



Review

Liver resection for noncolorectal liver metastases: the good, the bad, and the ugly



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ABSTRACT

Background: Noncolorectal liver metastases (NONCOLMETs) are composed of a heterogeneous group historically associated with poor outcomes. Advances in systemic therapy and liver interventions have renewed interest in liver resection (LR) for selected patients. However, evidence remains inconsistent, and indications vary across tumor types.

Methods: A comprehensive MEDLINE and Embase search up to February 2025, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, identified studies assessing the outcomes of liver interventions for NONCOLMETs. The studies were grouped by primary tumor. The extracted and summarized data included overall survival (OS), prognostic determinants, and comparisons with nonsurgical management.

Results: From 899 screened records, survival after LR varied markedly. The most favorable outcomes were seen in neuroendocrine tumors (median OS, 84–120 months) and gastrointestinal stromal tumors (GISTs) responding to tyrosine kinase inhibitors (TKIs; median OS, 70–90 months). Breast and selected urogynecologic cancers showed a median OS of > 36 months. However, esophageal, gastric, and pancreatic cancers showed benefit only in exceptionally selected, chemoresponsive liver-only disease. Across tumor types, specific favorable prognostic factors included oligometastatic and liver-only disease; longer disease-free interval; radiologic or biomarker response to systemic therapy, such as carbohydrate antigen 19–9 decline in pancreatic cancer, estrogen receptor/progesterone receptor positivity in breast cancer, human epidermal growth factor receptor 2 or programmed death-ligand 1 expression in gastroesophageal cancer, and TKI response in GIST; and well-differentiated histology. Comparative and propensity-matched analyses consistently suggested a survival benefit from LR in favorable subsets of patients with NONCOLMETs.

Conclusion: LR may provide meaningful survival benefit in carefully selected patients with biologically favorable, liver-dominant NONCOLMETs. Multidisciplinary evaluation and tumor-specific selection criteria remain essential. Prospective studies are needed to refine the indications.

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Introduction

Liver metastases (LMs) represent a final common pathway for systemic dissemination across various malignancies. Historically considered a manifestation of terminal disease, hepatic involvement is now recognized as a potentially controllable event in selected patients treated with multimodal strategies [1]. Over the past few decades, the combination of improved systemic regimens and hepatic surgery has redefined the role of liver resection (LR) and other local interventions for selected patients with LMs originating not only from the colon or rectum but also from noncolorectal LMs (NONCOLMETs) [2–5].

In patients with NONCOLMETs, reported survival varies widely, largely reflecting differences in primary tumor type, disease burden, and tumor biology [5]. Neuroendocrine tumors (NETs) display the most favorable outcomes, with 5-year overall survival (OS) rates of 60% to 80% after LR [6,7], reflecting their less aggressive behavior and the feasibility of repeated interventions. In contrast, gastrointestinal (GI) tumors, such as gastric, esophageal, or pancreatic cancers, demonstrate only marginal benefit from LR and only in highly selected cases. When LR is combined with tyrosine kinase inhibitors (TKI), such as imatinib, sunitinib, or regorafenib, good disease control can be achieved in specific tumor types, such as GI stromal tumors (GISTs) [8]. Similarly, selected patients with hormone receptor-positive breast cancer and those with some gynecologic, urological, melanoma, or soft tissue sarcoma (STS) LM may achieve durable survival with multimodal treatment [9–14].

Despite the heterogeneity of tumor origins, several cross-tumor principles have emerged to guide patient selection for liver-directed therapy. One of the most consistent determinants of benefit is limited hepatic-only disease, typically solitary or oligometastatic lesions [15]. Metachronous metastases and a disease-free interval (DFI) of > 12 months are consistently associated with improved survival [3,5]. Conversion to resectability after systemic therapy may identify subgroups with less aggressive tumor biology [2,3,5]. Biomarkers, such as carbohydrate antigen 19-9 (CA 19-9), decline in pancreatic cancer, hormone receptor status, and more specifically, estrogen receptor (ER)/progesterone receptor (PR) status in breast cancer, human epidermal growth factor receptor 2 (HER2) expression in gastroesophageal adenocarcinoma, and molecular response to TKI in GIST further refine multidisciplinary decision-making [8,15–18]. Ultimately, LR for NONCOLMETs should be considered only after comprehensive multidisciplinary evaluation, ensuring oncologic rationale and technical feasibility within an integrated framework [3,5,19].

The current scoping review summarizes the current state of the art in the management of NONCOLMETs, reporting survival outcomes after liver interventions compared with systemic therapy alone in the era of modern, personalized systemic treatment, including targeted therapies and biological agents. In addition, using an anatomical, biological, and conditional (or patient-related) framework, it synthesizes prognostic and selection factors that may help liver surgeons distinguish patients likely to benefit from LR from those in whom surgery should be avoided.

Materials and methods

Search strategy

The search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for scoping review [20]. A comprehensive search of MEDLINE and Embase was performed for reports published before February 11, 2025, using combined text and Medical Subject Headings terms, with no language restrictions. Search terms included “non colorectal,” “non-colorectal,” “noncolorectal,” “liver metastases,” and tumor-specific

keywords. The references of retrieved articles were cross-checked to identify additional relevant studies.

Study selection

Studies included in the review met the following criteria: (i) patients aged > 18 years, (ii) patients who underwent any type of liver intervention for NONCOLMETs, and (iii) experimental or observational (prospective and retrospective) and case series regarding the treatment of patients with NONCOLMETs. The exclusion criteria were animal studies, case reports, editorials, and comments. When duplicate reports from the same cohort were identified, only the most recent publication or the one with the longest follow-up period was included. Full-text articles were retrieved for further assessment if they were not excluded during the initial screening. In addition, reference lists of the included papers were cross-checked to identify additional eligible studies.

Data collection

To determine eligibility, several researchers assessed titles and abstracts of selected papers, grouped by primary tumor diagnosis. The full articles were reviewed in detail. Extracted data included country of study, design, number of participants, type of liver intervention, oncologic outcomes, and determinants of outcomes.

Statistical analysis

The authors independently evaluated the included studies for quality according to the study design. No specific tool for quality assessment was used because of the high heterogeneity of the included studies.

Data were summarized descriptively with numbers and percentages, proportions, and medians, along with corresponding ranges. No quantitative synthesis was planned due to heterogeneity in populations, interventions, and outcome reporting. Figures and tables were generated using Microsoft Office.

Results

The literature search yielded 899 records. The article selection process and full-text retrieval were performed separately for each tumor subtype. Fig. 1 and Tables 1 and 2 present a global overview of the evidence identified in the literature.

Reported survival

Survival outcomes after LR or other liver interventions for NONCOLMETs were highly heterogeneous, largely reflecting tumor-specific biology. The reported median OS ranged from 20 to 30 months in gastric, esophageal, and pancreatic primaries to more than 60 to 80 months in NETs and GISTs treated using targeted or multimodal strategies. Of note, the 5-year OS remained below 15% in pancreatic, gastric, and esophageal cancers; was 25% to 35% in breast and selected gynecologic tumors; was 30% to 50% in GISTs and STSs, and exceeded 50% to 70% in NETs. Table 1 and Fig. 1 present the reported survival outcomes for NONCOLMETs treated with LR or other liver interventions.

Comparative outcomes between surgery and nonsurgical management

Several determinants of favorable outcomes emerged consistently across tumor types. Oligometastatic disease, defined as limited hepatic tumor burden (solitary or ≤3 lesions with unilobar distribution) and resectability with negative (R0) margins, represented the most consistent predictor of long-term survival.

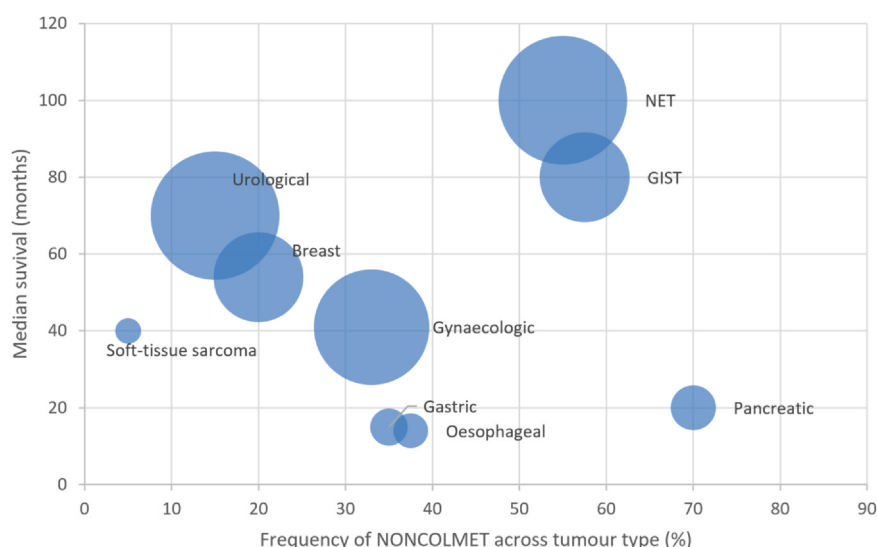


Figure 1. Bubble plot of NONCOLMET. The figure shows the frequency of liver metastases (x-axis) vs the expected median overall survival (y-axis) in months. GIST, gastrointestinal stromal tumor; NET, neuroendocrine tumor; NONCOLMET, noncolorectal tumor liver metastasis.

Metachronous presentation, a prolonged DFI (> 12 months), and objective radiologic or biomarker response to systemic or targeted therapy (eg, CA 19-9 decline in pancreatic cancer, TKI response in GIST, or hormonal or HER2 positivity in breast cancer) further identified biologically indolent disease suitable for LR. The absence of uncontrolled extrahepatic spread, good performance status, and integration of surgery within a multimodal treatment plan were universal prerequisites for benefit. Table 2 presents the cross-tumor determinants of favorable outcomes.

Esophageal cancer LMs

LMs were present in 35% to 40% of patients with esophageal cancer at diagnosis [21,22], with a median survival of only 5 to 10 months under chemotherapy alone [23,24].

The role of LR in oligometastatic esophageal cancer LMs (ECLMs) has been controversial, as confirmed by the European clinical practice guidelines on OligoMetastatic Esophagogastric Cancer (OMEC-4)

[15]. The literature search retrieved only a few retrospective mono- or multicentric studies [24,25], including 2 national registries, the Spanish AGAMENON [17] and the Dutch registry [22], but with relatively low patient numbers, therefore not suitable for forming robust recommendations.

Consistent factors for considering LR included low hepatic tumor burden, defined as solitary or ≤ 3 lesions, DFI > 12 months [22,26–28], and chemotherapy response before LR [29,30]. Conversely, synchronous presentation, diffuse lesions, or uncontrolled extrahepatic spread predicted poor outcomes. No specific esophageal cancer-related factors for a favorable or unfavorable prognosis were identified.

Overall, selected patients treated with a multimodal approach involving LR seemed to show a more favorable prognosis than those who did not undergo surgery [31], with 3-year survival rates in 21% to 50% of patients [5,17,25,32]. In the 2 studies with the longest OS after LR, 77% of the patients had solitary LMs, 15% of patients had 2 liver lesions, and only 1 patient was treated for 3 LMs [26,27]. Liu et al. [27] showed that the outcomes of patients who underwent

Table 1
Summary of reported survival after liver resection for noncolorectal liver metastases.

Primary tumor	Median OS (mo)	Main prognostic factors	Best candidates for local therapy
Neuroendocrine LM	84–120	Lower grade, cytoreduction $\geq 70\%$ feasible, limited hepatic disease, and no extrahepatic spread	Parenchymal-sparing resection achieving $\geq 70\%$ cytoreduction, repeatable liver-directed interventions
Breast cancer LM	12–84	ER/PR positivity, longer DFI, R0 resection, limited hepatic disease, and no extrahepatic spread	Liver-only disease under good systemic control
GIST and STS LM	70–90 (GIST)/ 30–50 (STS)	Response to TKI (GIST), metachronous presentation, R0 resection, limited hepatic disease, and no extrahepatic spread	Surgery after maximal TKI response for GIST. Resection of isolated or limited lesions for STS
Gynecologic LM (ovarian > endometrial > cervical)	27–54	Response to chemotherapy, complete cytoreduction (R0), limited disease, and no peritoneal carcinomatosis	Liver involvement included within planned cytoreductive surgery in which R0 is achievable
Urologic LM (RCC, GCT, selected bladder cancer)	27–120	Response to chemotherapy, longer DFI, R0 resection, and limited hepatic disease	Resection of isolated or limited lesions for RCC, GCT, or highly selected bladder LM
Pancreatic cancer LM	11–40	Response to chemotherapy, longer DFI, and very limited liver-only disease	Very selected liver-only disease with strong radiologic and biomarker response to modern chemotherapy
Gastric cancer LM	6–31	Response to chemotherapy, longer DFI, and very limited liver-only disease	Very selected liver-only disease with strong radiologic and biomarker response to modern chemotherapy
Esophageal cancer LM	5–27	Response to chemotherapy, longer DFI, and very limited liver-only disease	Very selected liver-only disease with strong radiologic and biomarker response to modern chemotherapy

DFI, disease-free interval; ER, estrogen receptor; GCT, germ cell tumor; GIST, gastrointestinal stromal tumor; LM, liver metastasis; NET, neuroendocrine tumor; OS, overall survival; PR, progesterone receptor; R0 resection, microscopically margin-negative resection (no residual tumor); RCC, renal cell carcinoma; STS, soft tissue sarcoma; TKI, tyrosine kinase inhibitor.

Table 2

Cross-tumor determinants of favorable outcome after liver-directed therapy for noncolorectal liver metastases.

Category	Favorable (Proceed to surgery)	Borderline	Unfavorable (Surgery contraindicated)
Patient factors	ECOG 0–1; age < 70; good nutritional status	ECOG 2; mild comorbidities	ECOG ≥ 3; severe comorbidities; malnutrition
Primary tumor biology	NET (lower grade), GIST (under effective TKI), sarcoma (low grade), breast (ER/PR+), ovarian or endometrial cancer (chemosensitive)		Undifferentiated/high-grade, small-cell, or anaplastic histology; aggressive mucinous, signet ring; or chemoresistant phenotypes
Liver metastasis biology	Chemoresponsive tumor, longer DFI, favorable biomarker trend → For pancreatic cancer CA 19-9 ↓ → For GIST TKI response	Partial chemoresponse or stable disease; modest or equivocal biomarker improvement	Progressive chemoresistant disease, increasing tumor markers, uncontrolled extrahepatic spread
Liver metastasis burden	“Oligometastatic disease”	Borderline resectable lesions	Diffuse/bilobar lesions, vascular encasement/invasion
Technical feasibility	Preserved hepatic reserve, R0 → For NET ≥ 70% cytoreduction		Limited hepatic reserve, R2 expected

CA 19-9, carbohydrate antigen 19-9; DFI, disease-free interval; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; GIST, gastrointestinal stromal tumor; LM, Liver metastasis; NET, neuroendocrine tumor; PR, progesterone receptor; R0, complete microscopic tumor resection; R2, macroscopically incomplete tumor resection; TKI, tyrosine kinase inhibitor.

surgery for metachronous ECLMs improved when the DFI was > 12 months. Seesing et al. [22] reported superior survival rates in 11 patients after the resection of mainly metachronous ECLMs, with a DFI between 11 and 27 months.

Gastric cancer liver LMs

LMs occurred in 30% to 40% of patients with gastric cancer, representing one of the most frequent metastatic sites, with poor prognosis under systemic therapy alone and a median OS of 6 to 11 months [33–36].

Gastric cancer LMs (GCLMs) are usually managed with palliative intent as indicated by the OMEC-4 guidelines [15]. However, emerging data suggest that LR is feasible in a selected subset of patients with oligometastatic GCLMs. The literature search retrieved retrospective studies and systematic reviews with no randomized controlled trials (RCTs) [37–41], including a national registry, the Italian Meta-Gastro register [42], and the Italian Research Group for Gastric Cancer (GIRCG) [43].

The indications for liver interventions included oligometastatic disease, generally defined as ≤3 nodules with a tumor size of ≤3 cm, metachronous presentation, and response to chemotherapy [37,44–46]. Recent papers considered the term “oligometastatic” to identify a subgroup of patients who could benefit from surgical treatment in the context of a multimodal approach [15,18,47,48]. Improved response to newer combinations, including triplet regimens with fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) and docetaxel, cisplatin, and fluorouracil, was shown to select potential candidates [49]. In addition, improved outcomes were observed in HER2 positive patients treated with systemic therapy in combination with trastuzumab [50] and in those with a programmed death-ligand 1 (PD-L1) expression who were treated with immune checkpoint inhibitors, such as nivolumab or pembrolizumab [51,52].

Liao et al. [38] published a systematic review that compared LR with other treatments. A total of 196 patients who underwent LR showed a median OS of 23.7 months compared with 7.6 months in those in the control group, with a 1-year OS of 69% vs 27%. Marte et al. [39] reported a 5-year OS of 26% and disease-free survival (DFS) of 22% in the LR group. In addition, Conde Monroy et al. [40] reported 1-, 3-, and 5-year OS rates of 70%, 35%, and 25%, respectively, and 1-, 3-, and 5-year DFS rates of 41%, 23%, and 20%, respectively. Better outcomes were associated with metachronous presentation, smaller tumor size, and unilobar and solitary lesions.

Data from the Italian prospective Meta-Gastro registry considered GCLMs as nonresectable in 120 of 142 patients. At re-evaluation, 8% of patients were deemed resectable and, thus, underwent surgical resection. The median survival estimates of patients deemed operable at diagnosis and those receiving conversion therapy were 14.8 and 27.6 months, respectively, whereas the median survival estimates of patients who received palliative surgery and those who received chemotherapy alone were 13.4 and 10.9 months, respectively [42]. The efficacy of conversion surgery was confirmed in a multicenter cohort study of the GIRCG [43].

These findings laid the groundwork for the German ENAISSANCE (AIO-FLOT5) RCT [18], which compared patients with limited metastatic disease who received FLOT plus trastuzumab if HER2 positive and nivolumab if PD-L1 positive and those who underwent radical complete surgical resection vs chemotherapy alone. The results are still awaited.

Pancreatic cancer LMs

Pancreatic ductal adenocarcinoma exhibited hepatic metastases in more than 70% of nonlocalized diseases [26,27], with a median OS of 11 to 13 months [53,54].

Although systemic therapy remains the standard of care for pancreatic cancer LMs (PCLMs), a carefully selected subset of patients seemed to benefit from multimodal strategies that included LR [1,55–58]. The literature search retrieved systematic reviews based on retrospective studies with no RCTs [59–61] and a national registry from Spain [62].

Patients displaying a more indolent clinical course and considered for surgical resection presented with limited liver burden, absence of extrahepatic disease, and durable responses to chemotherapy [53,55]. Regimens, such as FOLFIRINOX or gemcitabine plus nab-paclitaxel, have modestly improved the median OS, which ranges from 11 to 13 months [63,64]. Tumor marker dynamics, particularly CA 19-9, and radiographic evaluation were increasingly used to evaluate treatment response and guide management among responders [65,66].

The role of liver-directed therapies remained controversial [53,67,68]. The reported median survival typically ranged from 27 to 34 months for synchronous disease and 24 to 40 months for metachronous LM [16,59,60,69] after LR. These findings laid the groundwork for the Italian multicenter prospective SONAR trial (identification number: NCT06690528), which was designed to evaluate the feasibility and benefit of surgical resection in patients with liver-only metastatic pancreatic cancer.

Neuroendocrine LMs

NETs have presented a strong propensity for hepatic dissemination, affecting 21% to 90% of patients [6]. Surgical series consistently reported a 5-year OS between 60% and 80% [70,71] due to their less aggressive nature and responsiveness to multimodal therapy. Integration with systemic options, such as somatostatin analogs or peptide receptor radionuclide therapy, further extended disease control.

The literature search retrieved several retrospective series with no RCTs [7,70,72–91], with the most common sites for primary tumors being the pancreas and small bowel. Several studies have focused exclusively on small bowel NETs [72,84] and pancreatic NETs [81,88], which are known to have a higher tendency to develop LMs (50% and 75% of cases, respectively) [89,90] than NETs arising from other GI sites. According to the European Neuroendocrine Tumor Society (ENET) guideline, surgery with curative intent should be considered in grade 1 and grade 2 NETs, even in the presence of LM [92].

Optimal outcomes have been achieved in patients with unilobar disease and no extrahepatic spread [93]. R0 resection remains ideal but not mandatory, as meaningful cytoreduction significantly improves both survival and hormonal control [83,94]. NET-related predictors of prognosis included well-differentiated tumors and $\geq 70\%$ tumor debulking.

A meta-analysis of 35 studies (N = 4834) [95] demonstrated a median OS of 84 to 120 months, markedly superior to that of nonsurgical cohorts (38–52 months). Recurrence rates reached 70% to 95%, predominantly intrahepatic, but iterative interventions maintained long-term survival [96]. Survival rates showed an increase over time, as demonstrated by Gudmundsdottir et al. [76], with a 5-year OS increasing from 71% to 78% to 81% during 3 distinct periods. The most outstanding survival was reported by Fairweather et al. [70], who reported a 5-year OS of 90% for 58 patients [76]. Modern management emphasized parenchymal-sparing hepatectomy, often in combination with intraoperative local ablation to achieve cytoreduction. Minimally invasive liver surgery has been increasingly adopted, offering reduced morbidity and similar DFS to open surgery [75,78]. In addition, many studies [74,81,82,85–87,91] showed a marked trend toward R1/R2 resections, achieving good symptom control and equivalent survival outcomes. The threshold of liver debulking was progressively lowered from 90% to 70%, without affecting survival outcomes [83,93,94,96]. Recurrence rates after resection were up to 95%, generally intrahepatic, with a 5-year DFS ranging from 13% to 46%. However, patients who underwent repeated resections showed favorable outcomes [83,85,86,93,94,96].

GIST and STS LMs

Of note, 50% to 65% of metastatic GISTs were found to involve the liver, frequently as the dominant site of spread. In contrast, STS metastases to the liver are rare, accounting for <1% of hepatic metastases, with leiomyosarcoma being the most common [3,5,14].

LRs are commonly performed for GIST responding to TKI and rarely for selected sarcomas. Up to 80% of GISTs respond to TKI before developing resistance due to acquired secondary mutations in KIT or platelet-derived growth factor receptor alpha [97,98]. Because remission is rarely observed, LR should be performed at the maximal TKI response. The literature search yielded 1 RCT from China [8] and systematic reviews based on observational studies, including a prospective study [99] and several retrospective studies [100–104].

More favorable outcomes occurred in subjects with R0 resection, metachronous presentation, and no extrahepatic disease. The GIST-related predictors of good outcomes included partial or complete

radiologic response to TKI. In STS, R0 resection was a key-positive predictor of outcomes, whereas incomplete (R1/R2) resection led to rapid recurrence (<12 months) [8,14,99].

Combining surgery with TKI therapy yielded a median OS of 70 to 90 months for GIST, significantly exceeding that of TKI monotherapy, which was 40 to 50 months [102,105]. LR was typically performed at the maximal TKI response to minimize viable tumor [106]. In their RCT, Du et al. [8] recruited 41 patients with metastatic GISTs. Preliminary results showed 2-year progression-free survival (PFS) rates of 88.4% in the surgery group and 57.7% in the chemotherapy group. However, the imatinib-alone arm of the trial was closed early due to poor accrual.

For STS, pooled data showed a 1-year OS of 74% to 100% and a median OS of 30 to 50 months after resection [14]. Leiomyosarcoma is the most common histotype of resected sarcoma [14]. Incomplete resection and extrahepatic disease were the main predictors of poor OS [107,108].

Breast cancer LMs

The incidence of breast cancer LMs (BCLMs) ranged from 7.3% to 32%, with poor prognosis for patients treated with systemic therapy alone, with a median OS generally ranging from 18 to 24 months [109] and up to 24 to 84 months in surgical series [110–113].

Although systemic therapy remains the mainstay of treatment of BCLM, the role of liver-directed treatments remains controversial, especially in oligometastatic disease, and international guidelines, including the National Comprehensive Cancer Network and Advanced Breast Cancer [9,10], diverged in their recommendations. The literature search retrieved systematic reviews based on retrospective studies with no RCTs and national registries from Sweden, Spain, Greece, and Taiwan [110,114–116].

Significantly worse outcomes were reported in patients with multiple and larger metastases with a short DFI between breast surgery and diagnosis of BCLM. Additional adverse prognostic indicators included early progression of the disease under chemotherapy and the presence of extrahepatic spread [111–113,117–121]. In contrast, ER/PR positivity was consistently associated with improved outcomes, likely due to endocrine sensitivity. In addition, HER2 positivity was associated with good prognosis, although some studies reported discordant or nonsignificant results [122–124]. Triple-negative breast cancer was consistently associated with poorer survival in all studies in which this correlation reached statistical significance.

Data from propensity score-matched (PSM) analyses [117,125,126] and comparative cohort analyses [110,114,127,128] showed that LR was generally confirmed as an independent predictor of improved OS in selected patients. A meta-analysis based on 4070 subjects reported a pooled hazard ratio (HR) of 0.55 (95% CI, 0.44–0.69) in favor of surgery [110,117,125–128], and several PSM analyses confirmed improved OS and PFS of LR vs systemic therapy alone in selected patients [116,129–131].

Gynecologic cancer LMs

Liver involvement is a frequent event in advanced gynecologic malignancies, particularly ovarian and uterine cancers. Surveillance, Epidemiology, and End Results–based analyses reported hepatic metastases in 42% of ovarian cancer cases, 40% of uterine cancer cases, and 18% of cervical cancer cases with distant spread [132].

The literature search retrieved systematic reviews based on retrospective studies and 1 RCT [11].

The main determinants of a favorable outcome included limited hepatic involvement (solitary or few lesions ≤ 3 to 5 cm), complete cytoreduction (R0), chemoresponsive systemic disease, and absence

of peritoneal carcinomatosis or uncontrolled extrahepatic spread. The completeness of cytoreduction remained the strongest predictor of survival [12,19,132].

The DESKTOP III randomized trial [11] showed a significant survival benefit of cytoreductive surgery in patients with advanced ovarian cancer, with a median OS of 53.7 months compared with 46.0 months in those treated with systemic therapy alone. Good outcomes were further improved when complete (R0) cytoreductive surgery was achieved, with a reported OS of 61.9 vs 28.8 months. Of note, Mulligan et al. [19] demonstrated increased rates of complete cytoreduction, from 49.00% to 77.00%, and low mortality (0.68%) when the surgical procedure was performed not by gynecologists alone but in collaboration with a hepatobiliary team, supporting the importance of a multidisciplinary collaboration.

For endometrial cancer, Baldwin et al. [12] showed that adult women with metastatic endometrial cancer presented a survival benefit when treated with combined chemotherapy and LR. The 1-, 2-, and 3-year OS rates for chemotherapy plus LR vs chemotherapy alone were 67.8% vs 56.5%, 44.9% vs 33.4%, and 35.1% vs 23.1%, respectively.

Urologic cancer LMs

Among urological cancers, renal cell carcinoma (RCC), bladder cancer, and germ cell tumor (GCT) were the most frequent sources of LMs. In RCC, liver involvement occurred in approximately 20% of patients with disseminated disease, and only 5% of patients presented with isolated hepatic metastases [133]. The survival data reported in the literature were highly variable, with a median OS ranging from 16 to 140 months. For bladder carcinoma, LMs occurred in approximately 26.5% of cases, with an isolated liver disease occurring in 9% of cases. Visceral metastases from prostate cancer are relatively uncommon, with liver-only disease occurring in <1% of advanced cases [134].

Data showed that LR remains the cornerstone of curative-intent treatment of RCC, bladder cancer, and GCT metastases. However, for prostate primaries, LR and LA were rarely indicated. The literature search retrieved systematic reviews based on retrospective studies with no RCTs and a national registry from the Netherlands [135].

Favorable prognostic determinants were limited hepatic tumor burden, metachronous presentation, long DFI (>12 months), objective response to systemic therapy, and absence of uncontrolled extrahepatic disease. Conversely, progressive disease or extensive extrahepatic spread predicted poor outcomes and precluded hepatic intervention [3,5,133].

For RCC, a recent study on 40 patients who underwent hepatic resection for RCC metastases showed a significant improvement in median OS after the introduction of sunitinib in July 2006, with survival increasing from 27.5 to 45.2 months [136]. Although complete LR correlated with favorable outcomes, patient selection remained crucial, and integration with systemic immunotherapy and LR or LA was considered the standard of care [137].

For bladder carcinoma, a multicenter analysis of 508 patients with metastatic upper tract urothelial carcinoma showed that cytoreductive surgery improved survival (HR, 0.79; $P = .015$) and that the presence of LM predicted poorer outcomes (HR, 1.46; $P < .001$) [13]. LR was considered in highly selected cases with minimal disease burden and a favorable response to chemotherapy.

In GCTs, multimodal therapy combining chemotherapy and surgery led to long-term PFS, exceeding 90%, even in LM cases [133]. A multidisciplinary, individualized approach remains mandatory for these patients.

Melanoma LMs

The liver is a frequent site of LMs for both cutaneous and uveal melanomas. Historically, if untreated, survival was 1 to 8 months, reflecting the high aggressiveness of hepatic spread [5,138,139].

The optimal management of melanoma LMs remains a matter of considerable debate, with suggestions that LR might offer improved survival outcomes compared with nonsurgical approaches in selected patients [140–142].

Positive prognostic indicators identified included age <70 years [141], a prolonged DFI between primary resection and metastases, absence of extrahepatic disease, a limited number of hepatic metastases, unilobar involvement, and R0 resections [135,140,143–147].

The literature search identified studies that focused exclusively on uveal melanoma, cutaneous melanoma [139,147], or both [135,141,146,148–150]. Pawlik et al. [25] observed that metastatic uveal melanoma had a particular tropism for the liver and that cutaneous melanoma had a more systemic recurrence pattern. Therefore, patients who underwent LR for uveal melanoma had prolonged OS, which was also due to the limited number of lesions. Hau et al. [150] reported a relatively good OS among patients treated with LR in conjunction with multimodal therapy, with 1-, 3-, and 5-year survival rates of 28.1%, 15.6%, and 3.1%, respectively. In contrast, patients who received systemic therapy alone had significantly lower survival rates.

Discussion

Unlike in colorectal cancer, in which LR is well established, evidence of NONCOLMET is limited [2–5]. NONCOLMET differs markedly in natural history. However, a consistent observation is that a limited, biologically favorable disease can achieve meaningful survival after LR. Most available evidence is retrospective and subject to selection bias. Nonetheless, reproducible survival gains across independent series confirm the validity of these criteria.

The role of LR should be considered within this spectrum, guided by tumor biology and treatment response. Ideal candidates are those with liver-dominant disease, stable or regressing lesions after systemic treatment, and no uncontrolled spread [151]. Favorable biological and clinical features include good performance status and a long DFI. Tumor-specific characteristics, such as CA 19-9 decline or BRCA expression in pancreatic cancer [65,66], ER and PR status in breast cancer [122–124], HER2 [50] and PD-L1 expression [51,52] in gastroesophageal adenocarcinoma, or response to TKI in GIST, can provide additional guidance for multidisciplinary decision-making [8,14,99]. Ultimately, the literature review highlighted that LR for NONCOLMET should be considered but only after a comprehensive multidisciplinary evaluation, ensuring both oncologic rationale and technical feasibility within an integrated framework [3,5,19,152].

Several gray areas still exist in the management of NONCOLMET. The concept of oligometastatic disease, a state between localized and systemic dissemination, has gained prominence, reframing metastatic management toward tailored, dynamic strategies. This has been highlighted in gastroesophageal cancer [15] and pancreatic cancer [60]. However, no consensus exists on its definition. The criteria vary widely across studies, including number of lesions (often ≤ 3), timing, and treatment response, making comparison and trial design challenging [54,60,61]. Similarly, the definitions of “conversion surgery” and “curative-intent surgery” after successful disease control with chemotherapy require clarification. In addition, although achieving an R0 resection was indicated in several types of LM, cytoreduction provided comparable survival and symptomatic benefit specific to LM, including colorectal LMs [153]. Cytoreduction of $\geq 70\%$ showed favorable results in NETs [83,94] and demonstrated good outcomes in some ovarian cancer cases [12,154]. These are tumor types displaying a less aggressive clinical course, in which

ANATOMICAL–BIOLOGICAL–CONDITIONAL (ABC) FRAMEWORK FOR NONCOLMET LIVER RESECTION DECISION-MAKING

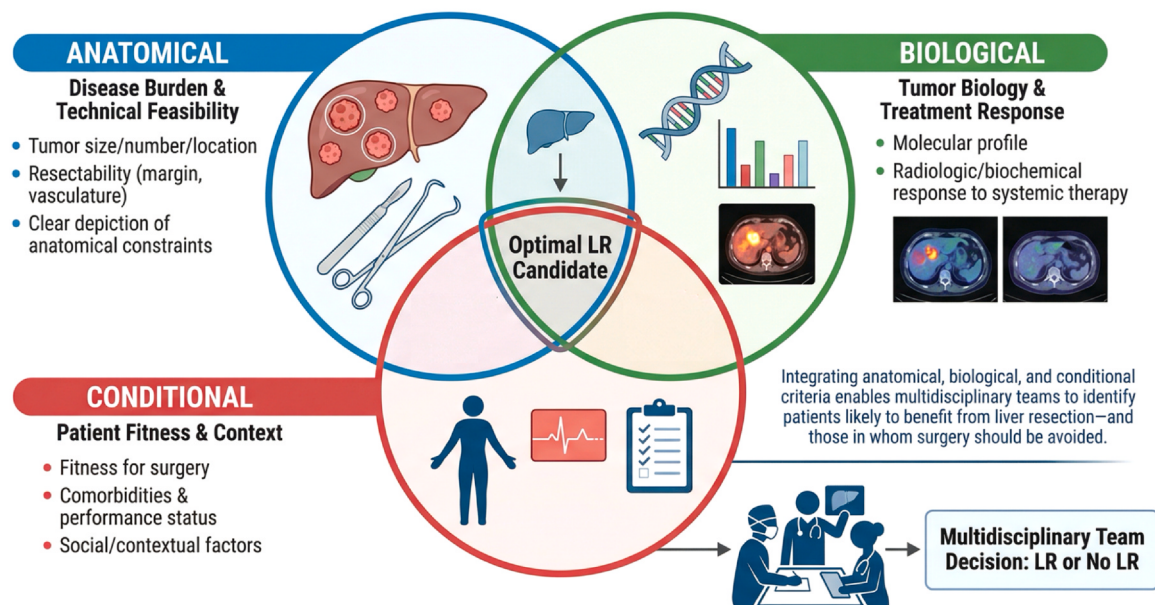


Figure 2. ABC framework for NONCOLMET LR decision-making. The figure shows the “ABC” model applied for NONCOLMET that should be used to identify the best candidates for LR. ABC, anatomical-biological-conditional; LR, liver resection; NONCOLMET, noncolorectal tumor liver metastasis.

surgical resection, even of recurrences, should be considered. Thus, the prognostic role of cytoreduction/debulking surgery in NONCOLMET without extrahepatic sites of disease should be investigated.

Several classification systems and risk models have been proposed for specific tumor types. However, none has achieved universal clinical acceptance. Yoshida et al. [48] proposed a 4-category biological classification for stage IV gastric cancer, based on the presence of macroscopic peritoneal dissemination and the technical and oncologic resectability of distant metastases. The classification ranged from category 1, which includes a technically resectable disease, to category 4, which encompasses peritoneal dissemination in combination with other organ metastases. An anatomical classification of ovarian LMs was proposed by Rosati et al. [155] to refine surgical planning. The authors described 5 types of hepatic involvement, ranging from type I with the Glisson capsule to type 5 with parenchymal metastases [155]. This classification was later validated in 615 patients, confirming that LR during cytoreductive surgery is safe (90-day mortality of 0.5%) and effective (complete cytoreduction of 86.7%) [154].

Beyond tumor-specific models, the anatomical-biological-conditional framework widely used to characterize pancreatic cancer resectability [156] offers a potentially transferable, pragmatic structure for NONCOLMET decision-making. The framework integrates disease burden and technical feasibility of LR (anatomical); tumor biology, including molecular profile and radiologic/biochemical response to systemic therapy (biological); and patient fitness and context (conditional). As synthesized in the current review, applying this lens may help liver surgeons and multidisciplinary teams identify patients most likely to benefit from LR and, equally importantly, those in whom surgery should be avoided (Fig. 2).

This review has several limitations, which are primarily related to the extreme heterogeneity and overall low methodological quality of the included studies. Furthermore, many historical series involve patients treated before the adoption of contemporary systemic regimens and modern principles of surgical oncology. The integration of molecular profiling and tumor biology into clinical pathways may

help refine patient selection beyond the radiologic criteria. Establishing standardized definitions of concepts, such as oligometastatic disease or conversion chemotherapy, and proposing validated prognostic scores will be crucial for translating heterogeneous retrospective evidence into robust clinical guidance. Prospective registries, such as the NONCOLMET study recently launched [157], aim to address some of these gaps by developing comprehensive contemporary datasets of patients undergoing LR for NONCOLMET, thereby providing high-quality data on clinical practice, outcomes, and biological and morphological prognostic factors. However, this review provides a comprehensive overview of the surgical treatment of NONCOLMET, which we believe may be very useful for the surgical oncologist approaching these different diseases.

Conclusion

Across NONCOLMET, LR can offer a significant survival benefit in highly selected patients with liver-dominant, biologically favorable disease. Thus, LR should not be excluded a priori. Selection must be based on an integrated assessment of the feasibility of LR; tumor biology, including molecular profile and response to systemic therapy; and patient conditions rather than the primary tumor site alone. Ongoing trials and multidisciplinary collaboration are essential to refine indications and optimize multimodal strategies, ultimately transforming liver-directed therapy from an exception based on local practice into an evidence-based component of comprehensive oncologic care.

Author contributions

M. Donadon and M. Di Martino contributed to the conceptualization of the study, design of the study, data collection, data analysis and interpretation, and manuscript writing. S. Ministrini, G. Tiberio, S. Conci, A. Ruzzenente, A. Maekawa, G. Perri, G. Marchegiani, A. Libia, M.G. Spampinato, F. Romano, M. Garancini, S.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare no competing interests.

Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.gassur.2026.102398.

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