Hepatic Oncology

The impact of intraoperative ultrasonography on the management of disappearing colorectal liver metastases

Felice Giuliani^{*,1}, Elena Panettieri¹ & Francesco Ardito¹

Hepatic resection for colorectal liver metastases (CRLM) is currently the only treatment option that can offer a chance of long-term survival, with 5-year survival rates of 40% [1–3], and exceeding 50% in selected patients [4–6]. However, resectability is the limiting factor; indeed, only 10–25% of patients with CRLM are candidates for surgical resection at the time of presentation [7].

More recently, the introduction of new and more effective chemotherapy regimens combined with targeted agents have improved the response rate over that of standard chemotherapy alone, from 30 to 60% [8–10]. For this reason preoperative chemotherapy for CRLM has been widely used and an increasing number of patients receive chemotherapy prior to liver resection, either as neoadjuvant strategy for initially resectable CRLM [11], or as conversion chemotherapy in patients with initially unresectable CRLM in attempt to convert them into surgical candidates [12,13].

The extensive use of chemotherapy may cause the shrinkage of CRLM and sometimes makes such lesions impossible to identify in radiological imaging studies. These lesions are called ‘missing’ or ‘disappearing’ CRLM [14]. Disappearing liver metastases (DLM) are defined as a disappearance of liver metastases on cross-sectional imaging after administration of preoperative chemotherapy, which means a complete radiological response or complete clinical response (CCR). This phenomenon has been reported by several centers and can occur in 5–25% of patients who undergo preoperative systemic chemotherapy [15–21]. Patients with multiple CRLM, with size <1 cm and those undergoing prolonged preoperative chemotherapy, presented significantly higher risk of developing DLM [18]. Different reported rates of DLM may depend on the quality and type of cross-sectional imaging [22]. Indeed preoperative chemotherapy can induce parenchymal changes to the liver

KEYWORDS

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¹Hepatobiliary Surgery Unit, Agostino Gemelli Hospital, Catholic University of the Sacred Heart, Rome, Largo Agostino Gemelli, 8-I-00168 Rome, Italy

*Author for correspondence: Tel.: +39 063 015 4967; Fax: +39 063 058 586; fgiulianti@rm.unicatt.it

“The rate of complete pathologic response in disappearing liver metastases is low and the intrahepatic recurrence rate in patients with untreated disappearing liver metastases is high. For this reason accurate intraoperative detection of all disappearing liver metastases should be mandatory.”

by increasing fatty content, defined as steatosis or steatohepatitis. In that setting the background liver appears less dense, with lower contrast between the parenchyma and the hypovascular metastases, hindering their detection [14,22]. Compared with computed tomography (CT), magnetic resonance imaging (MRI) with liver-specific contrast agents, presents higher sensitivity and better specificity to detect and differentiate CRLM, and can be considered as the best modality to image CRLM missing on CT scan, especially in case of chemotherapy-induced steatosis or steatohepatitis [14,22,23].

The crucial issue is that the presence of complete radiological response often does not mean cure, because many of the liver lesions disappearing on radiologic evaluation after successful chemotherapy, are still present and alive. For this reason the CCR does not reflect a complete pathologic response (CPR). Indeed in the literature the correlation between CCR and CPR ranges from 15 to 70% [15–21]. In a recent paper by Ferrero *et al.* [21], a CPR was noted in 26 of the 67 DLM analyzed (38.8%). These results are similar to those observed in our Institution where a CPR was noted in 32 of the 79 DLM analyzed (40.5%) [GIULIANTE F, UNPUBLISHED DATA].

Furthermore, the risk of intrahepatic recurrence at the site of a DLM left *in situ* is high and ranges from 30 to 74% [18,19,21]. For this reason, intraoperative detection of all DLM is fundamental in order to perform a radical resection. Indeed the goal of surgery, when possible, is to completely resect or ablate all sites of disease found during surgery as well as originally detected sites prior to chemotherapy. However, the accurate resection of a DLM may be difficult if the metastasis cannot be identified during the operation. Intraoperative ultrasound (IOUS) has been used as a key tool for this purpose to date.

The role of IOUS in liver surgery has been widely studied, but its value as a staging technique in patients with CRLM is still under debate [24–27]. The rate of additional CRLM intraoperatively detected by IOUS ranges from 8.2 [25] to 25.6% in a Japanese series [28]. In a recent bi-institutional paper [27], the authors showed that IOUS improved staging in patients undergoing resection for CRLM. Indeed, 280 new CRLM (17.6%) were found by IOUS on 515 patients with 1370 CRLM preoperatively detected [27]. These results were obtained even when adequate preoperative staging was performed. In particular, these data, coming from

a large population of patients who underwent liver resection in two tertiary Italian centers, were collected in recent years, during a short duration of the study period (5 years) and with an extensive preoperative work-up in every case, using high-quality cross-sectional and functional imaging [27].

Rate of intraoperative detection of DLM by IOUS is also extremely variable, ranging from 0.9 [17] to 30% [29]. The different surgeon's operative policy may explain these disparate results. Indeed the real impact of IOUS on the detection of DLM strictly depends on what is the surgical policy applied. In some centers major hepatectomies for CRLM are usually preferred instead of multiple IOUS-guided parenchymal-sparing liver resections. In those centers the careful detection of DLM in the liver to be resected may not be routinely performed because, for instance, the finding of new liver lesions in the right lobe does not impact the surgical strategy if a right hepatectomy has been preoperatively planned. In centers where IOUS-guided parenchymal-sparing liver resections are usually performed for CRLM, a careful and systematic IOUS exploration represents a fundamental step of surgical procedure and the impact of IOUS on the detection of DLM is significantly stronger with reported detection rates from 30 up to 58% [21,29]. It must be emphasized that the surgeon who performs the surgical procedure should carry out the IOUS, rather than assistants, radiologists, or technicians. This is because obtaining and interpreting the information requires skills and a background in ultrasound imaging. All intraoperative information about localization of lesions and their relationships with vascular structures must be fully comprehended by the surgeon in order to allow surgical maneuvers guided and carried out by the probe. IOUS should not be performed only at the beginning of the operation but several times during parenchymal transection. For this reason the optimal condition would be that IOUS and the operation are performed by the same person [30].

The ability to detect a DLM by IOUS represents a strong predictor of residual disease. In the experience of the authors, a residual disease was confirmed in 16 (72.7%) of the 22 resected CRLM, disappeared at preoperative imaging and detected by IOUS [GIULIANTE F, UNPUBLISHED DATA]. These results are similar to that reported by Ferrero *et al.* [21]. For this reason liver

resection should always be performed when a DLM is detected by IIOUS, even if the surgical strategy may change into a major hepatectomy. In case of missing DLM also by IIOUS, the initial site should be resected when possible and if the required hepatectomy is easy and feasible. If change of surgical strategy is not safe, leaving undetected lesions *in situ* with subsequent strict follow-up should be preferred.

The impact of contrast-enhanced intraoperative ultrasound (CE-IIOUS) on improving the surgical staging and the management of DLM is still controversial [21,31,32]. After intensive preoperative chemotherapy with subsequent steatosis and steatohepatitis, the background liver usually becomes hyperechoic and the contrast between the healthy parenchyma and the metastasis increases. The echogenicity of CRLM decreases and intraoperative detection by IIOUS may become easier [18]. Indeed in the study by Ferrero *et al.* [21], CRLM were hypoechoic at IIOUS in 87% of patients with moderate or severe steatosis. The natural increase of liver contrast in presence of steatosis may probably explain the poor impact of CE-IIOUS on detecting DLM in some European series where sulfur hexafluoride microbubbles (SonoVue, Bracco Imaging, Milan, Italy) are usually used as contrast agent [21]. On the other hand, a recent Japanese series [32] showed that CE-IIOUS using perflubutane provided additional value to conventional IIOUS for diagnosing CRLM. In this study nearly half of the DLM that were missed using IIOUS were identified using CE-IIOUS [32]. Indeed, CE-IIOUS

identified 79% of the 19 DLMs that were ultimately confirmed as liver metastases, whereas IIOUS identified 21% of them ($p < 0.004$). Furthermore, when considering patients with lesions of 1 cm or less in diameter, the sensitivity of CE-IIOUS for these tumors was superior to CT ($p < 0.04$) and IIOUS ($p < 0.04$), respectively [32]. The authors concluded that CE-IIOUS might be necessary after preoperative chemotherapy for DLM even if extensive preoperative imaging studies have been completed.

In conclusion, the occurrence of DLM on imaging after chemotherapy will increasingly be reported. The rate of CPR in DLM is low and the intrahepatic recurrence rate in patients with untreated DLM is high. For this reason accurate intraoperative detection of all DLM should be mandatory. The use of IIOUS continues to be fundamental for correct staging of patients with CRLM undergoing liver resection and showed an impact on the detection of DLM even in patients with adequate preoperative staging.

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References

- 1 Van Cutsem E, Nordlinger B, Adam R *et al.* European Colorectal Metastases Treatment Group. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur. J. Cancer* 42, 2212–2221 (2006).
- 2 Giulianti F, Ardito F, Pulitanò C *et al.* Does hepatic pedicle clamping affect disease-free survival following liver resection for colorectal metastases? *Ann. Surg.* 252(6), 1020–1026 (2010).
- 3 House MG, Ito H, Gonen M *et al.* Survival after hepatic resection for metastatic colorectal cancer: trends in outcomes for 1,600 patients during two decades at a single institution. *J. Am. Coll. Surg.* 210, 744–752 (2010).
- 4 Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. *Br. J. Cancer* 94, 982–999 (2006).
- 5 Rees M, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann. Surg.* 247, 125–135 (2008).
- 6 de Haas RJ, Wicherts DA, Andreani P *et al.* Impact of expanding criteria for resectability of colorectal metastases on short- and long-term outcomes after hepatic resection. *Ann. Surg.* 253, 1069–1079 (2011).
- 7 Wicherts DA, de Haas RJ, Adam R. Bringing unresectable liver disease to resection with curative intent. *Eur. J. Surg. Oncol.* 33(Suppl. 2), S42–S51 (2007).
- 8 Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. *Oncologist* 13, 51–64 (2008).
- 9 Nordlinger B, Van Cutsem E, Gruenberger T *et al.* European Colorectal Metastases Treatment Group; Sixth International Colorectal Liver Metastases Workshop. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. *Ann. Oncol.* 20, 985–992 (2009).
- 10 Loupakakis F, Cremolini C, Masi G *et al.* Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. *N. Engl. J. Med.* 371(17), 1609–1618 (2014).

- 11 Nordlinger B, Van Cutsem E, Rougier P *et al.* European Colorectal Metastases Treatment Group. Does chemotherapy prior to liver resection increase the potential for cure in patients with metastatic colorectal cancer? A report from the European Colorectal Metastases Treatment Group. *Eur. J. Cancer* 43, 2037–2045 (2007).
- 12 Adam R, Wicherts DA, de Haas RJ *et al.* Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *J. Clin. Oncol.* 27, 1829–1835 (2009).
- 13 Ardito F, Vellone M, Cassano A *et al.* Chance of cure following liver resection for initially unresectable colorectal metastases: analysis of actual 5-year survival. *J. Gastrointest. Surg.* 17(2), 352–359 (2013).
- 14 Zendel A, Lahat E, Dreznik Y, Zakai BB, Eshkenazy R, Ariche A. 'Vanishing liver metastases' – a real challenge for liver surgeons. *Hepatobiliary Surg. Nutr.* 3(5), 295–302 (2014).
- 15 Elias D, Youssef O, Sideris L *et al.* Evolution of missing colorectal liver metastases following inductive chemotherapy and hepatectomy. *J. Surg. Oncol.* 86(1), 4–9 (2004).
- 16 Tanaka K, Takakura H, Takeda K, Matsuo K, Nagano Y, Endo I. Importance of complete pathologic response to prehepatectomy chemotherapy in treating colorectal cancer metastases. *Ann. Surg.* 250(6), 935–942 (2009).
- 17 Auer RC, White RR, Kemeny NE *et al.* Predictors of a true complete response among disappearing liver metastases from colorectal cancer after chemotherapy. *Cancer* 116(6), 1502–1509 (2010).
- 18 van Vledder MG, de Jong MC, Pawlik TM, Schulick RD, Diaz LA, Choti MA. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? *J. Gastrointest. Surg.* 14(11), 1691–1700 (2010).
- 19 Goëré D, Gaujoux S, Deschamp F *et al.* Patients operated on for initially unresectable colorectal liver metastases with missing metastases experience a favorable long-term outcome. *Ann. Surg.* 254(1), 114–118 (2011).
- 20 Gaujoux S, Goëré D, Dumont F *et al.* Complete radiological response of colorectal liver metastases after chemotherapy: what can we expect? *Dig. Surg.* 28(2), 114–120 (2011).
- 21 Ferrero A, Langella S, Russolillo N, Vigano L, Lo Tesoriere R, Capussotti L. Intraoperative detection of disappearing colorectal liver metastases as a predictor of residual disease. *J. Gastrointest. Surg.* 16, 806–814 (2012).
- 22 Bischof DA, Clary BM, Maithel SK, Pawlik TM. Surgical management of disappearing colorectal liver metastases. *Br. J. Surg.* 100(11), 1414–1420 (2013).
- 23 Bipat S, van Leewen MS, Comans EFI *et al.* Colorectal liver metastases: CT, MR imaging and PET for diagnosis – meta-analysis. *Radiology* 237, 123–131 (2005).
- 24 Torzilli G, Makuuchi M. Intraoperative ultrasonography in liver cancer. *Surg. Oncol. Clin. North. Am.* 12, 91–103 (2003).
- 25 Tamandl D, Herberger B, Gruenberger B *et al.* Adequate preoperative staging rarely leads to a change of intraoperative strategy in patients undergoing surgery for colorectal cancer liver metastases. *Surgery* 143, 648–657 (2008).
- 26 Wagnetz U, Atri M, Massey C, Wei AC, Metser U. Intraoperative ultrasound of the liver in primary and secondary hepatic malignancies: comparison with preoperative 1.5-T MRI and 64-MDCT. *AJR Am. J. Roentgenol.* 196, 562–568 (2011).
- 27 Ferrero A, Langella S, Giuliante F *et al.* Intraoperative liver ultrasound still affects surgical strategy for patients with colorectal metastases in the modern era. *World J. Surg.* 37(11), 2655–2663 (2013).
- 28 Hata S, Imamura H, Aoki T *et al.* Value of visual inspection, bimanual palpation, and intraoperative ultrasonography during hepatic resection for liver metastases of colorectal carcinoma. *World J. Surg.* 35, 2779–2787 (2011).
- 29 Benoist S, Brouquet A, Penna C *et al.* Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J. Clin. Oncol.* 24, 3939–3945 (2006).
- 30 Torzilli G. Adjuncts to hepatic resection: ultrasound and emerging guidance systems. In: *Blumgart's Surgery of the Liver, Pancreas and Biliary Tract (5th Edition)*. Elsevier Inc., Amsterdam, The Netherlands (2012).
- 31 Torzilli G, Del Fabbro D, Palmisano A *et al.* Contrast-enhanced intraoperative ultrasonography during hepatectomies for colorectal cancer liver metastases. *J. Gastrointest. Surg.* 9(8), 1148–1153 (2005).
- 32 Arita J, Ono Y, Takahashi M, Inoue Y, Takahashi Y, Saiura A. Usefulness of contrast-enhanced intraoperative ultrasound in identifying disappearing liver metastases from colorectal carcinoma after chemotherapy. *Ann. Surg. Oncol.* 21, S390–S397 (2014).