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REVIEW

Anticancer Drugs Compared to No Anticancer Drugs in Patients with Advanced Hepatobiliary Cancer: A Mapping Review and Evidence Gap Map

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Introduction: Despite being commonly recommended, the impact of anticancer drugs (ACDs) on patient-important outcomes beyond survival for advanced hepatobiliary cancers (HBCs) may not have been sufficiently assessed. We aim to identify and map the evidence regarding ACDs versus best supportive care (BSC) for advanced HBCs, considering patient-centered outcomes.

Methods: In this mapping review, we included systematic reviews, randomized controlled trials, quasi-experimental, and observational studies comparing ACDs (chemotherapy, immunotherapy, biological/targeted therapy) versus BSC for advanced HBCs. We searched MEDLINE (PubMed), EMBASE (Ovid), Cochrane Library, Epistemonikos, PROSPERO and clinicaltrials.gov for eligible studies. Two reviewers performed the screening and data extraction processes. We developed evidence maps for each type of cancer.

Results: We included 87 studies (60 for advanced liver cancer and 27 for gallbladder or bile duct cancers). Most of the evidence favored ACDs for survival outcomes, and BSC for toxicity. We identified several evidence gaps for non-survival outcomes, including quality of life or quality of end-of-life care.

Discussion: Patient-important outcomes beyond survival in advanced HBCs are insufficiently assessed by the available evidence. Future studies need to address these gaps to better inform decision-making processes.

Keywords: liver neoplasms, gallbladder neoplasms, bile duct neoplasms, antineoplastic agents, immunotherapy, biological therapy, palliative care

Introduction

Hepatobiliary cancers (HBCs) —including hepatocellular carcinoma, intra- and extra-hepatic cholangiocarcinoma, and gallbladder cancer— represent more than 5% of all new cancers worldwide, constituting the third cause of death.[1,2] A considerable proportion of patients are diagnosed in advanced stages (17.9% for liver and intrahepatic bile duct cancer and 44.3% for gallbladder cancer) with a lack of curative treatment chance and a poor survival rate (one-year survival rate of 17.0% and 19.2%, respectively).[1]

Anticancer drugs (ACDs), a broad term that considers chemotherapy, targeted/biological therapy, and immunotherapy, are the main recommended treatment for these patients.[3–6] Nevertheless, they are associated with important toxicity and impact on quality of life (QoL), which may be in conflict with patient values and preferences and, therefore, may be

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considered an indicator of poor-quality and aggressive care.[6–10] Recommendations for ADCs are usually based on their impact on survival outcomes, with less consideration of other critically important outcomes, such as QoL or quality of end of life (EoL) care.[3,4,11] Additionally, some guidelines recognize evidence gaps for particular clinical scenarios, such as second-line treatments for advanced biliary tract tumors.[5] A reasonable alternative therapeutic strategy for these patients could be best supportive care (BSC) alone. This broad concept encompasses therapeutic efforts focused on symptom control and improvement in patients' QoL, including various treatments given by highly personalized multi-disciplinary teams to on-demand consultations.[12–14] In this clinical scenario, BSC with no ACDs can usually represent a valid alternative option through achieving similar survival results with lower toxicity.[15–17]

Currently, there is still uncertainty regarding the extent to which primary studies and evidence syntheses are assessing and reporting outcomes beyond survival for the comparison of ACDs versus BSC in patients with advanced HBCs. Characterizing if important outcomes are reported by the relevant body of evidence and identifying outcome-reporting gaps could help improve the awareness and inclusion of critical outcomes in decision-making processes. Therefore, the purpose of this study is to identify, describe, organize, and map the currently available evidence and potential gaps about the efficacy and safety of ACDs compared to BSC for patients with advanced HBCs.

Methods

We conducted a mapping review and evidence gap map,[18,19] adhering to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.[20] The protocol for this study was prospectively registered and is publicly available in Open Science Framework.[21] This study is part of the ASTAC (Appropriateness of Systemic Oncological Treatments for Advanced Cancer study) project, which aims to describe, map, and synthesize the available evidence regarding the efficacy and appropriateness of ACDs for advanced non-intestinal digestive cancers (including hepatobiliary, gastroesophageal, and pancreatic cancer). In this article, we present the results of the mapping review and evidence gap map regarding advanced HBCs.

Eligibility Criteria

We used the PICOT framework (Patients, Intervention, Comparison, Outcomes, Type of study) to guide our eligibility criteria.[22]

Type of Patients

We considered eligible studies including adult patients (over 18 years), with diagnosis of liver, bile duct, or gallbladder cancer, primary or recurrent, in an advanced stage or described as advanced or metastatic by the study authors at the moment of the intervention. For the purpose of this review, we considered as an advanced stage disease those patients with stage IIIb, IIIc, or IV liver cancer, stage IIIb or IV bile duct cancer, or stage IIIb or IV gallbladder cancer.[23] We excluded lymphatic, stromal, and neuroendocrine cancers.

Type of Interventions and Comparators

For the intervention arm, we considered any ACDs, including chemotherapy (either monotherapy or in combination), biological/targeted therapy, or immunotherapy, whether individual or combined, with or without supportive care. We excluded studies that considered only surgery or radiotherapy as intervention, as well as studies that considered chemotherapy only as an adjuvant or neoadjuvant therapy. We have also excluded studies that considered only local therapy such as TACE therapy or similar.

We considered as comparator any supportive treatment, administered with the purpose of symptomatic or palliative control, with no ACDs. This includes either usual treatment, supportive care, or BSC.[13] Studies that did not explicitly define the intervention of the control group, or studies with placebo as the control group, were also included. We excluded studies if the control group considered any type of ACD. We also excluded comparisons comprehending an intervention with non-palliative intent, such as surgery or radiotherapy with curative intent.

Type of Outcomes

We considered the following outcomes: Overall survival (OS); progression-free survival (PFS); functional status; toxicity; symptoms related to the disease; quality of life (QoL); admissions to hospital or long-term center, or emergency consultations; and quality of death (EoL care), including admission to hospital at the EoL, palliative care provided during the last year, and place of death. Appendix 1 provides a detailed definition of assessed outcomes.

Type of Studies

We included systematic reviews (SRs), randomized controlled trials (RCTs), quasi-experimental studies, and observational studies assessing the impact of ACDs on advanced or metastatic HBCs (including hepatocellular carcinoma, cholangiocarcinoma, and gallbladder cancer). In the case of SRs, we considered only those published from 2008 onwards, since a previous overview did not preliminarily identify relevant studies before that date.[6] We did not apply any publication date or language restrictions to primary studies.

We considered as a SR any type of secondary research that raised: i) an explicit eligibility criteria or research question, ii) a structured search strategy (defined as explicit search terms and data frame, in at least two databases), iii) explicit inclusion criteria and screening methods, iv) an explicit assessment of the quality or risk of bias of each included study, and v) explicit approach to data analysis and synthesis.[22,24] RCTs were defined as any experimental primary study with a random allocation of interventions. We considered as a quasi-experimental study design any research with a non-randomized allocation of interventions, such as interrupted time series or before–after studies. We considered as an observational study all case-control, cohort or cross-sectional studies, as long as they were controlled and included, at least, 30 patients. We excluded any descriptive studies, clinical practice guidelines, case reports, and non-systematic reviews (such as narrative reviews).

Search Methods for Identification of Studies

We performed electronic searches in MEDLINE (access via PubMed), EMBASE (access via OVID), the Cochrane Database of Systematic Reviews, CENTRAL, and Epistemonikos from inception until December 2019. We designed search strings adapted to the requirements of each database that combined controlled vocabulary and search terms related to the main concepts of our clinical question. Appendix 2 provides the search strategy for PubMed. As this study is part of a wider project (ASTAC-study), the search strategy included terms for gastro-esophageal and pancreatic cancer, besides hepatobiliary cancer. Since the COVID-19 pandemics delayed the conduction of this study, we later updated the searches in MEDLINE/PubMed until August 2022.

We also searched in PROSPERO and clinicaltrials.gov to identify protocols of potentially eligible studies, asked experts in the field for relevant studies, and conducted a citation search strategy, both backward (checking reference list of the included studies) and forward (identifying studies that cited included studies, using Google Scholar)

Selection of Studies

Two reviewers independently screened titles and abstracts of the retrieved search results. A third reviewer resolved disagreements. Afterward, two reviewers independently conducted the full-text screening, also with a third author solving any disagreement. For all this process we used Covidence.[25]

Data Extraction

Two reviewers independently extracted data from the included studies, using a previously piloted data extraction sheet. A third reviewer solved discrepancies. For each included study, we extracted the following data: year of publication, country, study design, total number of studies included regarding our question (for SRs), total number of patients included (for primary studies), interventions (broadly classified as chemotherapy, biological/targeted therapy, and/or immunotherapy), comparators (BSC, placebo, or non-specified), outcomes reported, and direction of effect, defined according to its statistical significance as "favors intervention", "favors comparison", or "no differences".

Data Synthesis and Analysis

We described study results in a tabular view, classifying each included study by cancer location, type of intervention, methodological design, reported outcomes, and direction of the effect. We used the R package "evimappr"[26] to produce the bubble plots for the evidence gap maps. We present a display that includes the interventions (chemotherapy, biological/targeted therapy, immunotherapy) in the rows, and the outcomes in the columns. The grids were populated with the corresponding studies at each intersection, classified by study design (SR, RCT, quasi-experimental study, or observational study). We identified evidence gaps as those spaces on the grid that did not contain studies. Due to space limits, if a column (or outcome) did not contain any study for any intervention, it was not plotted within the bubble plot.

Results

Our initial search strategy yielded a total of 76,338 records. After removing duplicates, we screened a total of 57,042 references, of which 54,060 were excluded by title and abstract screening. Of the 2982 references included after this initial stage, we could not retrieve 108 reports; therefore, we assessed 2982 full-text studies for eligibility, and we excluded 2676 reports. Finally, we included a total of 198 studies for all cancer locations (hepatobiliary, gastroesophageal, and pancreatic), 87 of which were related to hepatobiliary cancer. One additional study was identified through citation search. Figure 1 summarizes the screening process. Appendix 3 provides the list of the included studies and their publication threads, with references.

Liver Cancer

Sixty studies assessed patients with advanced liver cancer, including 17 SRs,[27–43] 27 RCTs,[16,17,44–68] two RCT protocols[69,70] and 14 observational studies.[71–84] Table 1 provides the characteristics of the included studies.

Of the 17 SRs included, nine compared biological/targeted therapies to placebo (n=3) or to a not clearly specified comparator (n=6); seven compared biological/targeted and immunotherapy to placebo (n=3), BSC (n=2), placebo or no treatment (n=1) or standard care (n=1); and only one compared immunotherapy to placebo.

Among the 27 RCTs, 22 compared biological/targeted therapies to either placebo (n=18), BSC (n=3) or placebo plus BSC (n=1); three compared chemotherapy to placebo (n=1), BSC (n=1), or to a not clearly specified comparator (n=1); and only two compared immunotherapy to placebo plus BSC. Almost half of the RCTs (n=13) did not specify the lines of therapy. Sorafenib was the most evaluated treatment (n=6).

Finally, among the 14 observational studies included, nine compared biological/targeted therapies to either BSC (n=5) or to a not clearly specified comparator (n=4); one study compared biological/targeted and immunotherapy to BSC; one compared chemotherapy and biological/targeted therapies to no treatment; and three compared chemotherapy to BSC (n=2) or to a not clearly specified comparator (n=1). Half of the studies (n=7) did not specify the lines of therapy.

Figure 2 shows an overall summary of the evidence retrieved, classified by the type of ACD administered and by outcome. This figure only shows those outcomes for which there is no study. Therefore, evidence gaps are not shown here. Figure 3 provides details about the outcomes assessed by each study and the direction of the reported effect.

The most reported outcomes were related to survival (as OS or PFS), mostly favoring intervention, with no studies favoring the comparator. Half of the included studies reported clear data for toxicity, mostly related to ACDs. Very few studies evaluated quality of life and no studies included quality of death as outcome.

Gallbladder and Bile Duct Cancers

Twenty-seven studies assessed patients with advanced gallbladder and bile duct cancers, including two SRs,[85,86] eight RCTs,[15,87–93] one RCT registration,[94] one quasi experimental study[95] and 15 observational studies.[96–110] Table 2 provides the characteristics of the included studies.

Both SRs compared chemotherapy to placebo (n=1) or to a not clearly specified comparator (n=1) as first- or second-line therapies.

Among the eight RCTs, two compared biological/targeted therapies to either placebo (n=1) or placebo plus BSC (n=1), five compared chemotherapy either to BSC (n=3), active symptom control (n=1), or to a not clearly specified

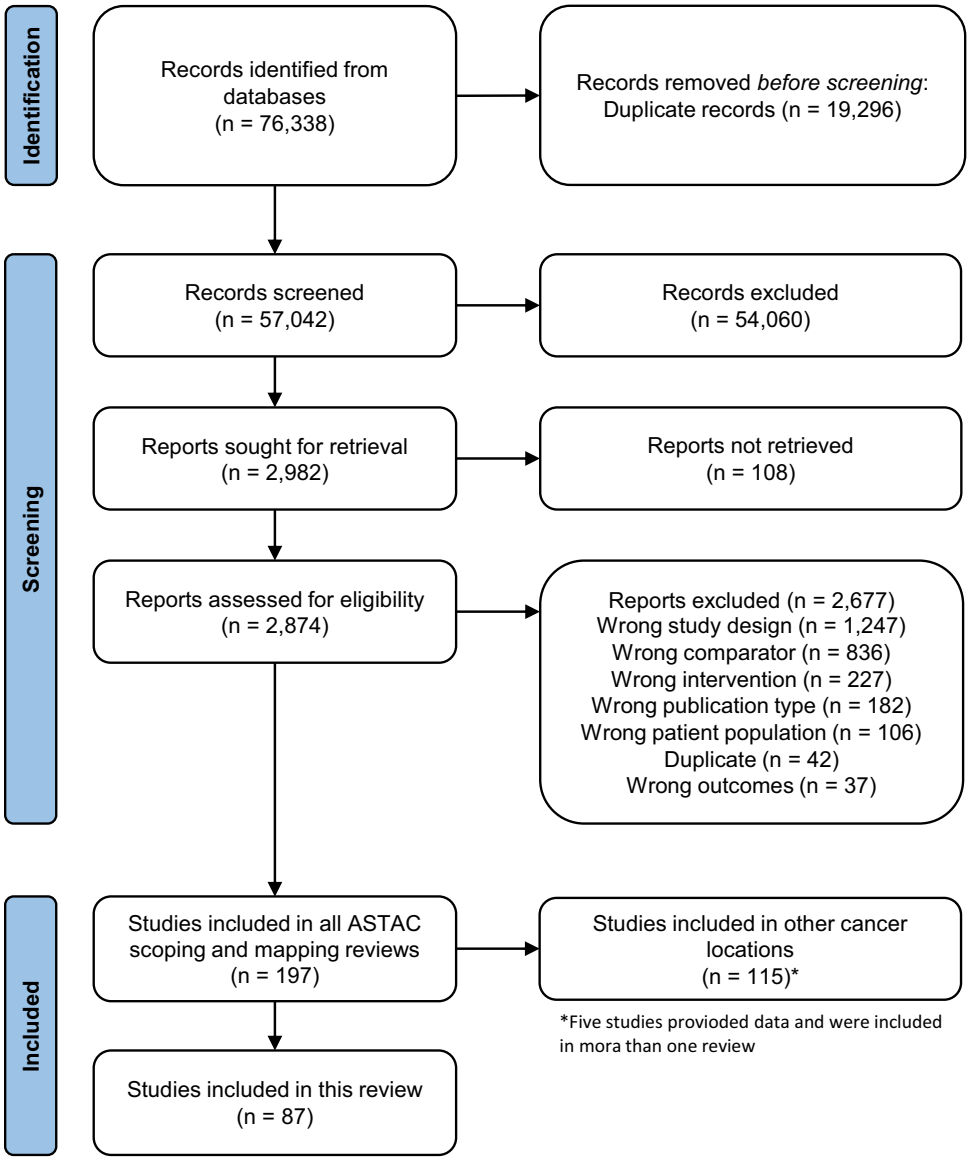

Figure 1 PRISMA flowchart. *Five studies provided data and were included in more than one review. Adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.

comparator (n=1) and one compared chemotherapy and biological/targeted therapies to BSC. More than half of the studies (n=5) did not specify the lines of therapy.

Finally, among the 15 observational studies included, 13 compared chemotherapy to either BSC (n=10) or to a not clearly specified comparator (n=4); and two compared chemotherapy and biological/targeted therapies to BSC (n=1) or no ACDs (n=1). More than half of the studies (n=8) did not specify the lines of therapy.

Figure 4 provides an overall evidence map for ACDs in patients with advanced gallbladder and bile duct cancers, classified by type of administered ACD and by outcome. This figure only shows those outcomes for which there is any study. Therefore, evidence gaps are not shown here. Figure 5 provides a detailed assessment of the direction of the effect for each prespecified outcome within the included studies.

The most reported outcomes were related to survival (mostly OS followed by PFS), mainly favoring intervention, with no studies favoring comparators. Only four studies reported clear data for toxicity. Very few studies evaluated quality of life and no studies included quality of death as outcome.

Table 1 Characteristics of the Included Studies Providing Data for Advanced Liver Cancer

Study ID	Country	Study Design	N*	Type of ACD	Specific Drugs Used	Treatment Line	Comparison
Abdel Wahab 2010[44]	Egypt	RCT	100	CT	Cap, Cis	NS/NC	PLB
Abdelmaksoud 2021[71]	Egypt	OBS	71	BIO/TT	Sor	NS/NC	BSC
Abou-Alfa 2016[45]	USA	RCT	185	BIO/TT	Cod	NS/NC	PLB
Abou-Alfa 2018[46]	USA	RCT	635	IT	ADI-PEG 20	2nd or more	BSC + PLB
AHELP[47]	China	RCT	400	BIO/TT	Apa	2nd	PLB
Asia-Pacific[17]	Taiwan	RCT	226	BIO/TT	Sor	1st	PLB
BOOST[69]	Italy	Protocol of RCT	-	BIO/TT	Sor	NS/NC	BSC
BRISK-PS[48]	USA	RCT	395	BIO/TT	Bri	NS/NC	BSC + PLB
CELESTIAL[16]	USA	RCT	707	BIO/TT	Cab	2nd or more	PLB
Chen 2021[27]	China	SR	4	BIO/TT	Reg, Cab, Ram	2nd	PLB
Chen 2022[72]	Taiwan	OBS	41	CT and BIO/TT	Sor / Len / Oxa and 5-FU	2nd	No SOT
Ding 2020[28]	China	SR	10	BIO/TT	Sor, Van, Ora, Bri	1st	NS/NC
Du 2019[73]	China	OBS	46	CT	S-1	NS/NC	BSC
El Baghdady 2020[74]	Egypt	OBS	55	BIO/TT	Sor	1st	BSC
EUCTR2007-007629-32-IT 2008[49]	USA	RCT	52	BIO/TT	TAC-101	2nd	PLB
EVOLVE-1[50]	USA	RCT	546	BIO/TT	Eve	NS/NC	PLB
Faruque 2014[29]	Canada	SR	2	BIO/TT	Sor	1st	NS/NC
Finn 2018[30]	USA	SR	2	BIO/TT	Sor	1st	NS/NC
Griffiths 2022[31]	Canada	SR	13	BIO/TT and IT	Sor, Tiv, Reg, Ram, Eve, Cab, Bri, Pem, Axi	NS/NC	BSC
Guo 2019[32]	China	SR	12	BIO/TT and IT	Sor, Van, Bri, Tiv, Ram, Axi, Cod, Cab	1st and 2nd	PLB or no SOT
Haber 2021[33]	USA	SR	13	BIO/TT and IT	Sor, Tiv, S-1, Reg, Ram, ADI-PEG20, Eve, Cab, Bri, Pem	1st and 2nd	PLB
Hiramine 2013[75]	Japan	OBS	65	BIO/TT	Sor	NS/NC	NS/NC
Hiraoka 2021[76]	Japan	OBS	63	BIO/TT	Len	3rd	NS/NC
Hsiao 2019[77]	Taiwan	OBS	401	BIO/TT	Sor	1sr or more	BSC
Hsu 2012[51]	Taiwan	RCT	67	BIO/TT	Van	NS/NC	PLB
Huang 2019[34]	China	SR	4	BIO/TT	Sor	1st and 2nd	NS/NC
Ishikawa 2001[52]	Japan	RCT	48	CT	UFT	NS/NC	BSC
Jácome 2021[35]	Brazil	SR	1	IT	Pem	2nd	BSC

(*Continued*)

Table 1 (Continued).

Study ID	Country	Study Design	N*	Type of ACD	Specific Drugs Used	Treatment Line	Comparison
Jang 2007[78]	South Korea	OBS	103	CT	5-FU	NS/NC	NS/NC
JET-HCC[53]	South Korea	RCT	195	BIO/TT	Tiv	1st and 2nd	PLB
Ji 2014[54]	China	RCT	189	BIO/TT	Sor	NS/NC	BSC
Kane 2009[55]	USA	RCT	602	BIO/TT	Sor	NS/NC	PLB
Kang 2015[56]	South Korea	RCT	202	BIO/TT	Axi	NS/NC	PLB
Kang 2018[79]	South Korea	OBS	65	BIO/TT	Sor	NS/NC	BSC
KEYNOTE-240[57]	USA	RCT	413	IT	Pem	2nd	BSC + PLB
Lai 1988[58]	China	RCT	106	CT	Dox	1st	NS/NC
Lesmana 2012[80]	Indonesia	OBS	88	BIO/TT	Sor	NS/NC	NS/NC
Ling-lin 2011[36]	China	SR	2	BIO/TT	Sor	2nd	PLB
Liu 2021[37]	China	SR	2	BIO/TT	Sor	2nd or more	PLB
METIV-HCC[59]	Italy	RCT	340	BIO/TT	Tiv	2nd	PLB
Meyers 2021[38]	Canada	SR	12	BIO/TT and IT	Reg, Cab, Bri, Tiv, Pem, Eve, ADI-peg 20, S-1, GC33	1st and 2nd	PLB
NCT01932385[70]	China	Protocol of RCT	-	BIO/TT	Sor	NS/NC	BSC
Niu 2016[39]	China	SR	8	BIO/TT	Sor, Ram, Eve, Tiv, Bri	NS/NC	NS/NC
Park 2021[40]	USA	SR	13	BIO/TT and IT	Sor, Reg, Cab, Ram, Apa, Pem, Bri, Tiv, Eve, Axi	NS/NC	BSC
PRODIGE 21[60]	France	RCT	157	BIO/TT	(a) Sor (b) Pra (c) Sor + Pra	NS/NC	BSC
REACH[61]	USA	RCT	565	BIO/TT	Ram	2nd	PLB
REACH-2[62]	USA	RCT	292	BIO/TT	Ram	2nd	PLB
RESORCE[63]	Spain	RCT	573	BIO/TT	Reg	NS/NC	PLB
Rimassa 2013[64]	Italy	RCT	101	BIO/TT	Sor	NS/NC	BSC
Sanoff 2016[81]	USA	OBS	807	BIO/TT	Sor	NS/NC	NS/NC
Santoro 2013[66]	Italy	RCT	107	BIO/TT	Tiv	2nd	PLB
S-CUBE[65]	Japan	RCT	334	BIO/TT	S-2	2nd or more	PLB
SHARP[67]	Spain	RCT	602	BIO/TT	Sor	NS/NC	PLB

(*Continued*)

Table 1 (Continued).

Study ID	Country	Study Design	N*	Type of ACD	Specific Drugs Used	Treatment Line	Comparison
Solimando 2022[41]	Italy	SR	14	BIO/TT and IT	Tiv, S-1, Reg, Ram, ADI-PEG20, Eve, Cab, Bri, Pem, Axi, Cod	2nd	Standard care
Sonbol 2020[42]	USA	SR	8	BIO/TT and IT	Sor, Pem, Reg, Cab, Ram, Bri	1st, 2nd	PLB
Stemmer 2021[68]	Israel	RCT	78	BIO/TT	Nam	2nd	PLB
Trevisani 2018[81]	Italy	OBS	229	CT	Cap, Metronomic Cap	2nd	BSC
Xia 2021[83]	USA	OBS	65	BIO/TT and IT	(a) Reg, Cab, (b) Niv, Pem, Ram	2nd	BSC
Zhang 2012[43]	China	SR	2	BIO/TT	Sor	1st	NS/NC
Zhang 2020[84]	China	OBS	92	BIO/TT	Apa	2nd	BSC

Notes: *N of patients/ N of studies relevant to our question/Number of studies included in the SR.
Abbreviations: OBS, observational study; PT, protocol; quasi-experimental study; RCT, randomized control trial; SR, systematic review; NS/NC, not specified/ not clear; ASC, active symptom control; PLB, placebo; BSC, best supportive care; ACDs, anticancer drugs; CT, chemotherapy; BIO/TT, biological/ target therapy; IT, immunotherapy; 5-FU, 5-fluorouracil; Apa, apatinib; Axi, axitinib; Bev, bevacizumab; Bri, brivanib; Cab, cabozantinib; Cap, capecitabine; Car, carboplatin; Cis, cisplatin; Cod, codrituzumab; Dox, doxorubicin; Epi, epirubicin; Erl, erlotinib; Eto, etoposide; Eve, everolimus; FU, fluorouracil; Gem, gemcitabine; Iri, irinotecan; Ivo, vosidenib; Len, lenvatinib; Let, letoposide; Mit, mitomycin; Nam, namodenoson; Niv, nivolumab; Ora, orantinib; Oxa, oxaliplatin; Pac, paclitaxel; Pem, pembrolizumab; Pra, pravastatin; Ram, ramucirumab; Reg, regorafenib; Sor, sorafenib; Tiv, tivantinib; UFT, tegafur/uracil; Van, vandetanib.

Discussion

In this mapping review, we have summarized the body of evidence regarding the effects of ACDs compared to BSC for patients with advanced HBCs in prespecified patient-important outcomes. Most of the studies assessed the effectiveness of biological/targeted therapy in advanced liver cancer, and chemotherapy in advanced gallbladder or bile duct cancers.

Regarding advanced liver cancer, most of the identified evidence reported findings that favored ACDs for survival outcomes and supportive care for toxicity. Nevertheless, less than half of the included studies provided clear comparative data for toxicity. Despite being the third most reported outcome, QoL was explicitly assessed in only nine studies, with most showing no significant differences between groups. Other outcomes were scarcely reported: only two studies

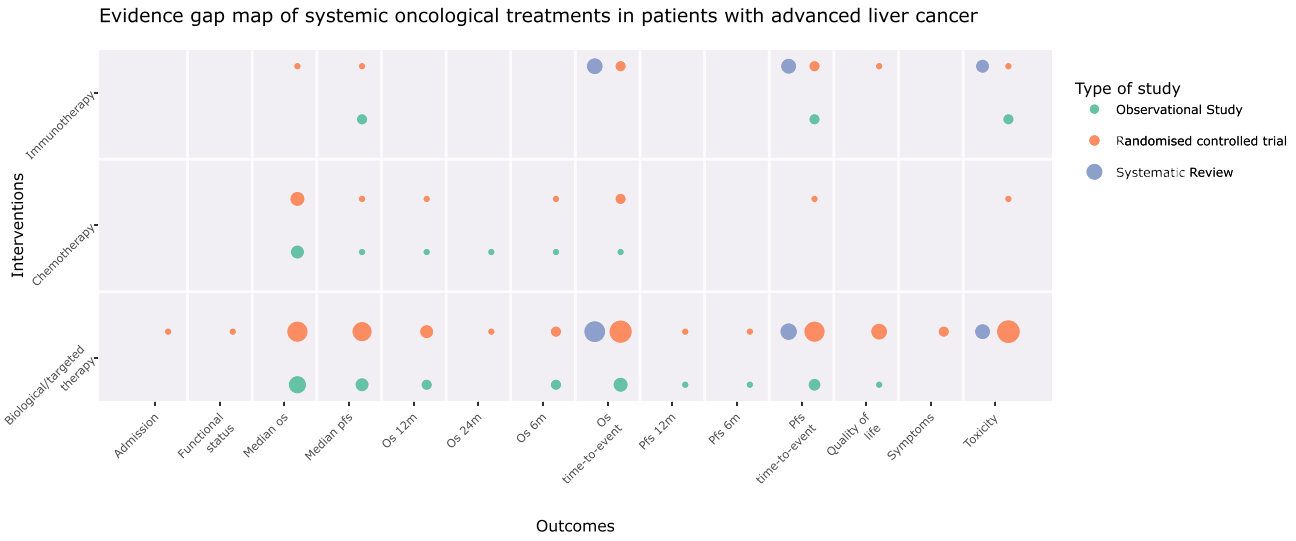

Figure 2 Evidence map for ACD in advanced liver cancer. The size of each dot represents the number of studies that address the intervention/outcome relationship. The color of each dot represents the methodological design of the study group.

Study ID	Study design	Type of ACDs	OS 6 mo	OS 12 mo	OS 24 mo	OS time-to-event	Median OS	PFS 6 mo	PFS 12 mo	PFS 24 mo	PFS time-to-event	Median PFS	Functional status	Toxicity	Symptoms	Quality of life	Admissions to hospital	Quality of death
Abdelmaksoud 2021	OBS	BIO/TT	NR	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
El Baghdady 2020	OBS	BIO/TT	FI	FI	NR	NR	FI	FI	FI	NR	FI	FI	NR	NR	NR	FC	NR	NR
Hiramine 2013	OBS	BIO/TT	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hiraoka 2021	OBS	BIO/TT	NR	NR	NR	NR	FI	NR	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR
Hsiao 2019	OBS	BIO/TT	NR	NR	NR	FI	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kang 2018	OBS	BIO/TT	NR	NR	NR	FI	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lesmana 2012	OBS	BIO/TT	NR	NR	NR	FI	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sanoff 2016	OBS	BIO/TT	ND	ND	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zhang 2020	OBS	BIO/TT	NR	NR	NR	FI	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Abou-Alfa 2016	RCT	BIO/TT	NR	NR	NR	ND	NR	NR	NR	NR	ND	NR	NR	ND	NR	NR	NR	NR
AHELP	RCT	BIO/TT	FI	ND	NR	FI	ND	FI	ND	NR	FI	FI	NR	FC	NR	NR	NR	NR
Asia-Pacific	RCT	BIO/TT	NR	NR	NR	FI	FI	NR	NR	NR	NR	NR	NR	FC	NR	NR	NR	NR
BRISK-PS	RCT	BIO/TT	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR	NR	FC	NR	NR	NR	NR
CELESTIAL	RCT	BIO/TT	FI	FI	FI	FI	NR	NR	NR	NR	FI	NR	NR	FC	NR	NR	NR	NR
EUCTR2007-007629-32-IT 2008	RCT	BIO/TT	NR	NR	NR	NR	ND	NR	NR	NR	NR	ND	NR	FC	NR	NR	NR	NR
EVOLVE-1	RCT	BIO/TT	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR	NR	FC	NR	NR	NR	NR
Hsu 2012	RCT	BIO/TT	NR	NR	NR	ND	ND	NR	NR	NR	ND	ND	NR	NR	NR	NR	NR	NR
JET-HCC	RCT	BIO/TT	NR	NR	NR	ND	ND	NR	NR	NR	ND	ND	NR	FC	NR	NR	NR	NR
Ji 2014	RCT	BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	ND	NR	ND	NR	NR
Kane 2009	RCT	BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	FC	NR	NR	NR	NR
Kang 2015	RCT	BIO/TT	NR	NR	NR	ND	ND	NR	NR	NR	FI	ND	NR	FC	FC	FC	NR	NR
METIV-HCC	RCT	BIO/TT	NR	NR	NR	ND	ND	NR	NR	NR	ND	ND	NR	ND	NR	ND	ND	NR
PRODIGE 21	RCT	BIO/TT	NR	NR	NR	NR	ND	NR	NR	NR	NR	ND	NR	ND	NR	ND	NR	NR
REACH	RCT	BIO/TT	NR	NR	NR	ND	ND	NR	NR	NR	FI	FI	NR	FC	NR	ND	NR	NR
REACH-2	RCT	BIO/TT	NR	NR	NR	FI	FI	NR	NR	NR	FI	FI	ND	FC	NR	ND	NR	NR
RESORCE	RCT	BIO/TT	NR	NR	NR	FI	FI	NR	NR	NR	FI	FI	NR	ND	NR	ND	NR	NR
Rimassa 2013	RCT	BIO/TT	NR	NR	NR	NR	NR	NR	NR	NR	ND	ND	NR	NR	NR	NR	NR	NR
Santoro 2013	RCT	BIO/TT	NR	NR	NR	ND	ND	NR	NR	NR	ND	ND	NR	FC	NR	NR	NR	NR
SHARP	RCT	BIO/TT	NR	FI	NR	FI	FI	NR	NR	NR	NR	NR	NR	FC	ND	NR	NR	NR
Stemmer 2021	RCT	BIO/TT	NR	ND	NR	ND	NR	NR	NR	NR	ND	NR	NR	ND	NR	NR	NR	NR
S-CUBE	RCT	BIO/TT	NR	ND	ND	ND	ND	NR	NR	NR	FI	FI	NR	FC	NR	NR	NR	NR
Chen 2021	SR	BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ding 2020	SR	BIO/TT	NR	NR	NR	ND	NR	NR	NR	NR	ND	NR	NR	FC	NR	NR	NR	NR
Faruque 2014	SR	BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	FC	NR	NR	NR	NR
Finn 2018	SR	BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Huang 2019	SR	BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ling-lin 2011	SR	BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Liu 2021	SR	BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	ND	NR	NR	ND	NR	NR	NR	NR
Niu 2016	SR	BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zhang 2012	SR	BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Xia 2021 (a)	OBS	BIO/TT and IT	NR	NR	NR	NR	NR	NR	NR	NR	ND	ND	NR	ND	NR	NR	NR	NR
Xia 2021 (b)	OBS	BIO/TT and IT	NR	NR	NR	NR	NR	NR	NR	NR	FI	FI	NR	ND	NR	NR	NR	NR
Guo 2019	SR	BIO/TT and IT	NR	NR	NR	ND	NR	NR	NR	NR	ND	NR	NR	ND	NR	NR	NR	NR
Sonbol 2020	SR	BIO/TT and IT	NR	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Griffiths 2022	SR	BIO/TT and IT	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	ND	NR	NR	NR	NR
Haber 2021	SR	BIO/TT and IT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Meyers 2021	SR	BIO/TT and IT	NR	NR	NR	ND	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Park 2021	SR	BIO/TT and IT	NR	NR	NR	ND	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR
Solimando 2022	SR	BIO/TT and IT	NR	NR	NR	ND	NR	NR	NR	NR	FI	NR	NR	FC	NR	NR	NR	NR
Du 2019	OBS	CT	NR	NR	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR
Jang 2007	OBS	CT	FI	FI	FI	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Trevisani 2018	OBS	CT	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Abdel Wahab 2010	RCT	CT	NR	NR	NR	ND	ND	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ishikawa 2001	RCT	CT	FI	FI	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lai 1988	RCT	CT	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	FC	NR	NR	NR	NR
Chen 2022	OBS	CT and BIO/TT	NR	NR	NR	FI	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Abou-Alfa 2018	RCT	IT	NR	NR	NR	ND	NR	NR	NR	NR	ND	NR	NR	ND	NR	NR	NR	NR
KEYNOTE-240	RCT	IT	NR	NR	NR	FI	ND	NR	NR	NR	FI	ND	NR	NR	NR	ND	NR	NR
Jácome 2021	SR	IT	NR	NR	NR	FI	NR	NR	NR	NR	FI	NR	NR	FI	NR	NR	NR	NR

Figure 3 Summary of the direction of the effect for each study and outcome in patients with advanced liver cancer.

Abbreviations: OBS, observational study; RCT, randomized control trial; SR, systematic review; CT, chemotherapy; BIO/TT, biological/target therapy; IT, immunotherapy; OS, Overall Survival. PFS, Progression-free survival; mo, Months; FI, Favors intervention (ACD); ND, No difference; FC, Favors comparison (BSC/placebo); NR, Not reported.

Table 2 Characteristics of the Included Studies on Advanced Gallbladder and Bile Duct Cancers

Study ID	Country	Study Design	N*	Type of ACD	Specific Drugs Used	Treatment Line	Comparison
ABC-06[87]	England	RCT	162	CT	FU, and Oxa+ASC	2nd	ASC
Abdel-Rahman 2018[75]	Canada	SR	1	CT	Gem, Oxa	1st	NS/NC
Azarfane 2021[96]	France	OBS	82	CT and BIO/TT	Gem+Oxa/Gem+Cis/FU +Oxa/Gem alone/FU+Cis/ Gem, Oxa and Reg	1st	No SOT
Brunner 2004[97]	Germany	OBS	64	CT	5-FU, Cis, Gem, Mit	NS/NC	NS/NC
ClarIDHy[88]	USA	RCT	185	BIO/TT	Ivo	NS/NC	PLB
Dierks 2018[98]	Netherlands	OBS	208	CT	Cis, Gem	1st	BSC
Dover 2014[99]	USA	OBS	243	CT	5FU, Cap, Cis, Gem	NS/NC	BSC
Ghiassi-Nejad 2016[100]	USA	OBS	1241	CT	NS/NC	NS/NC	NS/NC
Glimelius 1996[89]	Sweden	RCT	37	CT	5-FU, Let	NS/NC	BSC
Ishii 2004[101]	Japan	OBS	89	CT	5-FU, Cis, Dox, Epi, Mit	1st	BSC
Ji 2018[102]	South Korea	OBS	604	CT	NS/NC	1st	BSC
Jiang 2021[86]	China	SR	1	CT	5-FU, or Gem/Oxa	1st and 2nd	PLB
Kataria 2019[90]	India	RCT	51	CT and BIO/TT	(a) Erl (b) Cap	NS/NC	BSC
Koch 2020[103]	Germany	OBS	220	CT and BIO/TT	Gem, 5-FU, Sor, Car, Pac, Oxa, Cap, Iri, Cis, Mit, Bev	1sr or more	BSC
Mao 2020[104]	China	OBS	4527	CT	NS/NC	NS/NC	NS/NC
Min Jae 2018[105]	South Korea	OBS	102	CT	Cis, Gem	NS/NC	BSC
Moik 2019[106]	Austria	OBS	80	CT	NS/NC	2nd	BSC
Park 2014[91]	South Korea	RCT	43	CT	S-1	1st	BSC
REACHIN[15]	Belgium	RCT	66	BIO/TT	Reg	2nd or more	BSC + PLB
Sharma 2010[92]	India	RCT	82	CT	(a) FU; (b) Gem+Oxa	NS/NC	BSC
Shin 2020[107]	South Korea	OBS	113	CT	Cis, Gem	NS/NC	BSC
Singh 2014[108]	India	OBS	50	CT	Gem, Oxa	NS/NC	BSC
Singh 2016[95]	India	Q-Exp	85	CT	Cis, Gem, Oxa	NS/NC	BSC
Takada 1998[93]	Japan	RCT	83	CT	5-FU, Dox, Mit	NS/NC	NS/NC
Yonemoto 2007[109]	Japan	OBS	304	CT	5-FU, Eto	NS/NC	BSC
Zaidi 2021[110]	Canada	OBS	136	CT	NS/NC	2nd	NS/NC

Notes: *N of patients/ N of studies relevant to our question/Number of studies included in the SR.

Abbreviations: OBS, observational study; PT, protocol; quasi-experimental study; RCT, randomized control trial; SR, systematic review; NS/NC, not specified/ not clear; ASC, active symptom control; PLB, placebo; BSC, best supportive care; ACDs, anticancer drugs; CT, chemotherapy; BIO/TT, biological/ target therapy; IT, immunotherapy; 5-FU, 5-fluorouracil; Apa, apatinib; Axi, axitinib; Bev, bevacizumab; Bri, brivanib; Cab, cabozantinib; Cap, capecitabine; Car, carboplatin; Cis, cisplatin; Cod, codrituzumab; Dox, doxorubicin; Epi, epirubicin; Erl, erlotinib; Eto, etoposide; Eve, everolimus; FU, fluorouracil; Gem, gemcitabine; Iri, irinotecan; Ivo, vosidenib; Len, lenvatinib; Let, letoposide; Mit, mitomycin; Nam, namodenoson; Niv, nivolumab; Ora, orantinib; Oxa, oxaliplatin; Pac, paclitaxel; Pem, pembrolizumab; Pra, pravastatin; Ram, ramucirumab; Reg, regorafenib; Sor, sorafenib; Tiv, tivantinib; UFT, tegafur/uracil; Van, vandetanib.

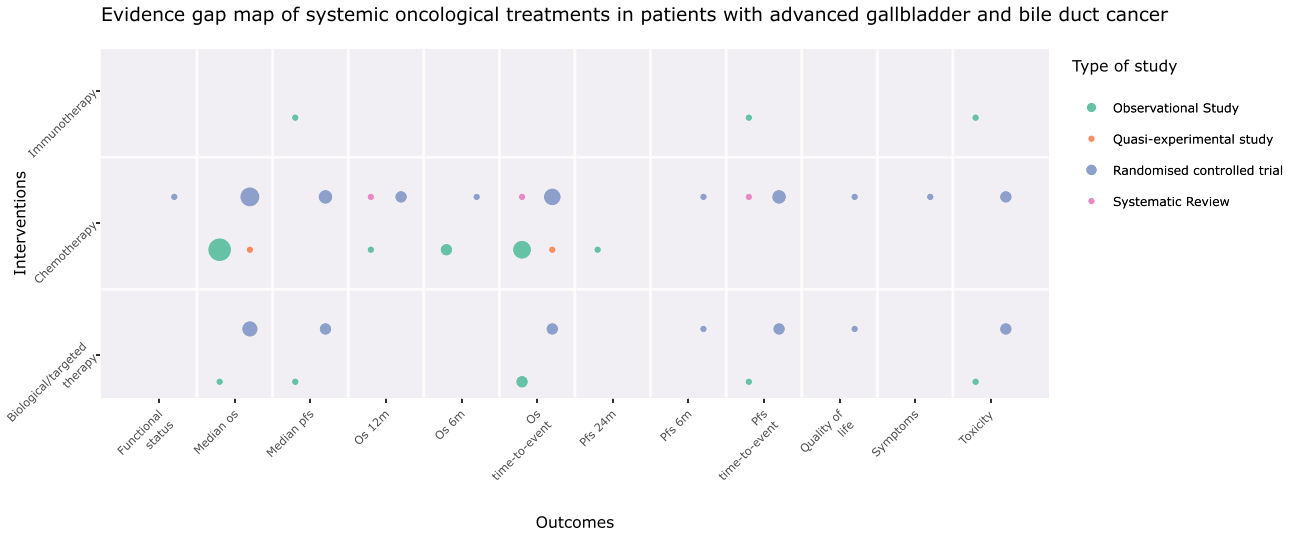

Figure 4 Evidence map for ACD in advanced gallbladder/bile duct cancers. The size of each dot represents the number of studies that address the intervention/outcome relationship. The color of each dot represents the methodological design of the study group.

reported symptoms, one reported functional status, one reported admission, and none reported outcomes related to quality of death. Despite showing a similar direction of effect in terms of survival outcomes, the mapping of gallbladder and bile duct cancers also revealed a scarce report for other outcomes, with only five studies clearly reporting toxicity, two reporting QoL, one reporting functional status and one reporting symptoms. None of these studies reported data related to hospital admissions or quality of death.

In the context of advanced HBCs, where a poor survival is expected, other outcomes related to patients' well-being should be considered critical for shared decision-making processes. Primary evidence and its synthesis through SRs are key components for making recommendations (eg, using evidence-to-decision frameworks); therefore, in order to improve quality of care, it is essential for the relevant body of evidence to consider these outcomes. Our results highlight the importance of assessing and reporting outcomes beyond survival-related ones, which are currently not being systematically considered. There are important gaps of evidence in terms of quality of death, admissions to hospital, symptoms, and functional status, and there is still room for improvement in reporting of adverse events.

The delivery of healthcare for patients with advanced cancer should be centered on proven high-value, safe, and effective treatments, ensuring its quality by including the values and preferences of patients and their caregivers.[111,112] The consideration of Core Outcome Sets (COS) when undertaking clinical research could close the gap to achieve this objective.[113] COS represent a minimum agreed set of outcomes that should be measured and reported in clinical research, which are relevant for key stakeholders, including patients and healthcare professionals.[114] The inclusion of Patient Reported Outcome Measures (PROMs) in COS is an area where consensus is still scarce.[115] A systematic review showed an important heterogeneity in the selection of PROMs, and the instruments or measures used in cancer populations.[116] In this sense, outcome report inconsistency has been elucidated as a cause of the scarce evidence informing clinical guidelines in care at the EoL.[117,118] Providing accurate and consistent information about predefined critical outcomes will help to identify both specific clinical questions that have been extensively studied, as well as evidence gaps that need further research. This will help to guide future primary research and evidence syntheses to make better recommendations for the treatment of these patients.

Our study has several strengths. We undertake a comprehensive search strategy on six databases, with additional efforts to identify eligible studies, such as the citation chase process. The screening process was performed by two independent reviewers, as well as the data extraction. We also showed a graphical display of our results. Our evidence map has a broad range of potential end-users including funding agencies, researchers, and clinicians. It complements other review methods for describing existing research, informing future research efforts, and addressing evidence gaps. The main limitation of our study is that the methodological quality of the studies and the magnitude of effect of the findings have not been assessed, as this is outside the scope of a mapping review. Therefore, the effect of the interventions must be interpreted with caution, since our

Study ID	Study design	Type of ACDs	OS 6 mo	OS 12 mo	OS 24 mo	OS time-to-event	Median OS	PFS 6 mo	PFS 12 mo	PFS 24 mo	PFS time-to-event	Median PFS	Functional status	Toxicity	Symptoms	Quality of life	Admissions to hospital	Quality of death
ClarIDHy	RCT	BIO/TT	NR	NR	NR	ND	ND	NR	NR	NR	FI	FI	NR	FC	NR	ND	NR	NR
REACHIN	RCT	BIO/TT	NR	NR	NR	ND	ND	FI	NR	NR	FI	FI	NR	ND	NR	NR	NR	NR
Brunner 2004	OBS	CT	NR	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dierks 2018	OBS	CT	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dover 2014	OBS	CT	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ghiassi-Nejad 2016	OBS	CT	ND	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ishii 2004	OBS	CT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ji 2018	OBS	CT	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mao 2020	OBS	CT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Min Jae 2018	OBS	CT	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Moik 2019	OBS	CT	FI	FI	NR	FI	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shin 2020	OBS	CT	NR	NR	NR	FI	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Singh 2014	OBS	CT	NR	NR	NR	NR	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR	NR	NR
Yonemoto 2007	OBS	CT	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zaidi 2021	OBS	CT	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Singh 2016	Q-Exp	CT	NR	NR	NR	FI	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ABC-06	RCT	CT	ND	ND	NR	FI	ND	NR	NR	NR	NR	NR	NR	FI	NR	NR	NR	NR
Glimelius 1996	RCT	CT	NR	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR	NR	FI	FI	NR	NR
Park 2014	RCT	CT	NR	FI	NR	FI	FI	FI	NR	NR	FI	FI	NR	ND	NR	NR	NR	NR
Sharma 2010 (a)	RCT	CT	NR	NR	NR	ND	ND	NR	NR	NR	ND	ND	NR	NR	NR	NR	NR	NR
Sharma 2010 (b)	RCT	CT	NR	NR	NR	FI	ND	NR	NR	NR	FI	FI	NR	NR	NR	NR	NR	NR
Takada 1998	RCT	CT	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR	ND	NR	NR	NR	NR	NR
Abdel-Rahman 2018	SR	CT	NR	ND	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jiang 2021	SR	CT	NR	NR	NR	FI	NR	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR	NR
Azarfane 2021	OBS	CT and BIO/TT	NR	NR	NR	FI	ND	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Koch 2020	OBS	CT and BIO/TT	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kataria 2019 (a)	RCT	CT and BIO/TT	NR	NR	NR	NR	FI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kataria 2019 (b)	RCT	CT and BIO/TT	NR	NR	NR	NR	ND	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Figure 5 Summary of the direction of the effect for each study and outcome in patients with advanced gallbladder and bile duct cancers.
Abbreviations: OBS, observational study; RCT, randomized control trial; SR, systematic review; CT, chemotherapy; BIO/TT, biological/target therapy; IT, immunotherapy; OS, Overall Survival; PFS, Progression-free survival; mo, Months; FI, Favors intervention (ACD); ND, No difference; FC, Favors comparison (BSC/placebo); NR, Not reported.

methods do not intend to appraise the internal validity of the findings nor to provide a synthesized estimate. Another possible limitation is publication bias, although we tried to limit this by searching in public study registries.

This evidence mapping shows the current landscape of research for ACDs and BSCs for patients with advanced HBCs. It complements other evidence synthesis methods to better inform research areas that need further attention. We highlight critical evidence gaps regarding non-survival outcomes in both primary studies and evidence syntheses assessing ACDs for patients with advanced HBCs. Future research should explicitly assess and report outcomes that can be critical for decision-making processes, such as toxicity and QoL.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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