordant results have been reported regarding the prognostic impact of satellite lesions [18,19].

The aim of this study was therefore to systematically review survival outcomes after resection of multiple iCCA, stratified according to distribution and number of multiple lesions.

2. Materials and methods

The PRISMA 2020 guidelines were followed in reporting this review [20]. The PRISMA 2020 Checklist for the study is presented in Supplemental Table 1. The study was preregistered in the International prospective register of systematic reviews (PROSPERO, study ID: CRD42021244952) [21].

2.1. Literature search

A broad systematic search of MEDLINE (Ovid) (28 April 2021) and Embase (4 May 2021) was undertaken in consultancy with specialized librarians at the Karolinska Institutet university library. The database searches were repeated on 15 December 2021 before finalisation of study screening. Medical subject headings (MeSH) and synonyms for 'surgical resection', 'intrahepatic cholangiocarcinoma' and 'prognosis' were combined. The search was limited to reports in English, published 2010 and later. The search was not limited to records mentioning tumour multiplicity/multifocality or synonyms thereof in title or abstract. Duplicate records were removed before screening. The search strategy documentation is presented in Supplemental Tables 2 and 3

Two authors (HJ and CV) independently screened and assessed the identified records. Discrepancies were solved by discussion and input from a third reviewer (ES). The PRISMA 2020 flow diagram is presented in Fig. 1. Non-automated screening on title and abstract was performed in a reference manager for systematic reviews (Rayyan, Rayyan Systems Inc. Cambridge, MA, USA) [22]. Original research articles reporting prognosis after primary resection of iCCA were assessed for inclusion. Review articles reporting prognosis after primary resection of iCCA were also assessed for any additional records. Studies not reporting overall survival after primary resection of iCCA, or lacking comparative univariable survival data for patients with and without multiple tumours, were excluded, as were case reports/series of <10 patients. The outcome of interest was postoperative long-term survival and outcome data collected was limited to overall survival. Studies further stratifying survival outcomes depending on multiple tumour distribution (satellites i.e. nodules surrounding a primary lesion; or multiple lesions other than satellites) or for subgroups according to number of lesions were included for review, and assessed for inclusion in meta-analysis. For studies found to report overlapping cohorts, the largest or if similar cohort size the most recent, was chosen for comparison. When studies with overlapping cohorts reported additional data, they were included for comparison. For meta-analyses, no overlapping cohorts were included.

2.2. Data extraction

For included studies, the following demographic/clinicopathological characteristics were recorded: country/region, number of patients, time period and setting, staging modalities employed, any study specific limits to inclusion (e.g. only certain iCCA patient subgroups/iCCA subtypes), median follow-up time, median overall survival, median age, median tumour size, neoadjuvant/adjuvant therapy and proportion of patients with: lymph node metastasis (N1), microscopic tumour positive resection margin (R1), high tumour grade (poor tumour differentiation), mass-forming iCCA, underlying cirrhosis and viral hepatitis. The overall proportion of patients with multiple lesions as well as proportions with satellite

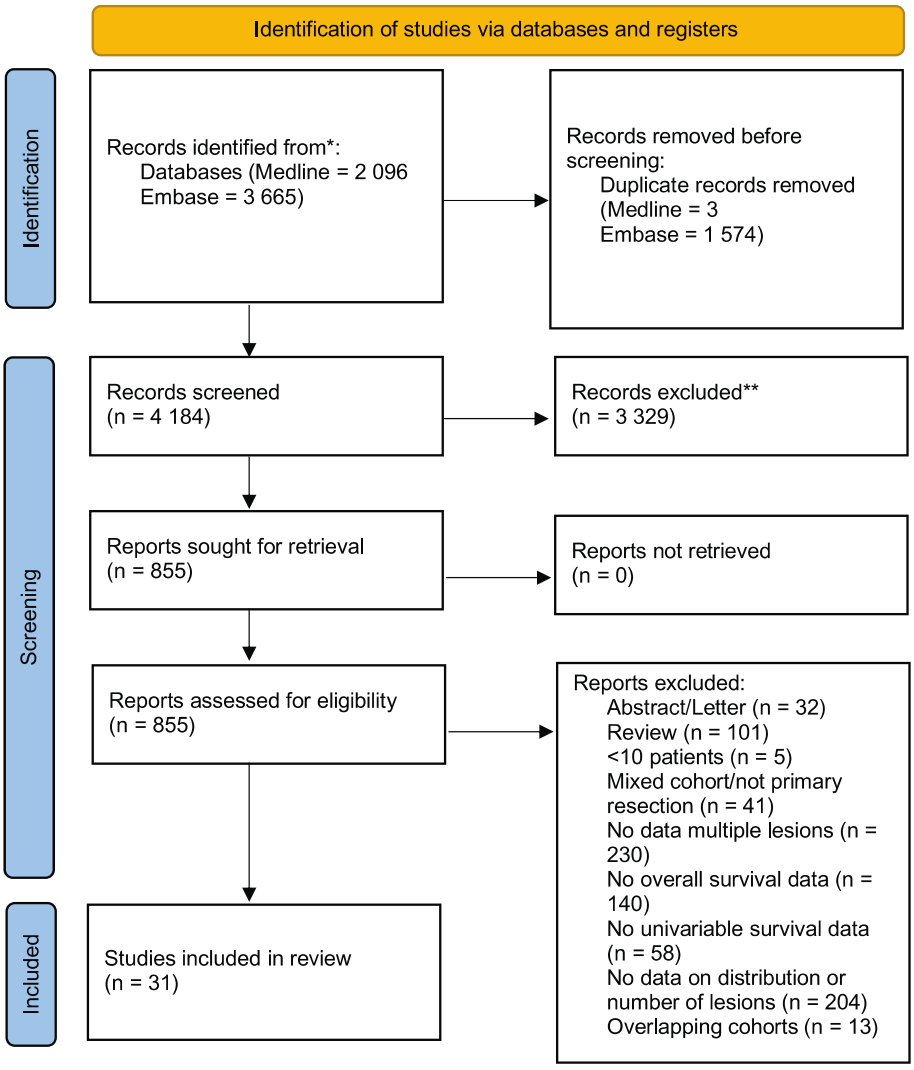


Fig. 1. Prisma 2020 Flow diagram.

lesions, multiple lesions other than satellites and in subgroups according to number of lesions were recorded. Overall survival for patients with a single tumour and for patients with multiple tumours (multiple all distributions, satellites, multiple other than satellites, subgroup according to number of lesions) was recorded. Non-automated data collection was performed by one reviewer (HJ), and recorded data assessed by a second reviewer (ES). Study quality and risk of bias was assessed independently with the Newcastle-Ottawa scale [23–25] by two reviewers (HJ and ES). For meta-analysis the hazard ratios with confidence intervals or the comparison group sizes, number of events and log rank p-values were recorded. For studies reporting event data only as Kaplan-Meier curves with numbers at risk, survival proportion data was extracted using Engauge Digitizer v12.1 [26]. Confidence of pooled estimates was further assessed for downrating according to the GRADE framework for prognostic studies [27].

2.3. Statistical analysis

Meta-analysis was performed in Review Manager v5.4 (The Cochrane Collaboration) [28], using the inverse variance method and the random effects model. To compute pooled hazard ratios, the standard error of the log hazard ratio was calculated from summary statistics according to Parmar et al. [29,30]. For studies reporting survival curve data, the log hazard ratio and its standard error were estimated according to Williamson et al. [30,31]. Heterogeneity was assessed by the I^2 statistic and Chi-square test, and publication bias assessed graphically with funnel plots. Categorical variables were reported with numbers and percentages, continuous variables with medians. Relative risks were presented as hazard ratios with 95% confidence intervals, when reported, or as estimated when sufficient data was available from published survival and follow-up. Sensitivity analyses were performed excluding studies with the highest risk of bias according to study quality assessment.

3. Results

3.1. Identification of studies

A total of 4184 unique records were identified after database searches of Medline (Ovid) and Embase, with deduplication. After first screening on title and abstract, 855 reports were assessed for eligibility. Reasons for exclusion are given in the PRISMA diagram in Fig. 1. Out of 248 reports with univariable overall survival data for patients with multiple lesions, 204 reports lacked data stratified for

distribution or number of lesions. Thirteen reports of overlapping cohorts were excluded [61,72–83], and are presented in Supplemental Table 4. A total of 31 studies, all retrospective cohort studies, were included in this review and are presented in Table 1. The included studies comprised 21 single center studies [18,19,32–50], nine multicenter studies [51–59], and one study reporting a nationwide survey [60]. Seventeen studies showed overlap between cohorts as evaluated according to reported center and study period (Table 1). Qualitative assessment according to the Newcastle-Ottawa scale is presented in Supplemental Table 5. The median score on the scale was seven stars. Three studies had a total score of four [33,37,49], and four studies had a total score of five [39,52,54,59], out of a maximal possible score of nine.

3.2. Demographic and clinicopathological data

Characteristics of the included studies and cohorts are presented in Table 1. The proportion of resected iCCA patients with satellite lesions ranged from 8 to 44%, while the proportion of patients resected with multiple lesions ranged from 15 to 47%. The proportion of patients with multiple lesions not including satellites was reported in 10 studies, ranging from three to 17%. Among patients with multiple lesions, the proportion with two or two-three lesions was reported in five studies, ranging from 40 to 71%. Twenty studies reported data for iCCA patients in general, while 11 studies reported data only for patients with a disease subtype (i.e. mass-forming iCCA), or within a certain prognostic group (e.g. patients with radical/non-radical resection margin or underlying cirrhosis).

3.3. Overall survival and surgical data

Overall survival outcomes, median follow-up times and surgical data for the included studies are presented in Table 2. Median follow-up ranged from 18 to 55 months. Median overall survival for all resected patients ranged from 17 to 53 months. The proportion of patients undergoing major resections ranged from 40 to 86% and the proportion of patients operated with hepatic resection and associated lymphadenectomy ranged from 33 to 93%. In the five studies in which a majority of patients underwent lymphadenectomy, the proportion of patients with lymph node metastases ranged from 21 to 38%. While five studies limited inclusion to only patients with radical or non-radical resection, the proportion of patients with positive resection margin among the remaining studies ranged from six to 42%. Sixteen studies reported the overall proportions of patients treated with neoadjuvant or adjuvant oncological therapy. The proportion of patients with neoadjuvant therapy ranged from zero to nine percent, while the proportion of patients treated with adjuvant therapy ranged from 20 to 53%.

3.4. Systematic review: prognostic influence of number of lesions

Ten studies reported overall survival data stratified for number of lesions (Tables 1 and 2) [38,40,41,44,46,50,52,56,57,61], nine of which with some statistical comparison between groups [38,40,41,44,46,50,52,56,57], and with six studies reporting relative risk with hazard ratios (Table 2) [38,44,46,50,52,56]. Both the number of lesions chosen to subgroup patients, and the reference categories used when comparing survival, differed between studies (Tables 1 and 2), precluding any meta-analysis.

Four studies presented relative risk data for patients with two or three lesions compared to patients with a single lesion (Table 2 and Supplemental Figure 1) [38,46,50,52]. While Buettner et al. reported a significant risk increase for patients with two or three lesions (HR 1.75, 95% CI 1.39–2.19) [52], Bednarsch et al., Liu et al. and Wang et al. reported non-significant survival differences (HR 1.68, 95% CI 0.93–3.05, HR 0.77, 95% CI 0.47–1.26 and HR 1.39, 95% CI 0.89–2.17 respectively) [38,46,50], compared to patients with a solitary tumour. Chen et al. reported the relative risk increase per additional lesion in a cohort of resected iCCA patients with underlying cirrhosis, with hazard ratio 1.44 (95% CI 1.29–1.60) [33]. Tian et al. found no significant risk increase when comparing overall survival for patients with two lesions to patients with a single lesion [44]. Nuzzo et al. reported similar survival for patients with one or two lesions as for patients with a single lesion (both groups median OS = 29 months) [40]. Bednarsch et al. reported a significant survival difference only for patients with more than five lesions compared to patients with a single lesion (median OS = 10 months compared to OS = 32 months) [50].

3.5. Systematic review: prognostic influence of other categories of tumour distribution

Six studies reported tumour distribution with specific categories other than satellites or multiple lesions not including satellites, out of which five presented overall survival data for these categories (Tables 1 and 2). Limited data and heterogeneity between studies precluded any meta-analysis. While three studies reported data for patients with 'intrahepatic metastases' (Table 2), Kim et al. included patients with satellite lesions to this group and reported a significantly decreased survival [35]. Aherne et al. included all multiple lesions not specified as satellites and found no significant survival difference, without reporting survival or summary data [32]. Fu et al. did not specify criteria for the categorisation of lesions as intrahepatic metastases and reported a significant decrease in overall survival [34].

Two studies analysed survival in multiple iCCA with lesions also in the contralateral liver lobe (Table 2). While Addeo et al. found patients with multiple lesions in the contralateral hemiliver to have similar survival as patients with single lesions [18], Bartsch et al. reported patients with multiple lesions and a 'translobar' dissemination to the contralateral hemiliver to have significantly decreased survival [19]. Bartsch et al. included patients with diffuse tumour infiltration in the 'translobar' subgroup but found similar outcomes (no data reported) for patients with and without diffuse infiltration [19].

3.6. Meta-analysis: prognostic influence of satellite lesions

Seventeen studies presented data on overall survival for patients with and without satellites, 14 reporting hazard ratios or data allowing hazard ratio calculation (Table 2). The study by Addeo et al. was excluded from meta-analysis as it included all patients presenting with multiple lesions confined to one liver lobe in the satellite lesion subgroup [18], in contrast to definitions of satellites according to histopathology [43,49,51,59] or proximity to the main lesion on radiology (within 10 mm [32], 20 mm[19] or the same liver segment [53]). Five studies with overlapping cohorts were also excluded from meta-analysis [33,36,42,45,58], including the study by King et al. where four patients with other multiple lesions than satellites were included in the satellite lesion group in survival analysis [36].

The meta-analysis of nine non-overlapping studies comparing survival for 2737 patients with and without satellite lesions is presented in Fig. 2 A and B. The pooled result indicated a significantly decreased overall survival for patients with satellite lesions (HR 1.89, 95% CI 1.67–2.13), with limited statistical heterogeneity among studies and no apparent bias as evaluated by funnel plot symmetry (Fig. 2B). Pooled data also including the study by Addeo et al. [18] are presented in Supplemental Fig. 2 A and B, with concurrent results (HR 1.91, 95% CI 1.69–2.14). Pooled data excluding

Table 1
Studies included for review: background characteristics of reported cohorts.

Study (year)	Time period/ Country or region	No. of pts.[&]/single- or multi-centre	iCCA sub-group	% Mass-form.	% Women	Md age (Y)/Md max size (mm)	Diagn.mod.	% Mult./ Satell.	% Other group	% Sub-group no. (no. of lesions)	% Cirrhosis/% HBV or HBV + HCV
Addeo (2019) [18]	1995–2017 FR	119 single				64 78[#]		47 33[a]	13[c]		
Aherne (2018) [32]	1993–2014 US	66 single	MF[l]	100	62	65 59	CT	– 18	6[d]		
Bartsch (2021) [19]	2000–2018 GER	125 single			49	64	CT/MRI	25 10	8[c¶]		
Bednarsch (2021) [50]	2010–2020 GER	139 single			56	65[#]	CT/M RI	29.5		12 (2–3) 7 (4–5) 10 (>5)	
Brustia (2020) [51]	2001–2018 EUR, BR, JPN	246 multi			48[e]	68[e] 50[e]	PAT[†]	– 20	9[$]		9[e] 18[e]
Buettner (2017) [52]	1990–2016 N. AM, EUR, ASIA, AUS	1054 multi[f]		92	46	59 61		– 23	7[d]		
Chen Q (2020) [33]	2006–2011 CHI	305 single[f]	CIR		13	52 50		41 20			100 87
Chen Y (2021) [59]	2009–2017 CHI	704 multi	R0		42		PAT	28 27			– 36
Conci (2018) [53]	1995–2015 IT	243 multi[k]			50	68 57	PAT	35 22	14[$]		
De Rose (2013) [54]	2000–2009 IT	79 multi[j]	MF	100	42	67 65	CT/MRI	– 44[b]			– 34
Fu (2020) [34]	2006–2011 CHI	110 single			44	53[#]		40 –	21[d]		
Kim (2014) [35]	2000–2009 KOR	77 single			35	61 50		– –	3[$] 17[d @]		– 21
King (2020) [36]	2003–2017 US	52[s] single[k]	MF	100	64[e]	63[e] 68[e]	CT	– 27[o]	5[$e]		4[e] 15[e]
Kudo (2021) [60]	2002–2013 JPN	3022 multi		71[&]	39[& ^]		PAT	15 –		6 (2) 9 (>2)	8[&]
Lee (2014) [37]	1995–2003 US	53 single			62[e]	61[#e] 79[#e]		– 32			
Liu (2018) [38]	2005–2011 CHI	214 single[i]			43	58 55		26 –			28 40
Lu (2016) [39]	2000–2005 CHI	303 single[g]	MF	100	32	52[#] 68[#]		– –			32 53
Moro (2019) [55]	1990–2016 N. AM, EUR, ASIA, AUS	1145 multi[f]		84[§]	45	60 60		– 20			10 17
Nuzzo (2010) [40]	1997–2008 IT	55 single		86	45	64 60[#]		36 –		15 (2) 22 (>2)	– 38
Scheuermann (2013) [41]	1997–2012 GER	130 single			50	65 70	PAT	– –		75 (1–3) 25 (>3)	– 3
Shen (2018) [42]	2009–2013 CHI	91 single[h]			49	57 64[#]		– 20	8[$]		15 86
Spolverato (2015) [56]	1990–2013 N. AM, EUR, ASIA, AUS	342 multi[f]	≥70 mm or mult.		49	60 85		– –			9
Tabrizian (2015) [43]	1995–2011 US	81 single[k]			51		PAT	– 24	11[$]		9
Tian (2020) [44]	2005–2011 CHI	168 single[i]	R0		41	– 60		20 –		12 (2) 8 (>2)	43
Tsilimigras (2020) [57]	1990–2017 N. AM, EUR, ASIA, AUS	1146 multi[f]		87[§]	44	60 60		18 –		13 (2–3) 5 (>3)	11
Wang T (2020) [45]	2008–2018 CHI	398 single[h]	R0		47		RAD[‡] PAT[†]	32 16			13 32
Wang Y (2013) [46]	2002–2007 CHI	367 single[f]			33	53	PAT	– –		89 (1–2) 11 (>2)	21 51
Yeh (2015) [47]	1977–2007 TWN	84 single	R1+R2	26				– 8	10[$]		
Zhang (2017) [58]	1990–2016 N. AM, EUR, ASIA, AUS	1023 multi[f]		80	44	59	PAT	– 22	17[$]		11
Zhou (2011) [48]	2005–2007 CHI	155 single[f]				55[#]		– 25[q]	12[$]		29 56
Zhu (2021) [49]	2015–2018 CHI	126 single	R0	94		59[#] 64[#]		– 29	10[$]		

three studies with a score of five or less on the Newcastle-Ottawa scale are presented in Supplemental Fig. 3 A and B, with similar results (HR 2.05, 95% CI 1.75–2.39).

3.7. Meta-analysis: prognostic influence of multiple lesions not including satellites

Six non-overlapping studies reported overall survival data for 1589 patients depending on presence or absence of multiple lesions not including satellites (Table 2), with a meta-analysis presented in Fig. 3 A and B. The overlapping study by Zhou et al. was excluded [48]. For this comparison, a higher degree of statistical heterogeneity was present between studies ($I^2 = 35\%$ $P = 0.18$). The pooled result indicated a significant decrease in overall survival for patients with multiple lesions other than satellites (HR 2.41, 95% CI 1.72–3.37). Pooled data excluding one study with a score less than five on the Newcastle-Ottawa scale is presented in Supplemental Fig. 4 A and B, with similar results (HR 2.53, 95% CI 1.64–3.91).

3.8. Assessment of evidence

Considering GRADE domains for rating of evidence for the pooled hazard ratio for satellite lesions, concerns for risk of bias remained also after sensitivity analyses. Included studies lacked data on diagnostic modalities [55], reported exclusion of patients from survival analysis (such as incomplete follow-up or post-operative mortalities) [19,43,51] or lacked reported data on median length of follow-up [19,51,53,55]. Inconsistency among results was evaluated with limited heterogeneity. Directness, or generalisability for the pooled estimate, was assessed with only one study limiting inclusion to a subgroup of resected patients [32]. The imprecision of the pooled estimate for the full meta-analysis implied a risk increase spanning from 69 to 114% for patients with satellites. There was no evidence of publication bias.

Considering GRADE domains for pooled estimates for multiple lesions other than satellites, concerns for risk of bias were similar to studies reporting outcomes for patients with satellite lesions. Included studies lacked data on diagnostic modalities [35,42,49], reported exclusion of patients [42,43,49,58] or lacked data for median length of follow-up [35,42,43,49,53,58]. Concerns for inconsistency were present, with low to moderate heterogeneity. Funnel plot analysis revealed asymmetry suggesting possible bias. Directness was assessed with only one study limiting inclusion to a subgroup of patients [49]. Imprecision was more pronounced with a pooled estimated risk increase spanning from 72 to 237%. Grade evidence profiles are summarised in Supplemental Table 6.

3.9. Multivariable comparisons

Among the nine studies included for meta-analysis of the prognostic influence of satellite lesions, five studies reported multivariable analyses incorporating satellite lesions with other risk factors including lymph node status [19,43,51,53,55]. Of these studies, two found satellite lesions to be a significant independent factor (Conci et al.: HR 3.10, 95% CI 1.55–6.20[53];Moro et al.: HR 1.65, 95% CI 1.34–2.04[55]), while the study by Bartsch et al. reported significance for a compound prognostic score including number and distribution of lesions, tumour size, extension and volume [19]. Brustia et al. and Tabrizian et al. both reported non-significance for satellites on multivariable analysis including lymph node metastasis (Brustia et al.: HR 1.42, 95% CI 0.88–2.30[51], Tabrizian et al.: no multivariable HR or P-value reported [43]).

Five out of six studies in the meta-analysis of multiple lesions not including satellites also reported multivariable models with lymph node status [35,42,43,53,58]. Conci et al. found multiple lesions not including satellites to be an independent prognostic factor (HR 4.06, 95% CI 1.83–9.05) [53], while four studies reported non-significance (Zhang et al.: HR 1.5, 95% CI 0.9–2.2[58], Kim et al. [35], Shen et al. [42] and Tabrizian et al. [43]: no multivariable HR or P-value reported).

4. Discussion

As noted in current discussions about prognostic factors in resectable iCCA, the term multiple lesions can incorporate a considerable heterogeneity among patients regarding tumour distribution (satellites and other multiple lesions) and number of lesions. This heterogeneity could extend to prognostic differences

AUS: Australia; BR: Brazil; EUR: Europe; HBV: hepatitis B virus; HCV: hepatitis C virus; CHI: China; CIR: cirrhosis; CT: computerized tomography; FR: France; GER: Germany; IT: Italy; JPN: Japan; KOR: Korea; Md: median; MF: Mass-forming; mm: millimeter; MRI: magnetic resonance imaging; mass-form: mass-forming; mult: multiple; N.AM: North America; No: number; PAT: histopathology; pts: patients; R0: microscopically tumour negative resection margin; R1: microscopically tumour positive resection margin; R2: macroscopically tumour positive resection margin; RAD: radiology; sat: satellites; TWN: Taiwan; US: United States.

[&] with multiple lesion data
[^] of all patients resectable and unresectable.
[§] including intraductal growing.
[!] patients with genetic mutational profiling.
[#] mean.
[†] satellites.
[‡] multiple.
[a] all lesions within ipsilateral hemiliver.
[b] category reported: “satellitosis”.
[c] contralateral.
[¶] including diffuse infiltration.
[d] intrahepatic metastasis.
[$] multiple not including satellites.
[@] including satellites and microscopic noduli.
[o] including multiple lesions other than satellites in statistical analysis.
[q] category reported: "microscopic satellite lesions".
[r] data for years 2012-2013 only
s subset with computerized tomography
[e] of all patients assessed/wider cohort.
[f] overlap of cohorts (Buettner, Chen Q, Moro, Spolverato, Tsilimigras, Wang Y, Zhang, Zhou).
[g] overlap with same cohorts as f except Chen Q.
[h] overlap of cohorts (Shen, Wang T, Wang L).
[i] overlap of cohorts (Tian, Liu).
[j] overlap of cohorts (Conci, De Rose).
[k] overlap of cohorts (King, Tabrizian).

Table 2
Overall survival and surgical data for included studies.

Study (year)	Overall md FU/md OS (months)	Md OS (months) Single/ Multiple/Satellites	HR (95% CI) Multiple Yes vs No/ Satellites Yes vs No/Other	HR (95% CI) Subgroup number of lesions [Subgroup vs Ref. group]	% Major hep./LND	% NAT/ AT	% N1/ R1/G3
Addeo (2019)	–	36.5	1.8 (1.2–2.8)		78	0	38
[18]	28	21	2.2 (1.4–3.7)[a] [est]		93	20	14
		20	1.1 (0.5–2.3)[c] [est]				22
Aherne (2018)	41	–	–		–	8	–
[32]	53	–	3.3 (1.4–8.0)		–	–	–
		–	NS (no data)[d]				–
Bartsch (2021)	–	27	–		75	–	28
[19]	22	–	1.4 (0.7–3.1) [est]		–	–	10
		21.5	5.0 (1.8–13.8)[c¶] [est]				28
Bednarsch	54	32	–	1.7 (0.9–3.1) [2–3 vs 1]	76	9	37
(2021) [50]	25	–	–	1.7 (0.8–3.8) [4–5 vs 1]	–	33	12
		–		2.8 (1.5–5.4) [>5 vs 1]			30
Brustia (2020)	–	–	–		48	7	22
[51]	26	–	1.7 (1.1–2.5)		–	21	18
		–					27
Buettner (2017)	–	–	1.9 (1.5–2.3)	1.8 (1.4–2.2) [2–3 vs 1]	59	–	18
[52]	38	–	–	2.5 (1.7–3.6) [>3 vs 1]	45	–	13
		–	–				–
Chen Q (2020)	–	–	1.4 (1.3-1-6)[y]		–	–	–
[33]	_	–	1.7 (1.3–2.4)		–	–	–
		–					–
Chen Y (2021)	–	–	1.6 (1.3–2.0)		57	0	16
[59]	_	–	1.7 (1.4–2.1)		33	–	0
							20
Conci (2018)	–	–	–		60	8	26
[53]	46	–	2.0 (1.2–3.3) [est]		–	41	27
		–	5.1 (2.7–9.9)[$] [est]				36
De Rose (2013)	26	–	–		70	0	24
[54]	40	–	P = 0.272[¡b]		77	53	19
		–					32
Fu (2020) [34]	55	–	6.1 (3.5–10.8)		–	–	32
	–	–	–		–	–	42
		–	9.3 (4.9–17.7)[d]				12
Kim (2014) [35]	–	–	–		86	–	–
	–	–	–		–	–	16
		–	1.9 (0.3–14.3)[$]				–
			2.1 (1.6–6.7)[d @]				
King (2020)	–	–			–	0	25
[36]	_	–	1.9 (0.9-4.1)[o]		–	–	–
		–					49
Kudo (2021)	–	64	–	–	64[&]	–	22[&]
[60]	_	35[++] 17[f]	–	–	49[&]	–	6[&]
		–					–
Lee (2014) [37]	–	–	–		–	–	23
	34	–	1.8 (0.9–3.4)		–	–	8
		–					85
Liu (2018) [38]	29	–	–	0.8 (0.5–1.3) [2–3 vs 1]	–	–	17
	_	–	–	2.7 (1.7-4.2) [>3 vs 1]	–	–	–
		–					38
Lu (2016) [39]	–	–	–		–	–	–
	_	–	P = 0.006		–	–	–
		–					–
Moro (2019)	–	–	1.2 (1.2–1.3)[?]		62	6	16
[55]	21	–	2.1 (1.8–2.6)		–	28	14
		–					19
Nuzzo (2010)	–	29	P = 0.285	P = 0.089 [>3 vs ≤ 2]	78	–	26
[40]	30	21	–		73	–	20
		–					32
Scheuermann	–	–	–	P = 0.030 [>3 vs ≤ 3]	81	–	29
(2013) [41]	28	–	–		–	37	27
		–					31
Shen (2018)	–	–	–		–	–	20
[42]	18	–	2.4 (1.3–4.5) [est]		–	–	8
		–	2.4 (1.0–6.1)[$] [est]				73
Spolverato	22[e]	–	–	1.7 (1.2–2.4) [>3 vs ≤ 3]	76[p]	–	21
(2015) [56]	21	–	–		56	51	19
							29

(*continued on next page*)

Table 2 (*continued*)

Study (year)	Overall md FU/md OS (months)	Md OS (months) Single/ Multiple/Satellites	HR (95% CI) Multiple Yes vs No/ Satellites Yes vs No/Other	HR (95% CI) Subgroup number of lesions [Subgroup vs Ref. group]	% Major hep./LND	% NAT/ AT	% N1/ R1/G3
Tabrizian (2015) [43]	27 – –	41 27 24	– 2.1 (1.1–4.1) [est] 1.9 (0.8–4.7)[$ [est]]		73 –	– 28	26 24 40
Tian (2020) [44]	45[e] 28[e] –	– – –	– –	1.2 (0.6–1.3) [2 vs 1]	– –	0 –	5 0 30
Tsilimigras (2020) [57]	– – –	– 21[+++] 15[g] –	– –	Md OS months (95% CI): 15 (10–19) vs 21 (16–27) [>3 vs 2–3]	61 – 	7 –	17 13 18
Wang T (2020) [45]	– – –	– – –	1.8 (1.3–2.3) 1.7 (1.3–2.4)		61 –	– –	25 0 –
Wang Y (2013) [46]	39 21 –	– – –	– –	1.4 (0.9–2.2) [2–3 vs. 1]	– –	– –	22 – –
Yeh (2015) [47]	– – –	9.5 10.5 4	– –		– –	– 46	31 100[μ] 29
Zhang (2017) [58]	– 37 –	– – –	– 2.1 (1.7–2.6) 2.0 (1.6–2.5)[$]		59 47	– –	17 13 17
Zhou (2011) [48]	– 17 –	– – –	– P < 0.001[n] P = 0.007[$]		– –	– –	21 – 24
Zhu (2021) [49]	18 29 –	– – –	– 1.5 (0.7–2.0) 2.1 (1.0–4.2[$]		– 63	1 34	26 0 41

AT: adjuvant therapy; CI: confidence interval; FU: follow-up; G3: grade 3 (low differentiation); hep: hepatectomy; HR: hazard ratio; LND: lymph node dissection; md: median; N1: lymph node metastasis; NAT: neoadjuvant therapy; No: number; NS: reported not significant; OS: overall survival; R0: microscopically tumour negative resection margin; R1: microscopically tumour positive resection margin; R2: macroscopically tumour positive resection margin; Ref: reference; vs: versus.
[e] of all patients assessed/wider cohort.
[++] 2 lesions.
[f] > 2 lesions.
[+++] 3 lesions.
[g] > 3 lesions.
[est] estimated from summary statistics.
[a] all lesions within ipsilateral hemiliver.
[c] contralateral.
[¶] including diffuse infiltration.
[d] intrahepatic metastasis.
[y] per additional lesion.
[$] multiple not including satellites.
[@] including satellites and microscopic noduli.
[n] category reported: "microscopic satellite lesions".
[o] including multiple lesions other than satellites in statistical analysis.
[†] satellites.
[b] category reported: “satellitosis”.
[?] not specified if per additional lesion.
[&] data for years 2010–2011 only.
[p] hemihepatectomy/extended hemihepatectomy.
[μ] including R2.

within the group of iCCA patients diagnosed with multiple intrahepatic lesions, and impact therapeutic choices when considering resection or locoregional oncological therapies.

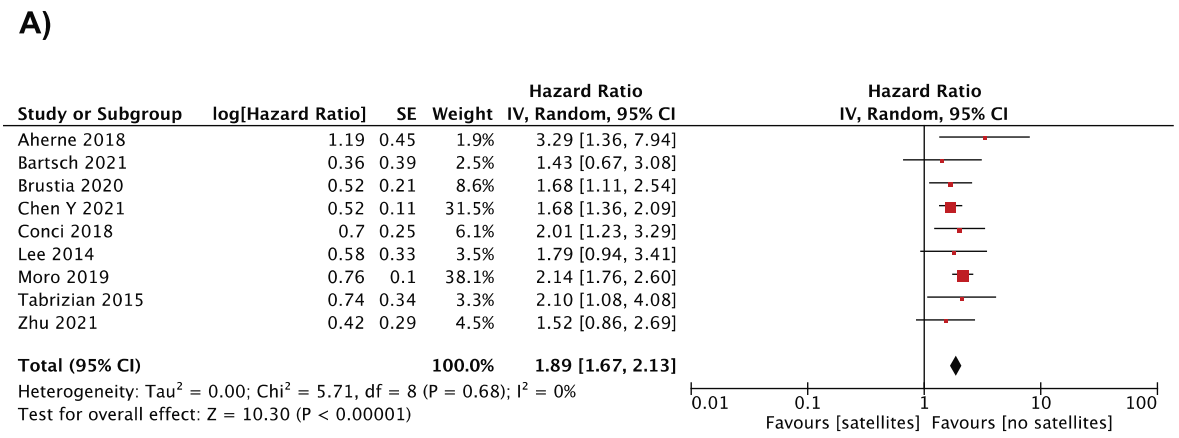
While one previous study found patients with satellite lesions to have outcomes not significantly inferior to those with a single tumour [19], others have reported satellite lesions, but not separate multiple lesions, to be negatively associated to survival [18].

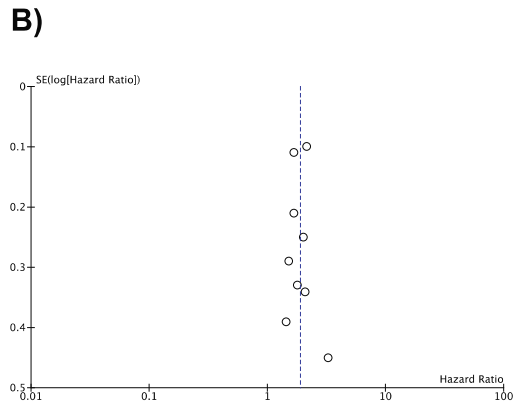
In this systematic review, with a meta-analysis including nine studies reporting univariable survival data for 2737 patients with/without satellites, from a variety of settings and including both radiologically and histopathologically diagnosed lesions, satellite lesions were found to be a significant negative prognostic factor after resection for iCCA. The statistical heterogeneity among studies was low, and with no apparent publication bias.

When analyzing outcomes for patients with/without multiple lesions other than satellites, in a meta-analysis including six studies and 1589 patients, multiple separate lesions were likewise found to be a significant negative prognostic factor, but with a higher degree of heterogeneity among studies.

In the broader review, different categories of multiple lesions other than satellites were reported, with conflicting data from the two studies reporting outcomes in multiple iCCA with contralateral lesions [18,19]. A possible explanation to such opposing outcomes could be underlying differences in other prognostic factors, e.g. tumour size and tumour number between studies and subgroups.

To what degree multiple lesions other than satellites represent intrahepatic metastases of iCCA or multifocal synchronous lesions, and whether such a differentiation would have a prognostic significance, is not clear from the reviewed literature. In a recent study, performing genomic profiling on multiple tumours from a





CI: confidence interval; df: degrees of freedom; iCCA: intrahepatic cholangiocarcinoma; IV: inverse variance; SE: standard error

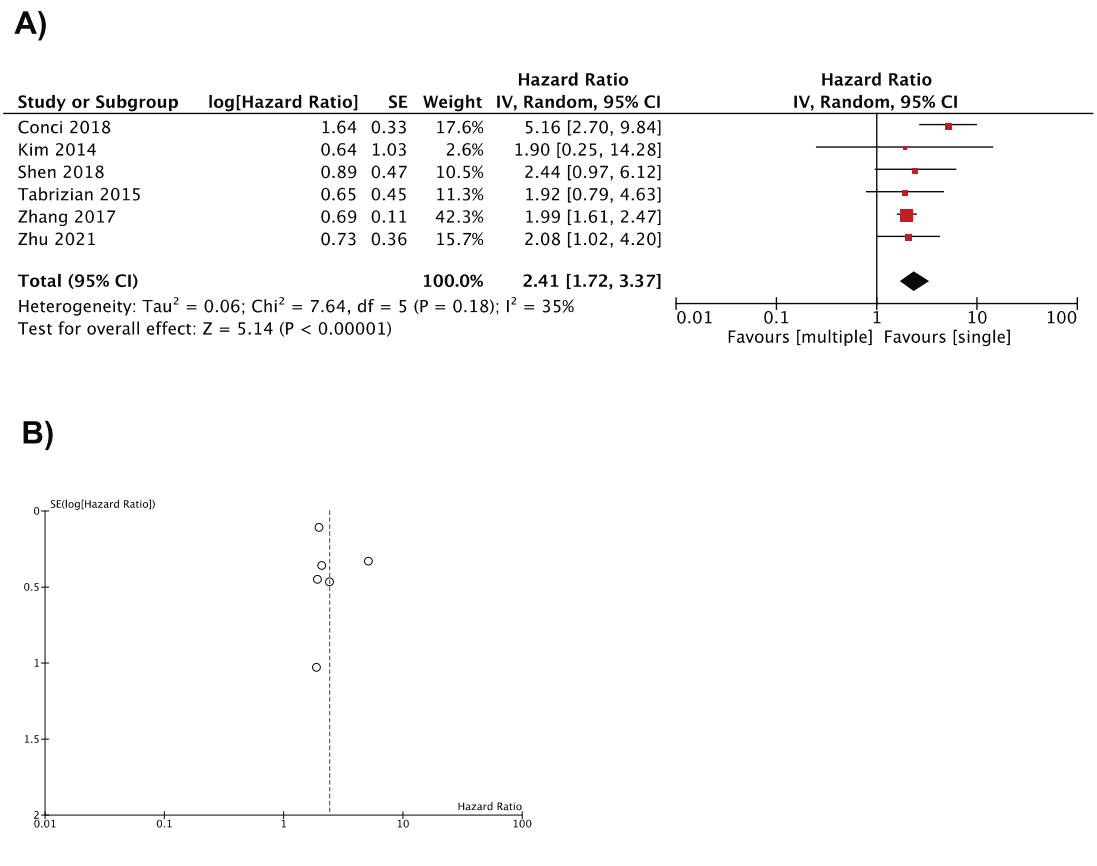
Fig. 2. Meta-analysis of satellite lesions as prognostic factor for overall survival after resection for iCCA, A) Forest plot B) Funnel plot.

small group of patients, all multiple lesions (including satellites) were found to represent metastases [62]. Of note, all multiple lesions in this analysis were within 50 mm of the main lesion [62]. It could be hypothesised that multifocal synchronous lesions on a background of chronic liver disease could imply a better oncological prognosis compared to metastasized iCCA, but criteria to differentiate metastases from multifocality remain to be defined, and any possible associated survival difference to be further studied.

The degree of overlap and of collinearity between prognostic factors also needs to be considered. While negative prognostic factors overlap in some patients, a proportion of patients with satellites but without other multiple lesions, or vice versa, were presented in several studies [19,47,53]. If, and to what extent, underlying differences in other prognostic factors (such as presence of lymph node metastasis) between patients with and without multiple lesions explain the observed survival differences is not clear. Moro et al., with the largest international multicentric cohort in this review, reported satellite lesions to be an independent negative prognostic factor in a multivariable model adjusted for important variables such as lymph node metastasis, tumour differentiation, resection margin and tumour size [55].

The broader question of clinical benefit of resection, compared to other therapy options for patients with multiple iCCA, which has been addressed in several studies in recent years, was beyond the scope of this review. While single-center regional therapy cohorts (hepatic arterial infusion [63] or transarterial chemoembolization/hepatic arterial infusion [64]) have reported similar survival as with surgical resection, analysis of data from a United States national registry (SEER) found improved survival in resected patients with multiple lesions, also when adjusting for chemoradiotherapy in a multivariable model [65]. In a large European multi-center cohort (ENSCCA), when surgery was analysed as a univariable prognostic factor, resection in patients with multiple iCCA was associated with improved survival [15]. Which iCCA patients with multiple lesions would benefit most from resection surgery, and how surgery compares to locoregional therapies in different risk groups within the multiple lesion group, remains to be further studied. The overall proportion of patients receiving neoadjuvant therapy reported from cohorts in this review remained low, and the role for neoadjuvant systemic chemotherapy in iCCA with multiple lesions or other negative prognostic factors is an important focus for clinical trials [66]. The overall proportion of patients receiving adjuvant therapy, when reported, remained below 50% in nine out of eleven studies. How real-world outcomes of surgery will develop with current implementation of adjuvant chemotherapy after recent randomized controlled trials also remains to be studied [67,68].

This systematic review was based on a broad search of the current literature, focusing specifically on resected iCCA patients,



CI: confidence interval; df: degrees of freedom; iCCA: intrahepatic cholangiocarcinoma; IV: inverse variance; SE: standard error

Fig. 3. Meta-analysis of multiple lesions (not including satellites) as prognostic factor for overall survival after resection for iCCA, A) Forest plot B) Funnel plot.

evaluating overall survival outcomes for patients with multiple lesions according to both tumour distribution and number. Furthermore, it permitted the meta-analysis of relative risks according to distribution of multiple lesions, the first such analysis to date to our knowledge. A previous systematic review of prognostic factors for overall survival in patients undergoing resection for iCCA, published in 2014, included five studies with data on multiple tumours in meta-analysis, without further stratification [69]. A recent systematic review on prognostic factors for early recurrence included only three studies in a meta-analysis, also with unstratified data [70]. With a comprehensive search, the current study was able to include nine and six studies respectively in meta-analyses, with granular data on tumor distribution and relative risks, allowing sensitivity analyses and presenting a synthesis of best available current evidence to shape further scientific discussion and research specifically for the sizable group of patients with multiple iCCA.

However, the study also had several limitations. A considerable heterogeneity was found among studies regarding definitions, diagnostic modalities and patient cohorts. Several criteria to define satellite lesions have been proposed, such as lesions within 10 mm of the main tumour [32] or lesions within the same segment [71], and different definitions of proximity to the primary lesion were employed in the reviewed studies. Most studies did not specify which diagnostic modalities were used to determine tumour multiplicity. Among studies reporting survival for patients with satellite lesions compared to patients without satellites, it is possible that the reference category in some reports could include multiple lesions without satellites, and not only patients with single lesions. Regarding terminology for tumour distribution, the terms bilobar or bilateral iCCA were not investigated in this review, as they also describe patients with large or central single lesions engaging both hemilivers [19,58,72]. A majority of studies reported single center data. For studies reporting survival curves with numbers at risk, relative risks were estimated from summary data. Upon review, data was limited for number of lesions and other categories of tumour distribution, only permitting qualitative synthesis. For meta-analyses, assessment of evidence indicated risk of bias both for studies reporting data on satellite lesions and other multiple lesions, with further limitations for the meta-analysis on multiple lesions not including satellites, with a higher degree of imprecision in the pooled estimate and further possible bias.

In conclusion, this systematic review and meta-analysis of the prognostic influence of multiple lesions in resectable iCCA found patients with satellite lesions, as well as patients with multiple lesions not including satellites, to have significantly decreased overall survival. Data stratified for number of lesions was limited, but suggested increased risk per additional lesion. Number of tumours, presence of satellite lesions and presence of multiple lesions other than satellites should be separately reported, to allow further analysis as possible additive prognostic factors. To evaluate these variables separately, together with other prognostic factors, could permit an improved risk stratification for the considerable proportion of iCCA patients presenting with multiple lesions, rather than contraindicating surgery for an entire patient group.

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Data availability statement

The data collected and analysed during the current review are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Hannes Jansson: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Christina Villard:** Conceptualization, Investigation, Writing – review & editing. **Lynn E. Nooijen:** Investigation, Writing – review & editing. **Poya Ghorbani:** Writing – review & editing. **Joris I. Erdmann:** Conceptualization, Writing – review & editing. **Ernesto Sparrelid:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Supervision, All authors contributed to interpretation of data, critical revisions, and approved the final version of the manuscript.

Conflict of interest disclosure

Hannes Jansson, Christina Villard, Lynn E. Nooijen, Poya Ghorbani, Joris I. Erdmann and Ernesto Sparrelid have no conflicts of interest do disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2023.01.006.

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