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Overview

Navigating Disappearing Liver Metastases in Colorectal Cancer: A Review of Surgical and Non-Surgical Approaches

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Abstract

Colorectal liver metastases pose a significant clinical challenge for the multidisciplinary team (MDT), with the phenomenon of disappearing liver metastases (DLMs) following chemotherapy adding further complexity. DLMs, defined as the radiological disappearance of liver metastases after systemic therapy, require careful evaluation as the pathological complete response is not always guaranteed. To comprehensively address and analyse the key aspects of this complex issue, we performed a literature search using PubMed and Embase, focussing on studies reporting outcomes of different treatment approaches, imaging techniques, and prognostic factors.

The current evidence emphasises the pivotal role of advanced imaging modalities-such as gadolinium ethoxybenzyl dimeglumine-enhanced magnetic resonance imaging (MRI) and contrast-enhanced intraoperative ultrasound-in accurately assessing high-risk patients with DLMs (eg, lesions <2 cm, synchronous metastases or those treated with oxaliplatin-based chemotherapy). Using these techniques both preoperatively and intraoperatively is crucial for precise localisation of DLMs. The literature also highlights the importance of an MDT approach to optimise patient management, ensuring treatment decisions are tailored to individual patient and tumour characteristics. A 'watch-and-wait' strategy may be appropriate for selected patients with favourable prognostic factors, whereas locoregional treatments are preferable for fit patients with adequate residual liver volume or DLMs adjacent to visible residual disease. To support clinical decision-making, our group has developed a simplified algorithm to guide clinicians.

Key words: Colorectal liver metastases; hepatic metastases; missing metastases; radiologic complete response; vanishing liver metastases

Abbreviations: EGFR, epidermal growth factor receptor; APC, adenomatous polyposis coli; AUC, area under the ROC curve; AI, artificial intelligence; AR, augmented reality; BED, biological equivalent dose; CI, confidence interval; CR, complete response; CRC, colorectal cancer; CRLMs, colorectal liver-only metastases; ctDNA, circulating tumuor DNA; CT, computed tomography; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DFS, disease-free survival; DLMs, disappearing liver metastases; DWI, diffusion-weighted imaging; FOLFIRI, folinic acid, fluorouracil, irinotecan; FOLFOX, fluorouracil, folinic acid, oxaliplatin; FOLFOXIRI, fluorouracil, folinic acid, oxaliplatin, irinotecan; Gd-EOB-DTPA, gadolinium ethoxybenzyl dimeglumine; HAI, hepatic artery infusion; HR, hazard ratio; ICIs, immune checkpoint inhibitors; IOUS, intraoperative ultrasonography; LC, local control; MRI, magnetic resonance imaging; mPFS, median progression-free survival; mCRC, metastatic disease; MSI-H, microsatellite instability-high; dMMR, mismatch repair deficient; MSS, microsatellite stable; MWA, microwave ablation; MDT, multidisciplinary team; ORR, objective response rate; OS, overall survival; partial response (PR), pCR, pathological complete response; PS, performance status; PET, positron emission tomography; PET-FDG, positron emission tomography-FDG; PD-1, programmed cell death protein 1; RFA, radiofrequency ablation; RFS, recurrence-free survival; R0, resection zero; RECIST, Response Evaluation Criteria In Solid Tumours; SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiation therapy; SOC, standard of care; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation; CE-CT, contrast-enhanced computed tomography; CE-IOUS, contrast-enhanced intraoperative ultrasonography; W&W, watch and wait; 3D, three dimensional.

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with 1.1 million new cases annually, and the second leading cause of cancer-related death [1]. At diagnosis, 15%–30% of patients present with metastatic disease and 20%–50% of those with localised CRC eventually develop distant metastases, predominantly in the liver [2].

Surgery is the standard curative approach for colorectal liver-only metastases (CRLMs), although only 20%–30% are initially resectable [3–7]. Conversion chemotherapy can downsize unresectable tumours, increasing resectability, especially with modern regimens that achieve higher response rates. In patients with limited disease, this may result in an extraordinary response known as disappearing liver metastases (DLMs) or vanishing metastases [8,9].

DLMs occur in an estimated 35% of cases, depending on imaging and patient characteristics [10].

Magnetic resonance imaging (MRI) and contrast-enhanced intraoperative ultrasonography (CE-IOUS) are the most accurate modalities for detection and are recommended for routine CRLM assessment [11]. However, DLMs pose a challenge for the multidisciplinary team (MDT) as radiological disappearance rarely corresponds to a pathological complete response (pCR); fewer than 20% of resected sites are truly tumour free [12].

Consequently, management remains controversial, with no consensus on whether to resect or observe lesions that vanished after chemotherapy [13].

This review explores current approaches to DLMs and examines key factors influencing the decision between locoregional intervention and 'watch and wait' (W&W).

Systemics and Locoregional Treatments for CRLM Management

Chemotherapy and DLMs

Chemotherapy plays a crucial role in managing CRLMs, including cases with DLMs.

Oxaliplatin-based doublets (eg, fluorouracil, folinic acid, oxaliplatin [FOLFOX]4) are recommended for resectable patients with unfavourable prognostic factors (eg, synchronous metastases, >3 lesions, bilobar involvement, and limited extrahepatic disease), improving 3-year median progression-free survival (mPFS) by 7.3% versus surgery alone (hazard ratio [HR]: 0.76, 95% confidence interval [CI]: 0.59–0.98, $P = 0.023$). The primary goal is to downsize metastases, enabling resection or ablation of cases initially deemed unresectable [14–16]. DLMs are more frequent with small lesions (<2 cm), synchronous metastases, with adenomatous polyposis coli (APC) mutations and prolonged chemotherapy [10,17,18]; each additional cycle is associated with an 18% increase in the likelihood of DLMs (ranges: 5–25 cycles) (Table 1) [19]. Oxaliplatin-based treatments are most associated with DLMs due to their higher efficacy [20,21].

However, extended preoperative chemotherapy can cause liver damage and postoperative hepatic insufficiency. Patients receiving ≥9 FOLFOX cycles have a quadrupled the risk of developing it (11% vs 4%; $P = 0.035$), without improvement in major response or pCR (57% vs 55%; $P = 0.74$) [22]. Bevacizumab may reduce oxaliplatin-induced sinusoidal injury (26% vs 42%; $P = 0.017$), though evidence is limited by study design [22]. These findings complicate surgical planning as chemotherapy may eliminate some metastases but may obscure microscopic residual disease.

Targeted agents are not routinely recommended perioperatively in resectable CRLMs but are used in unresectable cases. In *RAS/BRAF* wild-type, left-sided tumours, anti-epidermal growth factor receptor (EGFR) agents plus chemotherapy improve response rates (eg, CELIM trial, objective response rate [ORR]: 60% vs 32%, $P < 0.0001$) [23]. However, in the New EPOC trial, adding cetuximab to chemotherapy in operable disease found worse overall survival (OS) (HR: 1.45, 1.02–2.05; $P = 0.036$) [24]. For RAS/RAF-mutant tumours, anti-EGFRs are ineffective, while bevacizumab remains a viable option. In BECOME trial, bevacizumab plus modified (m)FOLFOX6 improved resectability in unresectable RAS-mutant CRLMs (resection zero [R0] in 27/121; $P < 0.01$) [25]. Triplet regimens have also been investigated: in CAIRO 5 study fluorouracil, folinic acid, oxaliplatin, irinotecan (FOLFOXIRI) plus bevacizumab improved response (54% vs 33%, $P = 0.0004$) and R0/R1 resection rates (51% vs 37%, $P = 0.013$) in right-sided or RAS/BRAFV600E-mutant initially unresectable CRLMs [15].

Conversely, in left-sided *RAS/BRAF* wild-type tumours, panitumumab did not improve outcomes and was more toxic than bevacizumab when combined with FOLFOX or folinic acid, fluorouracil, irinotecan (FOLFIRI) [15,16].

Summary of the regimens adopted in the available literature about DLMs is present on Table 1.

DLMs in Microsatellite Instability-High Metastatic Disease

DLMs have been observed with both chemotherapy and immunotherapy, particularly in microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) metastatic disease (mCRC). Immune checkpoint inhibitors (ICIs) have significantly improved outcomes in these patients [26].

In the phase III KEYNOTE-177 trial, pembrolizumab doubled PFS compared to chemotherapy (16.5 vs 8.2 months; HR: 0.60, $P = 0.0002$), with a higher complete response (CR; 11.1% vs 3.9%) and partial response rates [27]. The phase II CheckMate 142 study reported a CR in 3% and partial response (PR) in 52% of pretreated patients receiving nivolumab ± ipilimumab [28].

More recently, the CheckMate 8HW phase III trial demonstrated a 24-month PFS rate of 72% with nivolumab plus ipilimumab versus 15% of chemotherapy, reinforcing efficacy of ICIs, including liver metastases [29]. Botensilimab, a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor, plus balstilimab, a programmed cell death protein 1 (PD-1) inhibitor, showed promise in

Table 1
A summary of the regimens adopted in the available literature about DLMs.

Ref.	Systemic therapy regimen	Number of cycles needed to achieve DLMs
Elias, 2004 [86]	45% HAI (oxaliplatin) combined with systemic therapy; 55% systemic therapy (5FU plus oxaliplatin or irinotecan),	11-24 cycles
Benoist, 2006 [87]	100% systemic therapy (multiple 5-FU/leucovorin based regimens)	n.s.
Dy, 2007 [88]	100% systemic therapy (13% 5-FU, leucovorin and irinotecan; 69% FOLFOX4, 18% irinotecan and oxaliplatin)	n.s.
Elias, 2007 [89]	31% HAI (oxaliplatin, combined with systemic 5-FU and leucovorin); 69% systemic therapy (5-FU/leucovorin, FOLFOX, FOLFOXIRI)	6-24 cycles
Adam, 2008 [90]	100% systemic therapy (66% FOLFOX, 7% FOLFIRI, 28% other)	Median 8 (range 2-29)
Tanaka, 2009 [91]	68% HAI (5-FU, L-folinic acid and cisplatin), 11% systemic (5-FU and L-folinic acid combined with oxaliplatin or irinotecan), 21% both (5-FU, L-folinic acid and oxaliplatin)	Median 5 (range 2-34)
Van Vledder, 2010 [92]	100% systemic therapy (Various regimens including oxaliplatin-based, irinotecan-based, fluoropyrimidine monotherapy regimens. Bevacizumab and/or cetuximab in 41%)	Median 6 (SD 3.86)
Auer, 2010 [93]	18% HAI (floxuridine in combination with systemic oxaliplatin and irinotecan); 82% systemic therapy (5-FU leucovorin, oxaliplatin, irinotecan)	n.s.
Goere, 2011 [92]	85% HAI (oxaliplatin) combined with systemic therapy (5-FU and leucovorin); 15% systemic therapy (5-FU plus leucovorin alone or in combination with oxaliplatin or irinotecan)	n.s.
Ferrero, 2012 [94]	100% systemic therapy (5-FU and leucovorin or capecitabine with oxaliplatin and/or irinotecan)	Median 8+/- 3.5
Ono, 2012 [95]	100% systemic therapy (modified FOLFOX6 with or without bevacizumab)	5 patients with complete clinical response after 15,12,12,13 and 9 cycles
Oba, 2018 [96]	98% systemic therapy (95% oxaliplatin-based, 2%i irinotecan-based, 87% bevacizumab or anti-EGFR)	6 (2−31)
Boraschi, 2023 [97]	Doublets, Doublets + anti-VEGF, Doublets + anti-EGFR, Triplet + anti-VEGF or anti-EGFR	n.s.

5-Fluorouracil (5-FU), 5-FU/folinic acid/irinotecan (FOLFIRI), 5-FU/folinic acid/oxaliplatin (FOLFOX), 5-FU/folinic acid/oxaliplatin/irinotecan (FOLFOXIRI), capecitabine plus irinotecan (XELIRI), capecitabine plus oxaliplatin (XELOX), disappearing liver metastases (DLMs), Epidermal Growth Factor Receptor (EGFR), hepatic artery infusion (HAI), not specified (n.s.), Vascular Endothelial Growth Factor (VEGF). Table updated from reference [98].

refractory microsatellite-stable (MSS) mCRC without active liver metastases, with a 23% ORR and an mOS of 21.2 months [30]. Despite these advances, liver metastases can exhibit heterogeneity and radiologic disappearance may not equate to pCR. The strong immune response in MSI-H tumours may contribute to radiological regression, but residual microscopic disease can persist [31,32].

Most data on DLMs come from chemotherapy, so further research is needed to define biomarkers and management strategies for DLMs after ICIs in MSI-H mCRC [32].

Non-Surgical Locoregional Treatments and DLMs

Hepatic artery infusion (HAI) delivers chemotherapy directly to the liver and is gaining interest for improving response and resection rates in patients with liver metastases. The most used agent is floxuridine, a fluorouracil analogue with high hepatic extraction and low systemic toxicity, allowing its combination with systemic therapy [33]. In a phase II study of 49 patients with unresectable CRLMs treated with HAI-floxuridine plus systemic therapy, the ORR was 76% (including 4 CR cases). Conversion to resection was achieved in 23 patients (47%) at a median of 6 months. However, after a 39-month follow-up, 80% experienced recurrence (Table 1) [33].

Two alternative locoregional approaches for CRLMs are transarterial chemoembolisation (TACE) and transarterial radioembolisation (TARE). However, no evidence currently supports their use in the management of DLMs**.** The EPOCH randomised trial investigated the addition of TARE to second-line chemotherapy demonstrating a benefit of PFS (95% CI: 0.54 to 0.88; $P = 0.0013$) [34]**.**

Radiofrequency ablation (RFA) and microwave ablation (MWA) are valid alternatives to surgery, particularly for

patients with unresectable or oligometastatic liver metastases [2]. MWA is especially suitable for deep-seated lesions where surgery may result in excessive parenchymal loss or in patients with comorbidities precluding surgery. A recent meta-analysis suggests the efficacy of MWA for CRLMs <3 cm, either alone or combined with hepatectomy to increase resectability [35–37].

In one study, 20 DLMs in 11 patients were treated with MWA, 19 of 20 cases intraoperatively. Four DLMs were visible neither macroscopically nor with intraoperative ultrasound; ablation was performed based on anatomical landmarks. The 65% local recurrence rate highlights both the potential and limitations of ablative approaches for DLMs [38].

Compared to RFA, MWA enables larger coagulation zones in shorter time, is less affected by the heat-sink effect, and is preferred for perivascular lesions [35]. RFA may also be combined with surgery or chemotherapy [39,40].

The COLLISION study, an international phase III trial, randomised patients with ≤3 cm liver metastases to surgery or thermal ablation. Interim analysis (median follow-up: 28.9 months) demonstrated no significant difference in OS (HR: 1.05; noninferiority limit set at an HR value of 1.3), challenging the notion that ablation should be limited to unresectable cases [41].

Treatment decisions should be tailored to individual clinical profiles and guided by an MDT [4].

Further studies are needed to assess their impact on survival and recurrence.

Finally, stereotactic ablative radiotherapy (SABR) and stereotactic body radiation therapy (SBRT) have been demonstrated to be a useful noninvasive tool for the treatment metastatic tumours in patients with oligometastatic disease, with a high rate of local control (LC) and limited toxicity [42]. SABR-COMET, a phase II trial, evaluated palliative standard of care (SOC) versus SABR plus SOC in controlled primary tumour (n = 99) with oligometastatic disease (1–5 metastatic lesions) from various histologies. In the CRC subgroup (n = 18), the SABR arm showed an improvement in PFS (HR: 0.16; 95% CI: 0.0–0.76), with no major toxicity signals observed with extended follow-up, although the benefit in OS appeared less pronounced (HR: 0.59; 95% CI: 0.19–1.80) [43]. Currently, several phase III trials are investigating the impact of SABR on survival and quality of life while also aiming to identify biomarkers of oligometastatic disease that could help select patients most likely to benefit from this approach [44,45]. Several factors could affect the efficacy of SBRT, included prescription dose, and tumour size [46]**;** the use of an ablative prescription dose is a crucial starting point to make SBRT a valid therapeutic option in CRLMs since an increase in the biological equivalent dose (BED; group 1: ≤80 Gy, group 2: 100–112 Gy, and group 3 ≥132 Gy) correlates with 2-year LC (52%, 83%, and 89% respectively) and with a significant difference for LC between the 3 dose groups (HR: 0.44, 95% CI, $P = 0.03$ for group 2; HR: 0.17, 95% CI, $P = 0.01$ for group 3; $P = 0.01$ for total) [47].

A phase II trial conducted by Scorsetti *et al.* confirmed the safety and efficacy of high-dose SBRT, when delivered in highly specialised centres, for the treatment of liver metastases >3 cm in CRC, achieving a 5-year LC rate of 75%. These lesions are often unsuitable for other effective local ablative therapies [46].

To our knowledge, no real-world data are available on the management of DLMs with SBRT/SART. However, these approaches could be considered as potential options when surgery or other locoregional treatments are not feasible, although more prospective long-term data are needed.

DLMs and Imaging

Accurate imaging is essential for staging and managing DLMs as smaller lesions are more likely to 'vanish' after neoadjuvant therapy. DLMs occur in 7–37% of patients post neoadjuvant therapy, with up to 8% showing complete radiological disappearance [10]. However, residual disease is often detected during surgery or intraoperative ultrasonography (IOUS) [11].

Van Vledder *et al.* reported viable tumour cells in 80% of resected DLMs sites, highlighting the limitations of imaging alone and the need to combine advanced diagnostics with intraoperative assessment [19].

Evaluation is further complicated by variability in study design, patient populations, and assessment methods, as well as potential misclassification due to inaccurate baseline staging. Standardised staging protocols are needed to ensure consistent assessment and guide treatment strategies [19].

Contrast-Enhanced Computed Tomography and MRI

Radiological staging after systemic therapy often relies on computed tomography (CT), which, while widely available, is suboptimal for detecting viable tumour cells. Both CT and MRI show high sensitivity (>90%) for lesions >1 cm, but MRI outperforms CT for smaller lesions (53% vs 36%) [48].

Diffusion-weighted imaging (DWI) MRI is now considered the gold standard for detecting small liver metastases preoperatively. Choi *et al.* reported MRI sensitivity and specificity of 93.1% and 87.3%, compared to 82.1% and 73.5% for CT, respectively, [49].

In a study by Oba *et al.*, 764 CRLM lesions were identified by CE-CT at baseline (median lesion size: 8 mm). Of these, 275 lesions (36%) disappeared post chemotherapy [50].

Despite advances like gadolinium ethoxybenzyl dimeglumine (Gd-EOB-DTPA) MRI, Arita *et al.* found that IOUS and CE-IOUS still detected new lesions in about 10% and 9% of cases, respectively, underscoring the complementary role of intraoperative imaging [51].

Morin *et al.* further highlighted that Gd-EOB-DTPA MRI altered lesion counts in 43% of cases and influenced surgical planning in 17% of patients, reinforcing its value in DLM management [17,52].

Contrast-enhanced intraoperative ultrasonography

In patients with multiple small lesions, especially post chemotherapy, preoperative imaging often remains suboptimal. In this context, contrast-enhanced intraoperative ultrasonography (CE-IOUS) has demonstrated superior sensitivity and specificity to preoperative MRI [53].

CE-IOUS can detect additional metastases in 16–24% of patients, particularly those <10 mm, due to its higher spatial resolution [53]. Wiering *et al.* reported that 81% of 10-mm and 27% of 10- to 20-mm liver metastases found intraoperatively were missed by CT and/or positron emission tomography (PET) [54]. Papakonstantinou *et al.* found that DLMs identified intraoperatively, either by palpation or IOUS, had a higher rate of viability (72.29% vs 20.69%). A known limitation of IOUS is its operator dependency [55].

Direct liver contact after mobilisation reduces artifact from ribs, ligaments, and bowel peristalsis, improving detection of lesions in challenging locations, like segment 3. Contrast agents enhance differentiation between metastases and benign lesions, especially useful for isoechoic metastases. CE-IOUS improves staging and frequently alters surgical planning in chemotherapy pretreated patients [54,56].

Positron Emission Tomography-FDG

Positron emission tomography-FDG (PET-FDG) has lower sensitivity than MRI and CE-CT for detecting DLMs, particularly for lesions <1 cm [57]. A meta-analysis reported PET sensitivity at 51.7% versus 85.7% for MRI [10].

Due to limited postchemotherapy accuracy, PET is not recommended for assessing treatment response but may aid in identifying extrahepatic disease during presurgical restaging [57].

Kuhlmann *et al.* evaluated PET/CT in DLMs but relied on CT to define radiological CR and did not assess correlation with pathological response [10].

Role of Radiologists

In conclusion, a meticulous intraoperative assessment is crucial in patients at a risk for DLMs, including liver mobilisation, inspection, palpation, and CE-IOUS, particularly in cases with small or multiple lesions, prolonged chemotherapy, and chemotherapy-induced liver damage. Despite imaging advances, DLM detection remains challenging as most MRIs are performed postneoadjuvant therapy, when treatment-induced liver changes may obscure residual disease. Hepatocyte-specific contrast agents like Gd-EOB-DTPA have improved MRI accuracy by enhancing lesion detection during the hepatobiliary phase [53,58].

MDT discussions remain pivotal, with radiologists playing a key role in identifying high-risk DLM lesions, planning surgery, and interpreting post-treatment images. In selected cases, fiducial markers may aid lesion localisation and reduce the risk of DLMs [11].

Future Prospectives

Artificial intelligence in Radiology and Hepatobiliary Surgery

The future of radiology and hepatobiliary surgery is evolving with the integration of artificial intelligence (AI) tools, such as three-dimensional (3D) reconstruction and radiomics, positioning radiologists at the forefront of managing challenges like DLMs. Image-guided navigation systems using 3D models and CE-IOUS integration enhance surgical planning and intraoperative decision-making by providing real-time, comprehensive data for more precise interventions [59].

Role of Radiomics

Radiomics, by quantitatively extracting imaging-based textural and morphological characteristics, presents a promising approach for monitoring DLMs in CRC patients [60,61]. Despite advances in imaging and systemic treatments, conventional evaluations, primarily based on Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 criteria, still fail to detect residual microscopic disease, leading to recurrence rates of 20%–30% among patients initially deemed complete responders [57].

Radiomics may overcome these limitations by identifying microstructural alterations within hepatic tissue suggestive of residual or recurrent disease. Specifically, delta radiomics, which evaluates temporal changes in radiomic features across sequential scans, has shown improved diagnostic accuracy, with sensitivity and specificity approaching 85% in distinguishing complete responders from those at a risk of recurrence [57]. Entropy, homogeneity, and tumour density variation have demonstrated superior predictive value over traditional radiological evaluations [61,62].

The integration of radiomic data with machine learning and deep learning has further refined predictive models, with recent studies reporting area under the ROC curve (AUC) values approaching 0.90 [57,60].

Moreover, radiomic signatures correlate with tumour biology, providing insights into aggressiveness and treatment response [57,60].

The European Society for Medical Oncology (ESMO) consensus guidelines support a precision medicine approach in mCRC, recognising radiomics as a noninvasive, biomarker-driven tool to personalise therapy [4].

However, clinical implementation remains limited due to variability in imaging protocols, segmentation methods, and interoperator consistency [61,62].

Overcoming these barriers will require standardisation, multicentric studies, and the incorporation of advanced AI algorithms [63].

Ultimately, radiomics has the potential to enhance early detection and recurrence prediction in CRC patients with

DLMs, enabling more tailored and timely interventions [57,64].

Management of DLMs

A 2013 consensus recommended resecting all original CRLM sites, including DLMs, since pCR occurs in only 20%–40% of patients treated with systemic chemotherapy [65].

However, advancements in imaging and surgical techniques have complicated decisions as radiological disappearance does not always indicate true pathological response.

A 2022 systematic review by Nassar *et al.* found no significant differences in disease-free survival (DFS) or OS between patients with or without pCR after DLMs resection (HR: 0.40, 95% CI: 0.01–12.70 for DFS; HR: 0.36, 95% CI: 0.03–4.12 for OS) [66].

Moreover, DFS was similar between patients who received treatment (resection or ablation) and those managed with W&W strategy (HR: 0.72, 95% CI: 0.04–13.54) [10,17,66,67].

Similarly, Owen *et al.* reported no recurrence-free survival (RFS) benefit between resected and nonresected patients (483 days vs 360 days, $P = 0.49$) [68], while earlier studies highlighted improved RFS with surgery [69].

Other studies reported lower recurrence rates in resected versus unresected DLMs [8,19,55,68].

However, current evidence is inconclusive [17]. Further studies should consider tumour biology, lesion location, resection status, extrahepatic disease, lymph node involvement, and patient performance status (PS). The availability of local therapies like ablation should also inform treatment strategies.

Prognostic Role of DLMs

DLMs, observed in approximately 65% of patients, generally indicate a favourable prognosis and suggest beneficial tumour biology [11]. Kuhlmann *et al.* reported a longer mOS (51 vs 28 months, $P < 0.05$) and median relapse free survival (mRFS) (10 vs 3 months, $P = 0.003$) in patients with DLMs [13,38].

Papakonstantinou *et al.* also found improved outcomes in patients with pCR or complete surgical DLMs resection, compared to cases with residual disease or partial excision [55].

However, a separate review found no significant differences in DFS or OS in the case of presence or absence of pCR in resected DLMs [66].

Management of DLMs: Possible Strategies

After reviewing systemic therapies and imaging modalities for DLMs, a key clinical question arises: how should the MDT manage DLMs?

Nonresection of the DLM site increases liver recurrence risk, so resection of all original metastases sites is generally recommended when possible. However, 'blind' resections are technically challenging and may not guarantee complete disease clearance.

Guidelines recommend surgery as soon as metastases become resectable to reduce loss of DLMs and avoid chemotherapy-induced liver toxicity [4].

Management of patients at a high risk for DLMs requires a tailored, multidisciplinary approach, considering lesion size and location, chemotherapy response, liver function, and patient condition (age, comorbidities, PS, and RAS/BRAF status). Strategies range from locoregional treatment (resection, RFA, and MWA) to W&W [4,70].

Due to lack of standard guidelines, practice varies; some support observation [19], while others endorse surgery [8]. This reflects divergent interpretations of imaging versus pCR and the balance between surgical risks and the potential for regrowth. In a study by Ghazanfar *et al.*, 67 liver surgeons assessed virtual DLM cases scored for technical difficulty using the IWATE criteria, which consider tumour location, size, proximity to vessels, resection extent, and liver function [71,72].

Despite varying difficulty, treatment choices (56.7% surgery and 31.3% observation) were more influenced by the presence of both visible CRLMs and DLMs than individual lesion complexity [71].

Similarly, a survey by Melstrom *et al.* of 226 liver surgeons showed that 99% had experienced DLMs, 63% delayed definitive surgical/ablative treatment to assess response durability, 49% chose observation, and 31% opted for resection if the DLM was superficial [73].

Most patients have both DLMs and visible CRLMs, complicating management and highlighting the need for more consistent evidence-based guidance [71].

Surgical Management

Advances in liver surgery, including organ-sparing techniques, have expanded eligibility for liver metastasectomy. However, they also pose challenges in managing DLMs and small residual metastases that may be undetectable intraoperatively. Surgical resection at former DLM sites can further reduce the healthy liver tissue, potentially limiting future surgical options [8,8,9,12,74].

Thus, in cases where extensive resection would compromise liver function, it may be necessary to remove visible disease while leaving DLMs *in situ* [13].

W&W Strategy

An alternative strategy for DLMs is the W&W strategy as leaving DLMs *in situ* does not consistently worsen long-term OS, despite higher intrahepatic recurrence [8,19,55,69].

Recurrence rates range from 11% to 14%, mostly within two years, with about half being local recurrences [10,17].

For initially unresectable DLMs, a chemotherapy break with close imaging follow-up is recommended; if lesions reappear, typically within 6–8 months, surgery can be considered [17].

A presurgical pause also helps determine whether a complete response is durable as some DLMs left *in situ* relapse shortly after stopping chemotherapy [13]. While many recurrences are manageable with resection or ablation, delayed interventions may be more complex and percutaneous ablations are less effective than intraoperative ones [75].

Use of Fiducial Markers

Fiducial markers assist in locating DLMs intraoperatively after chemotherapy-induced shrinkage.

About 24% of clinicians place them in lesions <1 cm before neoadjuvant chemotherapy [73].

Kepenekian *et al.* examined 76 liver metastases (diameter <25 mm and depth >10 mm) in 43 patients; 30% became radiologically occult post chemotherapy but were successfully resected using fiducials [76]. Fiducials are recommended for lesions <20 mm (or <10 mm),

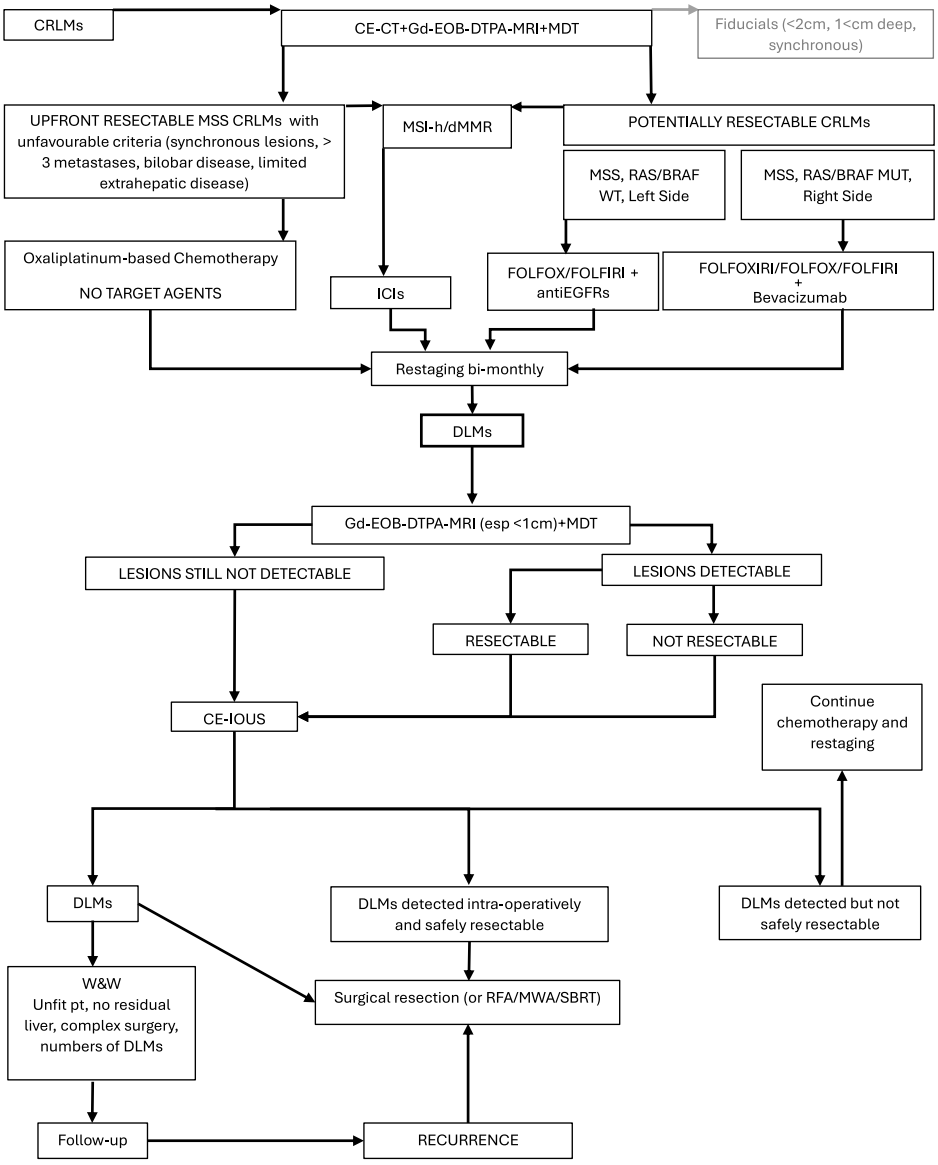

Figure 1. Proposed algorithm for DLM management

List of abbreviations: anti-EGFR (Epidermal Growth Factor Receptor), colorectal liver-only metastases (CRLMs), contrast-enhanced computed tomography (CE-CT), contrast-enhanced intraoperative ultrasonography (CE-IOUS), deficient mismatch repair (dMMR), disappearing liver metastases (DLMs), FOLFIRI (folinic acid, fluorouracil, irinotecan), fluorouracil, folinic acid, oxaliplatin (FOLFOX), fluorouracil, folinic acid, oxaliplatin, irinotecan (FOLFOXIRI), gadolinium ethoxybenzyl dimeglumine magnetic resonance imaging (Gd-EOB-DTPA-MRI), immune checkpoint inhibitors (ICIs), microsatellite instability-high (MSI-h), microsatellite stable (MSS), microwave ablation (MWA), multidisciplinary team (MDT), patients (pt), radiofrequency ablation (RFA), rat sarcoma viral oncogene homologue/, stereotactic body radiation therapy (SBRT), 'watch and wait' (W&W), wild-type (WT), mutated (MUT), especially (esp).

located deeper than 10 mm, and outside planned resection area [71]. Limitations include misplacement, vascular migration, and potential seeding of the metastatic track [77–80].

New Perspectives: Augmented Reality

Augmented reality (AR) is an emerging tool in surgery that enables development of a 3D virtual model of the patient's anatomy [81,82]. When superimposed on real-time images, AR provides a composite view that reveals deeper structures through overlying tissues [83]. A preliminary report demonstrated AR's potential in accurately guiding DLM resection, detecting all 4 DLMs in 3 patients and achieving R0 resection without local recurrence after 6–22 months of follow-up [84]. While promising, the role of 3D AR models in managing DLMs remains underexplored and warrants further investigation [17].

Discussion

Our group developed a simplified decision-making algorithm for DLM management (Fig 1). In patients with initially unresectable CRLMs, baseline imaging with Gd-EOB-DTPA MRI and CE-CT is crucial. The MDT should identify high-risk lesions (eg, <2 cm, synchronous, and oxaliplatin-treated) for close follow-up [19,50], considering fiducial markers for deep lesions outside planned resection areas. Per international guidelines, patients with unresectable disease due to unfavourable features (synchronous, >3 metastases, and bilobar or limited extrahepatic disease) should receive chemotherapy without biologics [2,4]. Conversely, potentially resectable cases may benefit from chemotherapy plus bevacizumab or anti-EGFR agents, depending on tumour biology. Imaging should be repeated bimonthly to enable timely surgery before lesion disappearance.

If disease becomes resectable, surgery should follow MTD discussion and preoperative CE-IOUS.

When imaging suggests DLMs, CE-IOUS confirms the absence of residual disease.

Treatment strategy should be individualised based on patient and tumour characteristics (intrinsic tumour biology, for example, the presence of a *RAS* mutation, could be an independent predictor of local progression after RFA) [85].

A W&W strategy may be considered for unfit patients or limited liver reserve as recurrence typically happens within 6–8 months post chemotherapy and may still be managed with surgery or ablation. Alternatively, surgery resection remains preferable in fit patients, especially when DLMs are adjacent to visible lesions. MRI-based surveillance may be sufficient in patients without chemotherapy-induced sinusoidal obstruction. However, if feasible, resection of residual metastases remains preferable [57]. RFA or MWA, alone or in combination, may offer alternative options that warrant further study.

Conclusion

Optimal DLM management remains debated. While resection may improve DFS, it does not consistently offer an OS advantage over W&W. Treatment should be individualised, considering patient factors, DLM characteristics, imaging quality, and salvage options.

If DLMs are undetectable on advanced imaging (Gd-EOB-DTPA MRI and CE-IOUS), surveillance may be a reasonable alternative to blind resection. High-quality imaging and multidisciplinary evaluation are key factors.

Further high-quality studies, focussing on the personalisation of treatment strategies based also on pathological biomarkers (such as molecular characteristics, circulating tumuor DNA [ctDNA], and APC mutations) in patients with known DLMs that could predict survival outcomes, are needed to guide clinical decision-making and support evidence-based recommendations.

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D.R., I.V., D.R., and C.C.: Conceptualisation, design, and initial drafting of the manuscript.

D.V. and D.L.: Conceptualisation, design, and critical revision of the manuscript.

D.L., L.A., D.P., and G. L. G.: Critical revision of the manuscript.

All authors reviewed and approved the final version of the manuscript.

Conflict of interest

D.R. reports relationships with Amgen, Pierre Fabre, Bayer, Takeda, and MSD, including participation in speaker's bureaus. L.A. reports relationships with Amgen, Roche, AstraZeneca, and Novartis involving royalties and with Merck Senoro in advisory role. The other authors declare no conflict of interest.

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