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Disappearing liver metastases: A systematic review of the current evidence

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ABSTRACT

Advances in systemic chemotherapy have resulted in a significant increase in the reported response rates of colorectal liver metastases (CRLM) over time. Although radiologic response is usually prognostic of favorable outcomes, complete shrinkage of CRLM after chemotherapy, namely "disappearing liver metastases" (DLMs) poses significant therapeutic dilemmas. A systematic review of the literature was conducted to evaluate the existing evidence on the imaging and management of patients with DLMs using the PubMed (Medline), Embase and Cochrane library through December 21st, 2018. The following algorithm was used: "(disappearing OR vanishing OR missing OR (residual tiny)) AND ((liver OR hepatic) AND (metastasis OR metastases OR metastatic OR secondary))." From the 225 records retrieved, 15 studies were finally deemed eligible. A total of 479 patients with DLMs with a median age of 59.5 years (range, 30–83) were identified. Median number of DLM per patient ranged from 1 to 8.8. Median size of LMs prior to chemotherapy was 1.07 cm (range 0.3–3.5). The systemic treatment used to achieve DLMs included systemic chemotherapy alone (only 2 studies) or in combination with targeted agents (11 studies). The median number of chemotherapy cycles in the included studies was 7.8 (range 6–12). Identified factors predisposing to the development of DLM were small size (< 2 cm), increased number of treatment cycles, oxaliplatin-based therapy, increased number of CRLM (≥ 3) and synchronous CRLM. Baseline and preoperative MRI with iv contrast showed the highest sensitivity for DLM detection. Fiducial placement facilitated pre- and intra-operative identification of DLM. Although resection of DLM decreased the local recurrence risk, there was no clearly demonstrated survival benefit after resecting all sites of disappearing lesions. Future randomized clinical trials are highly encouraged to provide strict, evidence-based recommendations for the treatment of patients with DLM.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide with approximately 1.65 million patients diagnosed with CRC each year. Nearly half of patients with CRC will develop liver metastases (LM) during the course of their disease resulting in two-thirds of all CRC-related deaths [1]. Although surgery remains the cornerstone of treatment for resectable colorectal liver metastases (CRLM), only 10–25% of patients with CRLM are candidates for surgical resection [2]. Among patients with unresectable CRLM, chemotherapy is the treatment of choice in the form of palliative or conversion chemotherapy [3]. In select cases, patients with initially resectable disease may also be treated with neoadjuvant chemotherapy in an attempt to reduce tumor burden prior to surgery [4].

Advances in systemic chemotherapy have resulted in a marked increase in reported response rates for CRLM over time [3]. Although radiologic response is usually prognostic of favorable outcomes, complete shrinkage or disappearance of CRLM after chemotherapy – so called "disappearing liver metastases" (DLMs) – can pose a therapeutic dilemma [5]. In general, DLMs occur among 5–25% of patients who receive preoperative chemotherapy with the reported incidence of DLM varying based on the type and quality of preoperative cross-sectional imaging [6]. To date, there is no consensus on the optimal management of patients with DLM. Resection of DLMs is not always feasible since such lesions may be hard to delineate or even be completely undetectable at the time of surgery. Currently, the optimal approach to DLM, including whether hepatic resection of the original sites of disease should be attempted versus observation and/or utilization of further

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systemic treatment, remains ill-defined [6,7]. Therefore, the objective of the current study was to summarize the existing literature on the imaging and management of patients with DLMs. Specifically, we sought to critically evaluate the imaging modalities that would best identify DLM lesions in the perioperative setting, as well as to assess the outcomes of patients relative to different treatment approaches.

2. Materials and methods

2.1. Search strategy and data sources

This systematic review adhered to the guidelines outlined by the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (Supplemental Table 1) [8]. A study protocol was agreed upon and strictly followed by all authors. Identification of eligible studies was performed by searching PubMed (Medline), Embase and Cochrane library through December 21st, 2018. The following algorithm was used: "(disappearing OR vanishing OR missing OR (residual tiny)) AND ((liver OR hepatic) AND (metastasis OR metastases OR metastatic OR secondary))." Two independent reviewers (DIT, INS) performed the literature screening. Reference lists of eligible studies were manually assessed in order to detect any potential relevant article ("snowball" procedure). Any disagreements were solved by consensus with a third author (DM).

2.2. Eligibility criteria

Eligible studies reported on patients with CRLM that disappeared on imaging after chemotherapy. Exclusion criteria included: 1) studies with patients with LM originating from organs other than colon or rectum, 2) case reports, 3) reviews and meta-analyses, 4) editorials and letters to the editors.

2.3. Data extraction and definitions

Two independent authors (DIT, INS) performed the data extraction and any discrepancies were resolved by team consensus. Extracted variables included: general study and patient characteristics (e.g. author, year of publication, study region, number of patients), size of DLM prior to chemotherapy, systemic chemotherapy used to achieve DLM, number of chemotherapy cycles, imaging modality used to characterize DLM, predictors of DLM, predictors of true complete response, macroscopic residual disease, complete pathologic response rates, type of therapy (hepatic resection, chemotherapy, targeted agents) and oncological outcomes. LMs were defined as "disappearing" or "missing" after use of different imaging modalities among eligible studies, including computed tomography (CT), magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography (FDG-PET). Recurrence free survival (RFS) was defined as the time from hepatic resection to intra- or extra-hepatic recurrence. Overall survival (OS) was defined as the time from hepatic resection or systemic therapy to death or last follow-up. Due to the heterogeneity of the available studies, a formal meta-analysis was not feasible.

3. Results & discussion

3.1. Patient and study characteristics

The successive steps of the selection process are depicted in Fig. 1. From the 225 records retrieved, 13 studies were deemed eligible, while 2 studies were identified through snowball procedure for a total of 15 included studies [9–23]. Three studies were excluded on the basis of overlapping population [24–26]. In total, 6 studies reported on radiological identification of DLMs [10,13,15,16,19,21], while 4 studies reported on management and outcomes of patients with DLMs [11,15,20,22]. A total of 479 patients with DLMs with a median age of 59.5 (range, 30–83) years were identified. Patients had a total of 1564 DLMs. Males comprised the majority of the patient cohort (n = 247/396, 62.4%). Median number of DLM per patient ranged from 1 to 8.8. Median size of LMs prior to chemotherapy was 1.07 cm (range 0.3–3.5). The systemic treatment associated with DLMs was cytotoxic systemic chemotherapy alone (2 studies) [9,20] or cytotoxic chemotherapy plus targeted agents (11 studies) [10–16,19,21,22]. The median number of chemotherapy cycles was 7.8 (range 6–12). The demographics of the patients included in the eligible studies are summarized in Table 1.

3.2. Factors predisposing to DLM

Several factors have been associated with the development of DLMs [22]. Among them, small size of the CRLM (generally less than 2 cm) and prolonged duration of preoperative chemotherapy have been strongly associated with the risk of DLM (Table 2) [4,15,21,22]. Among the included studies, median size of LMs that disappeared was 1.07 cm (range 0.3–3.5) prior to chemotherapy, which was generally smaller than CRLM that did not disappear [15,21,22]. In addition, the median number of chemotherapy cycles among DLM cases was 7.8 (range 6–12), which was higher than patients without DLMs (around 5.5 cycles) [22]. In fact, Van Vledder and colleagues noted a 18% increased likelihood of DLM with each additional cycle of chemotherapy [22]. The presence of three or more LMs was also associated with a higher chance of developing a DLM [21,22]. In addition, patients with synchronous metastatic disease were more likely to have disappearing lesions compared with patients who developed metachronous CRLM [15]. Oxaliplatin-based chemotherapy was also more frequent among patients with disappeared lesions [21]. Taken together, these factors may help identify which patients may be at highest risk of DLM with preoperative chemotherapy utilization.

3.3. Preoperative imaging and definition of DLM

The definition of DLM is dependent on the sensitivity and specificity of the cross-sectional imaging modality used to characterize the LM as "disappeared." To date, a number of modalities have been used to identify CRLM, including CT with or without contrast, MRI, FDG-PET and FDG-PET/CT. Among these studies, the majority of LM have been characterized as "disappeared" after CT imaging. Interestingly, the reported sensitivity and specificity of dual phase helical CT for detecting CRLM has been estimated at 70–90% and 85–90%, respectively [27–29]. Preoperative chemotherapy can lower CT and FDG-PET diagnostic accuracy by reducing the sensitivity of these modalities [30]. In particular, chemotherapy may induce parenchymal changes to the liver, such as steatosis, steatohepatitis and sinusoidal obstruction syndrome. In turn, these parenchymal changes can mitigate the contrast between the fatty liver and the liver metastases and, thus, hinder the detection of CRLM with CT [31,32].

FDG-PET has been considered a useful adjunct imaging modality for preoperative characterization of the CRLM burden; however, FDG-PET has failed to demonstrate superiority compared with contrast-enhanced CT [33]. Therefore, the hybrid FDG-PET/CT scan has gained popularity in terms of providing anatomical and functional information that is both valuable for formulating a personalized treatment plan and for prognostic purposes [34]. Interestingly, serial FDG-PET/CT may also be predictive of prognosis based on early response to treatment [35]. FDG-PET/CT has, however, only been evaluated on a limited basis relative to the assessment of DLM, as only a small proportion of studies have included patients who had undergone FDG-PET/CT [9,10,14,15,22]. As such, the role of FDG-PET/CT remains relatively unknown in the setting of DLM.

Rather, MRI has been reported to be the optimal imaging modalities compared with CT or PET/CT scan to detect DLM, as fat suppressing techniques may be able to compensate for any chemotherapy-induced steatosis [36]. Interestingly, a recent multi-institutional study revealed

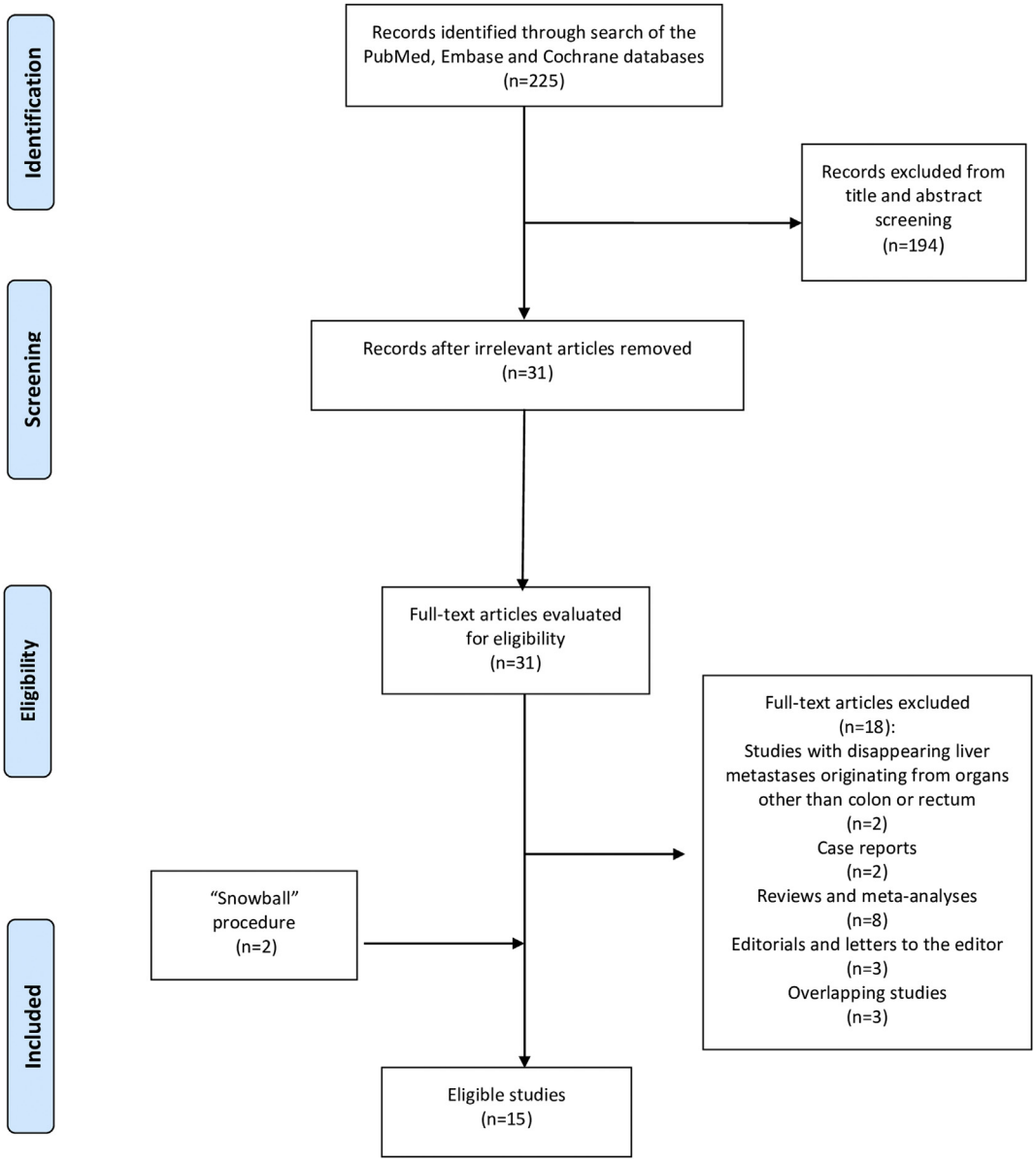

Fig. 1. Flowchart of the study selection process.

a higher positive predictive value for "true" DLM on MRI versus contrast-enhanced CT scan (78.0%, 95%CI: 63.7%–87.7% vs 35.2%, 95%CI: 25.1%–46.8%, $p < 0.001$) [16]. In a separate study, Ferrero et al. also demonstrated the superiority of MRI in terms of accurate DLM evaluation compared with CT ($p = 0.0013$) and FDG-PET ($p < 0.0001$) [10]. Auer et al. similarly reported that the inability to detect DLM on preoperative imaging was associated with the presence of steatosis and the omission of MRI before surgery [9]. Although the sensitivity of both CT and MRI to detect lesions larger than 1 cm may be greater than 90%, Sturesson et al. reported a superior sensitivity for MRI preoperatively to detect lesions measuring 1 cm or less (53% vs 36% for MRI and CT, respectively) [19]. A recent meta-analysis that examined the diagnostic performance of CT, MRI and PET/CT among patients treated with preoperative chemotherapy noted a pooled sensitivity of MRI for detecting CRLM of 85.7% versus 69.9% for CT, 54.5% for PET and 51.7% for PET/CT [37]. Another meta-analysis reported that gadoxetate disodium-enhanced MRI had the highest sensitivity among all modalities and the highest specificity even compared with PET/CT for CRLM detection [38]. While MRI was not routinely used in the preoperative setting among all the included studies, current data strongly suggest that MRI is superior in the identification of LMs considered "missing" compared with other imaging modalities following chemotherapy [9,10,12,21,36].

3.4. Intraoperative assessment of DLM

Since no imaging modality can offer a 100% detection rate, a portion of DLMs will be discovered at the time of surgical exploration [9,20,22]. In particular, DLM that were not identified on preoperative CT scan may simply have been "missed" rather than "disappeared." As such, patients with DLM should routinely undergo MRI as this modality has the highest accuracy to determine if the lesion has "truly" disappeared. If the lesion cannot be identified on MRI, a thorough intraoperative exploration at the time of surgery with palpation and intraoperative ultrasonography (IOUS) may identify the lesion. A meticulous intraoperative assessment, including full liver mobilization, visual inspection, palpation and IOUS should be performed, especially in the presence of risk factors for DLM (e.g. small and multiple lesions, extended course of chemotherapy, and chemotherapy-induced liver damage) [5]. Overall, macroscopic residual disease is discovered

Table 1
Demographics of the included studies.

ID	Institution, Country	Study period	Total no of pts	Age (years)[a]	Males, n (%)	DLM			Median no of LMs/ patients	Median no of DLMs/patient	Size of DLM (cm)[a]
						No of pts (%)	No of DLMs (%)	Total no of LMs			
Oba (2018)	Cancer Institute Hospital, Japanese Foundation for Cancer Research, Japan	2010–2015	184	59 (30–81)	42 (71)	59 (32)	275 (36)	764	4.15	4.66	0.8 (0.3–3.4)
Tani (2018)	Graduate School of Medicine, Tokyo, Japan	2010–2014	82	57.5 (34–77)	10 (50)	20 (18)	111 (17.9)	619	7.55	5.55	NR
Park (2017)	Seoul, Korea (Collaboration of 8 institutions)	2008–2011	87	58.6 ± 9.1	37 (77.1)	87 (100)	258 (65.6)	393	4.52	2.9	NR
Kim (2016)	Soonchunhyang University College of Medicine, Seoul, Korea	2010–2012	137	60.3 ± 10.4	28 (77.8)	36 (26.3)	168 (58.1)	289	7.5	4.7	1.07 ± 1.1
Passot (2016)	The University of Texas MD Anderson Cancer Center, Houston, Texas, USA	2005–2015	32	NR	NR	32 (100)	19 (46)	41	NR	NR	1.2 (0.6–2)
Owen (2015)	University of Kentucky, Washington University, University of Rochester; USA	2008–2014	23	53 (37–74)	NR	11 (47.8)	77 (38.5)	200	6	4	0.8 (0.3–3.2)
Spolverato (2015)[b]	Johns Hopkins Hospital, USA and Università di Padova, Padova, Italy	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sturesson (2015)	Lund University and Skane University Hospital, Lund, Sweden	2011–2014	179	68 (48–83)	20 (70)	29 (16.2)	66 (46.8)	141	5	2.3	NR
Ferrero (2012)	Ospedale Mauriziano “Umberto I”, Largo Turati, Torino Italy	2004–2008	292	62 ± 12.87	25 (75)	33 (11.3)	67 (43.8)	153	4	1	1.05 ± 0.48
Ono (2012)	Saitama Medical Center, Japan	2006–2010	125	60 (35–69)	2 (40)	5 (4)	44 (100)	44	8.8	8.8	1.8 (1–2.4)
Goere (2011)	Institut Gustave Roussy, Villejuif, Cedex, France.	1998–2007	523	52.4 ± 7.5	11 (40.7)	27 (5.2)	96	NR	9	3.5	NR
Auer (2010)	Memorial Sloan-Kettering Cancer Center (New York, NY)	2000–2003	435	53 ± 12.5	29 (73)	39 (9.0)	118 (71)	166	4.3	3	1.6 ± 0.9
Van Vledder (2010)	Johns Hopkins Hospital	2000–2008	168	NR	NR	40 (23.8)	127	NR	NR	NR	1 (0.3–3.5)
Tanaka (2009)	Graduate School of Medicine, Yokohama, Japan.	1992–2007	307	62 (46–77)	17 (73.9)	23 (7.5)	72[c]	NR	N/A	3.74	N/A
Benoist (2006)	Assistance Publique–Hôpitaux de Paris, Hôpital Ambroise Paré;	1998–2004	586	61 ± 12	26 (68.4)	38 (6.5)	66 (36)	183	4.8	1.74	2.2 ± 1.5

DLM: disappearing liver metastases; NR: not reported; N/A: not applicable.

[a] Presented as mean ± SD or median (range).

[b] Cost-utility analysis.

[c] 14 DLMs were excluded due to local ablation.

Table 2
Factors predisposing to the development of DLM.

ID	Predictors
Van Vledder (2010)	• smaller size [DLM: 1.0 cm (0.3–3.5) vs no DLM: 2.1 cm (0.4–16); p < 0.001] • number of cycles (OR 1.18; p = 0.03) • > 3 LMs (OR 13.1; p < 0.001)
Owen (2015)	• smaller size [DLM:0.6 cm (0.3–3.2) vs no DLM: 1.5 cm (0.3–15.1 cm)] • synchronous disease (OR 11.25; p = 0.015)
Tani (2018)	• higher number of LM [DLM: 14.5 (4–39) vs no DLM: 3.5 (1–30); p < 0.001] • smaller size [DLM: 0.6 cm (0.4–2) vs no DLM: 1.4 (0.3–13); p < 0.001] • platin-based chemo (DLM: 100% vs no DLM: 75.8%; p = 0.017)

DLM: disappearing liver metastases; LM: liver metastases; OR: odds ratio.

roughly among 11–45% of patients at the time laparotomy.

Systematic IOUS facilitates the detection of DLM [10]. Indeed, published series report a detection rate of up to 60% with the combination of palpation and IOUS [10]. Factors associated with IOUS detection of residual metastases include: moderate or severe hepatic steatosis, sub-glissonian localization of nodules and residual microscopic disease [10]. Importantly, the use of contrast enhanced IOUS (CE-IOUS) can further improve detection rates of DLM [19,24]. To this point, Arita et al. reported that the sensitivity of CE-IOUS to detect DLM was higher than CE-CT and simple IOUS [24]. Oba and colleagues suggested that the use of both gadoxetic acid-enhanced MRI and CE-IOUS had the best chance of identifying DLMs containing viable disease with the highest level of accuracy [13].

3.5. Novel imaging techniques

Augmented reality (AR) has recently been introduced into the surgical field, thereby allowing for the development of a 3D virtual model of patient anatomy [39,40]. When a 3D model is superimposed onto real-time patient images, a composite AR image can be generated that allows for visualization of deeper structures through the overlying tissues [40]. Interestingly, a preliminary report has proposed AR as a means to facilitate the accurate resection of DLMs [41]. In this study, AR helped detect all 4 DLMs in 3 patients and facilitated R0 resection without local recurrence after a follow-up of 6–22 months [41]. The superimposition and precise registration of the 3D virtual vascular anatomy onto the operative image was performed within 6 min. While 3D-modeling has already been used in a variety of open and minimally invasive oncologic procedures [42,43], its applicability in assessing patients with DLM LM has not yet been fully explored; as such, future studies will need to delineate its use for DLM.

3.6. Predictors of true complete response

Complete radiologic response does not necessarily signify complete pathologic response [30]. Among the included studies, complete pathologic response or no recurrence in situ ranged from 16.7% to 80.5% among lesions that had disappeared on cross-sectional imaging [14,23]. Several factors may be responsible for the high variability in finding residual disease among lesions believed to have disappeared. In particular, the failure to use MRI, which has the highest DLM detection accuracy, as well as the different types of chemotherapy administered may be associated with differential disease reponses [25]. Auer et al. reported that the use of hepatic arterial infusion (HAI) chemotherapy, inability to observe the DLM on a MRI and normalization of serum carcinoembryonic antigen (CEA) levels were associated with a “true” complete response [9]. In particular, homogenous rather than reticular hypointense signal intensity on MRI was associated with no recurrence among patients with DLM [12]. A separate study noted that LM with a smaller size at diagnosis (15.9 ± 14.3 mm vs 24.4 ± 22.3 mm, p < 0.001) and fewer microscopic satellite cancer deposits surrounding macroscopic tumors (21.7% vs 52.5%, p < 0.05) were more likely to have a complete pathologic response [20]. In a different study, Adam et al. reported that a complete pathologic response was more frequent in younger patients (≤60 years) with small lesions (≤3 cm), and a low initial CEA level (≤30 ng/ml) [44]. While there are no absolute criteria to predict a complete pathologic response among patients with DLM, patients 60 years or younger treated with HAI chemotherapy who had initially low CEA that normalizes after chemotherapy with no detectable disease on MRI are the most likely to have a “true” complete pathologic response. In turn, a complete pathologic disappearance constitutes a strong predictor of both prolonged survival and decreased risk of recurrence [20,44].

3.7. Challenges in the management of patients with DLM

Currently, there are no recommendations as to whether DLM should be resected or be left in situ. Proponents of resection note the relatively low incidence of complete pathological response (≈20%) and higher rates of recurrence for lesions left in situ (≈70%) [45]. The latter may be attributed to undetectable, residual disease, as well as to the presence of a favorable microenvironment for tumor relapse in the site of DLM and its surroundings [46]. In general, according to a consensus statement on hepatic resection for CRLM, the goal of surgery should be to remove all original sites of the disease [47]. Thus, for DLM all sites of metastases visualized before chemotherapy should be removed. However, complete eradication of the disease is sometimes difficult to accomplish due to the extended distribution of LMs and the risk of an inadequate future liver remnant after hepatic resection [48]. Furthermore, both disease molecular characteristics, such as RAS mutational status, and technical variables, such as optimal surgical margin width, should be considered on a case-by-case basis relative to the decision to resect DLM [49,50].

When considering resection of a lesion that is at high risk of disappearing, marking of the sites of metastasis with a fiducial before initiation of chemotherapy may facilitate accurate localization of possible DLMs intraoperatively [17,51]. Indeed, Passot et al. published a series of 32 patients who underwent fiducial placement for 41 CRLMs of which 19 LM disappeared on imaging. With the assistance of the fiducial placement, all LMs were able to be localized and eventually be resected or ablated with no recurrence of disease detected after a mean follow-up of 14 months [17]. Suggested indications for fiducial placement include metastases < 20 mm in size, located > 10 mm deep in the liver parenchyma and outside the planned field of resection [17,51].

Interestingly, Spolverato et al. conducted a cost-effectiveness analysis comparing the two treatment strategies for DLM: hepatic resection versus surveillance with additional chemotherapy [18]. Of note, six months of additional systemic chemotherapy followed by active surveillance without liver resection were highly recommended for patients older than 60 years. In this study, factors associated with a “true” complete pathological response included normalization of CEA levels, administration of HAI therapy, BMI ≤30 kg/m2, and utilization of MRI

Table 3
Assessing outcomes of different therapeutic strategies: OS and RFS.

ID	OS	RFS
Tanaka (2009)	NR	Surgery vs no surgery (lesions with recurrence): 11/45 (24.4%) vs 11/27 (40.7%)
Van Vledder (2010)	Surgery vs no surgery: 1-OS: 92.3% vs 93.8% 3-OS: 70.8% vs 63.5% 5-OS: 46.2% vs 63.5%, p = 0.66	Surgery vs no surgery: 1-year intrahep RFS: 68.8% vs 40.2% 3-year intrahep RFS: 35.1% vs 16.1%, p = 0.04 1-year any site RFS: 59.7% vs 33.1% 3-year any site RFS: 22.7% vs 13.2%, p = 0.06
Goere (2011)	No surgery: 3-OS: 87% 5-OS: 80%	No surgery: 3-DFS: 23% 5-DFS: 23%
Owen (2015)	NR	Surgery vs no surgery: average RFS: median 483 (111–861) vs 360 (109–519), p = 0.49.

NR: not reported; OS: overall survival; RFS: recurrence-free survival.

[18]. Resection was noted to be of borderline value for younger patients who had these favourable clinical factors [18].

3.8. Assessing outcomes of surgery versus surveillance: OS and RFS

Only a few studies have reported direct comparisons between the treatment approaches of patients with DLM in terms of OS and RFS (Table 3) [9,11,15,20,22]. In assessing outcomes of patients who developed DLM after chemotherapy that were then left in situ, Goere et al. reported a 5-year OS and RFS of 80% and 23%, respectively [11]. Of note, the incidence of intrahepatic recurrence was lower among patients who had received adjuvant oxaliplatin-based HAI compared with patients who had not (26.6% vs 83.3%, p = 0.006) [11]. Median time to recurrence in the non-surgical group ranged from 13.8 to 21 months [9,11]. Another study by Owen et al. noted that patients undergoing resection of DLM had a median RFS of 483 days versus 360 days among patients who did not undergo resection; however, the difference was not statistically significant (p = 0.49) [15]. Although Van Vledder and colleagues reported no difference in 1-, 3- and 5-year OS among patients undergoing surgery versus surveillance, there was a marked advantage in 3-year intrahepatic recurrence among the surgical group [22]. Similarly, Tanaka et al. reported that 11 out of 45 (24.4%) resected DLM developed recurrence, whereas 11 out of 27 DLMs (40.7%) left in situ recurred after a median follow-up of 44 months [20]. Perhaps not surprisingly, current evidence suggests that patients having all original sites of disease resected have a lower risk of intrahepatic recurrence versus patients with lesions left in situ [20,22,41]. Of note, a higher incidence of intrahepatic recurrence may not necessary translate, however, into a worse long-term survival [20,22,41].

3.9. Determining the appropriate therapeutic plan

Due to the complexity of the disease and the limited available evidence, patients presenting with DLM should be treated in a multidisciplinary setting. Patient characteristics (i.e. age, comorbidities and performance status), tumor features (i.e. tumour burden, localization and RAS/BRAF mutational status), along with toxicity profile and patient wishes should guide treatment decision-making [48,49]. Regarding patients fit for surgery, surgeons and oncologists should weigh the risks and benefits of treatment intensity relative to whether R0 resection of the original site of the disease can be achieved. In cases where all original sites of the disease cannot be technically resected, systemic chemotherapy or a chemotherapy "holiday" should be considered. These patients should be closely monitored with more frequent re-imaging and surgery considered if the DLM re-appears, which typically occurs within 6–8 months [11,48]. The basic principles in the management of DLM are summarized in Table 4.

Table 4
Basic principles of DLM diagnosis and management.

- ✓ DLM definition: complete response (disappearance) of CRLM after chemotherapy on cross-sectional imaging studies
- ✓ Frequency: 5–25% of CRLM cases receiving preoperative therapy
- ✓ Predisposing factors: small size (< 2 cm), increased number of treatment cycles, oxaliplatin-based therapy, increased number of CRLM (> =3), synchronous CRLM
- ✓ Imaging: baseline and preoperative MRI with IV contrast has highest sensitivity for DLM detection
- ✓ Intra-operative exploration with palpation and IOUS after full liver mobilization is mandated especially in the absence of preoperative MRI.
- ✓ Baseline imaging (CT and MRI) with fiducial placement may guide pre- and intra-operative identification and delineation of DLM.
- ✓ HAI administration in young patients (< 60 years old) with an initially low CEA that normalizes under chemotherapy who have no detectable lesion on both CT and MRI have the highest chance of a "true" pathological complete response.
- ✓ Resection of all DLM sites of disease is generally advocated
- ✓ Resection of all DLM sites of disease has been associated with lower intrahepatic recurrence
- ✓ Leaving DLM in situ has been associated with a higher incidence of intrahepatic recurrence, yet not necessarily a worse long-term overall survival
- ✓ Treatment of patients with DLM needs to be highly individualized and may involve surgical resection, additional systemic or local therapy, or close surveillance.

4. Conclusion

A complete CRLM response on imaging following chemotherapy does not necessarily imply a "true" complete response. While the current surgical dogma suggests removal of all tumor burden if feasible, the management of DLM remains controversial. Resection of DLM has been associated with a decreased incidence of recurrence. The higher incidence of intrahepatic recurrence associated with leaving DLM in situ has not universally translated into worse long-term OS. Further research into the factors predisposing to DLM, as well as the outcomes of patients with DLM, is needed to formulate more robust, evidenced-based guidelines for the treatment of patients with DLMs.

Conflicts of interest

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Appendix A. Supplementary data

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