



Case report

Pathological complete response of multiple liver metastases from colon cancer successfully treated with conversion surgery: A case report

Nao Kitasaki, Tomoyuki Abe^{*}, Masashi Inoue, Akihiro Kohata, Kazuhiro Toyota

Department of Surgery, National Hospital Organization Higashihiroshima Medical Center, Higashihiroshima, Hiroshima, Japan

ARTICLE INFO

Keywords:

Conversion surgery
Colon cancer
Liver metastasis
Neoadjuvant chemotherapy
Down-staging

ABSTRACT

Introduction and importance: Recently, the successful long-term survival of patients with unresectable distant metastases from colorectal cancer, who underwent conversion surgery after systemic chemotherapy, have been documented. Herein, we present a patient afflicted with ascending colon cancer and multiple unresectable liver metastases, who underwent conversion surgery, resulting in the complete disappearance of the pathological liver metastases.

Presentation of case: A 70-year-old woman visited our hospital with a chief complaint of weight loss. A diagnosis of ascending colon cancer (cT4aN2aM1a [H3]: TNM classification 8th edition) stage IVa with RAS/BRAF wild-type mutation was made (four liver metastases up to 60 mm in diameter were observed in both lobes). After 2 years and 3 months of systemic chemotherapy (capecitabine, oxaliplatin, and bevacizumab), the tumor marker levels had decreased to normal ranges and all liver metastases showed partial responses with remarkable shrinkage. After confirmation of a liver function and a preserved future liver remnant volume, the patient finally underwent hepatectomy, involving partial resection of S4 and subsegmentectomy of S8, along with a right hemicolectomy. Histopathologic examination revealed that all liver metastases had completely disappeared, while regional lymph node metastases had changed into scar tissue. However, the primary tumor failed to respond to chemotherapy, resulting in ypT3N0M0 ypStage IIA. The patient was discharged from the hospital on the 8th postoperative day without any postoperative complications. She is currently on the 6th month of follow-up without any recurring metastasis.

Clinical discussion: Curative surgery is recommended for resectable liver metastases of colorectal cancer (CRLM), be it synchronous or heterochronous. Up until now, the efficacy of perioperative chemotherapy for CRLM is limited. Chemotherapy has a double-edged aspect, where some cases have shown successful improvement in the treatment stage.

Conclusion: To obtain the maximum benefit from conversion surgery, it is critical to incorporate the appropriate surgical technique, at the correct stage, in order to avoid the progression to chemotherapy-associated steatohepatitis (CASH) in the patient.

1. Introduction

Colorectal cancer (CRC) holds the potential to metastasize to the liver and lungs. It is well-known that unresectable liver metastases are associated with a poor prognosis [1]. Surgical resection of colorectal

liver metastases (CRLM) has been reported to prolong survival, compared with systemic chemotherapy (CTx) and other therapies, such as radiofrequency ablation and radiation therapy [2,3]. Various trials have commenced to evaluate the efficacy of perioperative systemic CTx for resectable CRLM; however, evidence of its effect on the patient's

Abbreviations: CASH, chemotherapy-associated steatohepatitis; CAPOX therapy, capecitabine plus oxaliplatin; CT, computed tomography; CTx, chemotherapy; CRC, colorectal cancer; CRLM, colorectal liver metastases; DFS, disease free survival; DLM, disappearing liver metastases; EOB-MRI, ethoxybenzyl-magnetic resonance imaging; EORTC, European Organization for Research and Treatment of Cancer; FDG-PET, 18-fluoro-2-deoxy-D-glucose positron emission tomography; FOLFOX, 5-fluorouracil, oxaliplatin, and leucovorin; IOUS, intraoperative ultrasound; OS, overall survival; pCR, pathological complete response; PR, partial response; TSH, two-stage hepatectomy.

^{*} Corresponding author.

E-mail addresses: kitasaki-hma@umin.ac.jp (N. Kitasaki), t.abe.hiroshima@gmail.com (T. Abe), inoue.masashi.uv@mail.hosp.go.jp (M. Inoue), kohata.akihiro.bz@mail.hosp.go.jp (A. Kohata), toyota.kazuhiro.mg@mail.hosp.go.jp (K. Toyota).

<https://doi.org/10.1016/j.ijscr.2023.107935>

Received 17 January 2023; Accepted 16 February 2023

Available online 17 February 2023

2210-2612/© 2023 The Authors. Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

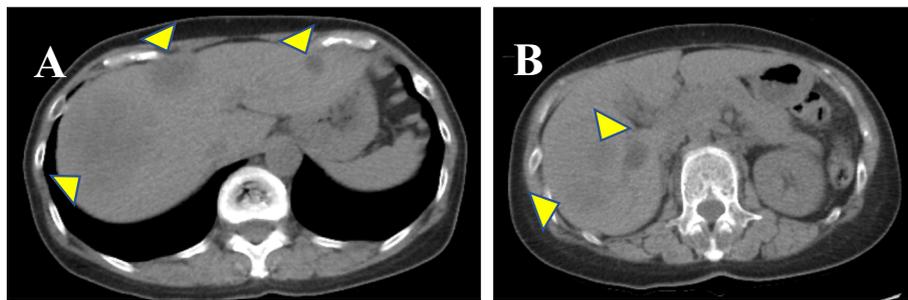


Fig. 1. Abdominal computed tomography (CT) findings.

A and B: CT shows multiple hepatic metastases up to 60 mm in diameter in both lobes of the liver.

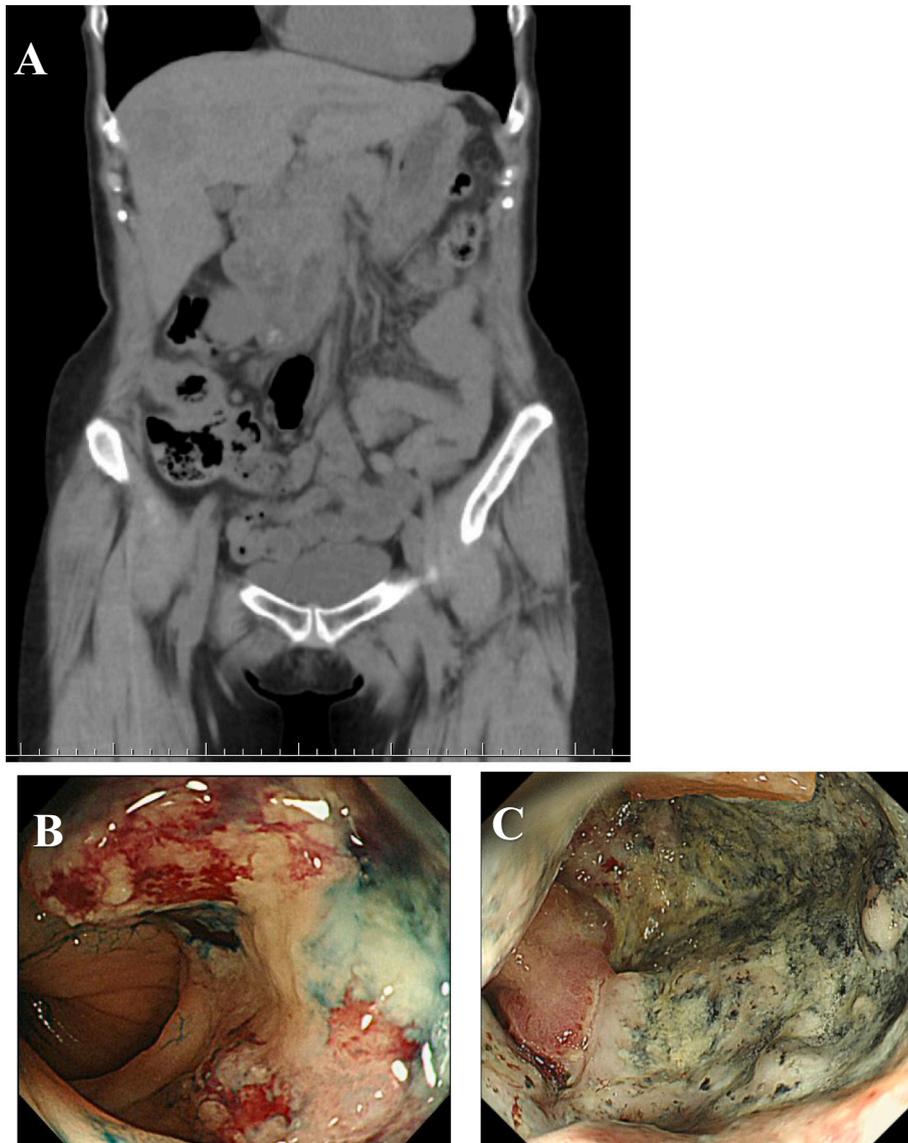


Fig. 2. A: The primary lesion is depicted as a wall thickening with a circumferential contrast effect in the ascending colon near the ileocecal valve. The nearby lymph nodes are also enlarged. B: Before CTx treatment, the ascending colon tumor is depicted as a fully circumferential type 2 tumor and is nearly occluding the colon. C: After CTx treatment, the tumor is noted to have shrunk, but ulceration occurred and the tumor itself persisted.

long-term survival remains limited [4,5]. Recent advancements and the widespread application of targeted therapy for CRLM have enabled unresectable states to become resectable, precipitating curative surgery. This process is defined as “conversion therapy,” which has been

associated with good prognoses under certain conditions [6].

Herein, we present a patient with ascending colon cancer and multiple unresectable liver metastases, who underwent conversion surgery after >2 years of CTx. The liver metastases had shown a pathological

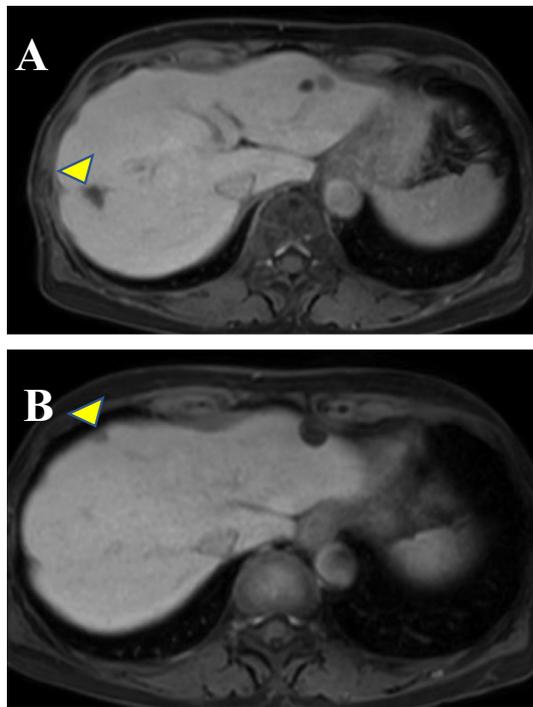


Fig. 3. Magnetic resonance imaging (MRI) findings.

A: A 12-mm large mass image with decreased gadoxetic acid (Primovist) uptake is seen in S8. B: A 9-mm-sized mass on the liver surface can be observed in S4 with decreased gadoxetic acid (Primovist) uptake.

complete response (pCR), requiring only a microscopically margin-negative (R0) resection. Along with this case report, a literature review on CRLM is also presented. This case was reported in accordance with the SCARE 2020 Guideline [7].

2. Presentation of case

A 70-year-old woman presented to our hospital with a primary complaint of weight loss. Blood tests demonstrated elevated tumor markers, particularly, carcinoembryonic antigens (17.7 ng/mL) and carbohydrate 19-9 antigens (1704.9 U/mL). Transabdominal ultrasonography indicated multiple tumors in both lobes of the liver with hypochoic areas. Computed tomography (CT) demonstrated a 30 mm irregular wall thickening at the ascending colon associated with four enlarged regional lymph nodes. Concomitantly, multiple tumors with a maximum diameter of 60 mm were observed in S4, S5/S8, and S6 of the liver. All liver metastases had internal low-density areas and irregular margins (Fig. 1). A colonoscopy examination revealed an ulcerating tumor located near the ileocecal valve. Biopsy identified the tumor as tubular adenocarcinoma. Neither a Kirsten rat sarcoma viral oncogene homolog (K-RAS) mutation nor a v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutation was detected. The patient was subsequently diagnosed with ascending colon cancer stage IVA (cT4aN2aM1a [H3]; TNM classification 8th edition) (Fig. 2). Capecitabine and oxaliplatin (CAPOX) with bevacizumab were administered for 2 years and 3 months. A liver function test demonstrated Child-Pugh grade A and liver-damage grade A. A post-chemotherapy revealed that the primary colon tumor remained unchanged and was still accompanied by four enlarged region lymph node swellings. Ethoxybenzyl-magnetic resonance imaging (EOB-MRI) showed a 13 mm and a 9 mm irregular marginal mass in S8 and S4, respectively. Both tumors had decreased EOB uptake in the hepatobiliary phase (Fig. 3).

Based on these findings, the patient underwent conversion surgery (partial resection of S4 and subsegmentectomy of S8), along with a right

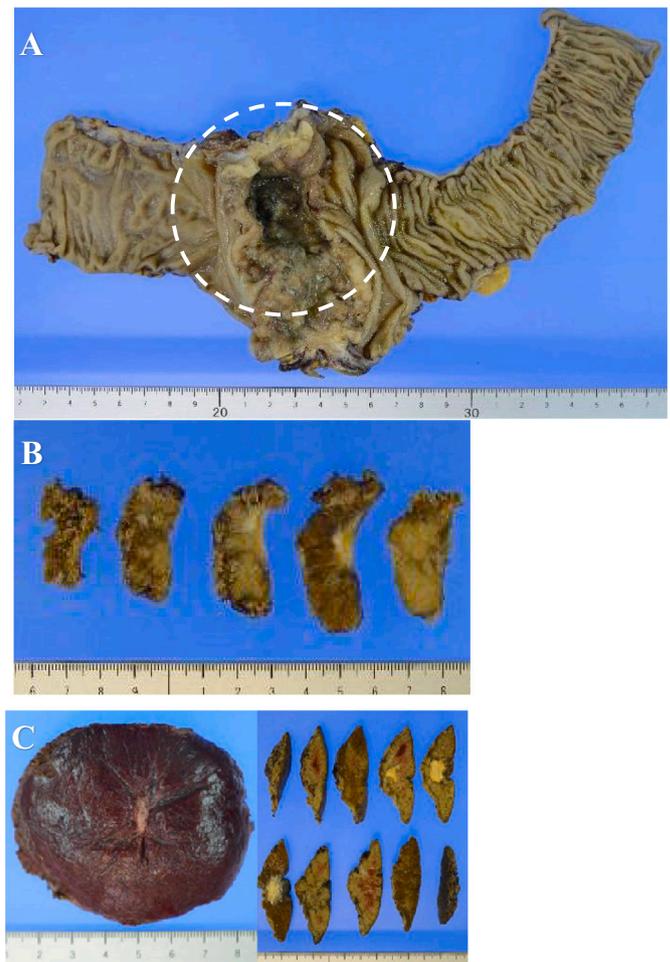


Fig. 4. A: The primary lesion is perceived as a type 2 tumor in the ascending colon, circumscribing the entire section of the colon. No obvious extra-serosal invasion is noted. B: The hepatic S4 lesion forms a yellowish-white mass image, and the resection margin is secured by at least 1 cm. C: The hepatic S8 lesion forms a yellowish-white mass image without tumor exposure at the resection margins. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

hemicolectomy. Operation time was 252 min and blood loss was 120 mL. The patient was discharged from the hospital on the 8th post-operative day without any complications. Macroscopically, the ascending colon contained a circumferential type 2 tumor without extra-serosal invasion. The S8 specimen weighed 38 g and presented as a continuous yellowish nodule (measuring 18 × 16 × 9 mm) on the liver capsule. The S4 specimen weighed 4 g (measuring 14 × 11 × 3 mm) and showed a similar morphology to the S8 tumor. Both specimens' surgical margins were secured. (Fig. 4). Pathological examination confirmed that the resected liver metastases were all multinodular necrotic and fibrotic lesions, indicating that the tumor cells had completely disappeared. None of twenty-two lymph nodes had a residual viable tumor. However, the primary ascending colon cancer was composed mostly of viable tumor cells with some irregular fibrosis, and a diagnosis of Grade 1a for treatment response was reached (Fig. 5). The final pathological staging was ypT3N0M0 ypStage IIA. The patient is currently at 6 months post-discharge without any signs of recurrence.

3. Discussion

Radical hepatectomy is the most effective treatment for patients with CRLM [8]. With the advancement of molecular-targeted mediators and other systemic chemotherapy agents for CRC, the presented case

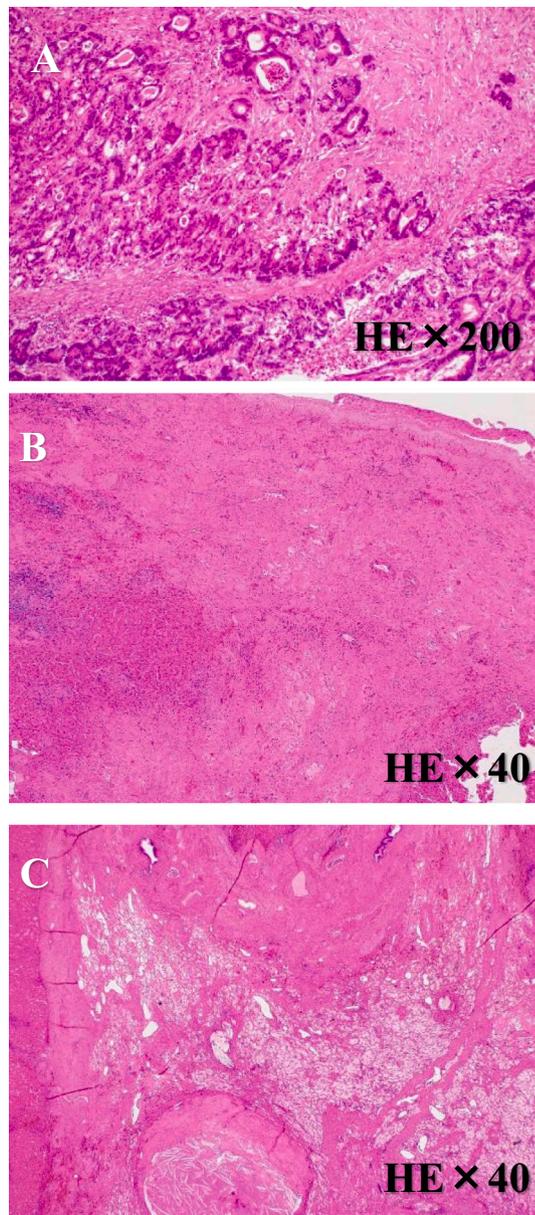


Fig. 5. A: Tumors of the ascending colon are seen to be >80 % viable, with invasion extending to the subserosa. B: Pathologically, all tumor cells are necrotic, without viable cells noted in the tumor. C: Hepatic plate atrophy and sinusoidal dilatation are seen around the central veins and the interlobular areas.

successfully underwent conversion therapy for CRLM [8]. In our case, pCR was achieved in the liver metastases and lymph nodes. In contrast, the pathological primary colon cancer failed to show any response by CTx. Regardless of long-term treatment via CTx, preserved liver function and remnant liver volume by tumor shrinkage allowed conversion therapy to be performed.

Well-known prognostic factors for CRLM, including multiple liver metastases (≥ 5 tumors), maximal metastasized tumor diameter (≥ 5 cm), extrahepatic metastases, and peritoneal dissemination, are reported as independent poor prognostic factors for overall survival (OS) and disease-free survival (DFS) [9–13]. Due to the large-sized and multiple synchronous CRLM, CTx was introduced for this patient as initial treatment. Exacerbations during the preoperative CTx were not detected, even after several courses of CTx, which is recognized as a poor prognostic factor for CRLM [13]. Recently, various reports have

demonstrated that two-stage hepatectomy (TSH) can be safely performed with a low incidence of morbidity and mortality [14]. Thus, it is imperative to surveil the patient closely in order to avoid missing the optimal timing for conversion surgery and progression to chemotherapy-associated steatohepatitis (CASH).

Disappearing liver metastases (DLM) is another obstacle to contend with at the time of conversion therapy. Regardless of high accuracy preoperative diagnosis via EOB-MRI and intraoperative ultrasound (IOUS), patients with undetectable liver metastases and DLM are still encountered [15,16]. Theoretically, complete resection for all detectable tumors and DLM is the recommended therapeutic strategy, in terms of providing maximum benefits to the patient. However, in clinical situations, intraoperative detection of small tumors is difficult as performing DLM resection is very challenging. Complete resection of DLM contributes to a lower incidence of intrahepatic recurrence [17]. Otherwise, as Barimani et al. [17] demonstrated, there is no significant difference in OS whether or not complete resection is performed for DLM. In cases requiring preoperative follow-up for CRLM, it is important to perform systemic evaluation by EOB-MRI in patients on CTx to avoid missing the ideal timing for hepatic resection.

In spite of its benefits, neoadjuvant chemotherapy has its disadvantages, which include increased postoperative complications due to injury to normal tissues and difficulty in resecting lesions that exhibit pCR on imaging. Typically, in multidrug therapy, increased frequencies of fatty liver and steatohepatitis (yellow liver) are associated with camptothecin (CPT)-11, while an increased risk of sinusoidal dilation (blue liver) is linked to oxaliplatin [18]. Moderate to severe fatty liver increases the risk of postoperative complications [18]. Furthermore, 5-fluorouracil, oxaliplatin, and leucovorin (FOLFOX) therapy increases the risk of postoperative complications and sinusoidal dilation with six or more CTx cycles [19,20]. Conversely, the use of oxaliplatin for <3 to 4 months has not been reported to increase the risk of sinusoidal dilation or postoperative complications. The median time to response to FOLFOX therapy has been reported to be four to six cycles [19]. Completion of the final cycles are considered to be a convenient time to initiate hepatic resection. Although our patient had received >20 courses of CTx, preoperative blood tests and ultrasound imaging revealed no obvious abnormalities in liver function or morphology.

4. Conclusion

We encountered a case of liver metastases from colorectal cancer in which successful conversion surgery was performed after systemic chemotherapy. In patients undergoing conversion surgery, it is crucial to monitor for the onset of CASH and the effect of tumor reduction, in order to avoid missing the appropriate timing for surgery.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Sources of funding

No.

Ethical approval

This paper has been granted ethical approval.

Author contribution

Nao Kitasaki is the first author, and Tomoyuki Abe is a corresponding author.

Nao Kitasaki, Tomoyuki Abe and Masashi Inoue contribute the study concept and design.

Nao Kitasaki, Tomoyuki Abe, Masashi Inoue and Akihiro Kohata contribute the data collection, data analysis and interpretation.

Nao Kitasaki, Tomoyuki Abe and Kazuhiro Toyota contribute the writing the paper.

Guarantor

Tomoyuki Abe

Research registration number

Not applicable.

Declaration of competing interest

No.

References

- [1] S. Manfredi, C. Lepage, C. Hatem, O. Coatmeur, J. Faivre, A.M. Bouvier, Epidemiology and management of liver metastases from colorectal cancer, *Ann. Surg.* 244 (2) (2006) 254–259.
- [2] S. Kopetz, G.J. Chang, M.J. Overman, C. Eng, D.J. Sargent, D.W. Larson, et al., Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy, *J. Clin. Oncol.* 27 (22) (2009) 3677–3683.
- [3] G.P. Kanas, A. Taylor, J.N. Primrose, W.J. Langeberg, M.A. Kelsh, F.S. Mowat, et al., Survival after liver resection in metastatic colorectal cancer: review and metaanalysis of prognostic factors, *Clin. Epidemiol.* 4 (2012) 283–301.
- [4] Y. Takakura, K. Shinozaki, S. Ikeda, H. Egi, Y. Hirata, M. Shimomura, et al., Pre-versus postoperative CAPOX plus bevacizumab (CAPOX-Bev) for resectable liver metastases from colorectal cancer (CLM): a randomized phase II/III trial (HiSCO-01), *J. Clin. Oncol.* 38 (15) (2020).
- [5] K. Ono, T. Abe, A. Oshita, Y. Sumi, T. Yano, H. Okuda, et al., Efficacy of upfront hepatectomy without neoadjuvant chemotherapy for resectable colorectal liver metastasis, *World J. Surg. Oncol.* 97 (2021).
- [6] G. Masi, E. Vasile, F. Loupakis, S. Cupini, L. Fornaro, G. Baldi, et al., Randomized trial of two induction chemotherapy regimens in metastatic colorectal cancer: an updated analysis, *J. Natl. Cancer Inst.* 103 (1) (2011) 21–30.
- [7] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, for the SCARE Group, The SCARE 2020 guideline: updating consensus Surgical CAse REport (SCARE) guidelines, *Int. J. Surg.* 84 (2020) 226–230.
- [8] R.B. Adams, T.A. Aloia, E. Loyer, T.M. Pawlik, B. Taouli, J.N. Vauthey, et al., Selection for hepatic resection of colorectal liver metastases: expert consensus statement, *HPB* 15 (2) (2013) 91–103 (Oxford).
- [9] Z. Dexiang, R. Li, W. Ye, W. Haifu, Z. Yunshi, Y. Qinghai, et al., Outcome of patients with colorectal liver metastasis: analysis of 1,613 consecutive cases, *Ann. Surg. Oncol.* 19 (2012) 2860–2868.
- [10] T.M. Pawlik, C.R. Scoggins, D. Zorzi, E.K. Abdalla, A. Andres, C. Eng, et al., Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases, *Ann. Surg.* 241 (2005) 715–722.
- [11] J. Hallet, A.S. Cunha, R. Adam, D. Goere, P. Bachellier, D. Azoulay, et al., Factors influencing recurrence following initial hepatectomy for colorectal liver metastases, *Br. J. Surg.* 103 (2016) 1366–1376.
- [12] A. Saiura, J. Yamamoto, K. Hasegawa, R. Koga, Y. Sakamoto, S. Hata, et al., Liver resection for multiple colorectal liver metastases with surgery up-front approach: bi-institutional analysis of 736 consecutive cases, *World J. Surg.* 36 (2012) 2171–2178.
- [13] T. Beppu, Y. Sakamoto, K. Hasegawa, G. Honda, K. Tanaka, Y. Kotera, et al., A nomogram predicting disease-free survival in patients with colorectal liver metastases treated with hepatic resection: multicenter data collection as a Project Study for Hepatic Surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery, *J. Hepatobiliary Pancreat. Sci.* 19 (2012) 72–84.
- [14] René Adam, Alexis Laurent, Daniel Azoulay, Denis Castaing, Henri Bismuth, Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors, *Ann. Surg.* 232 (6) (2000 Dec) 777–785.
- [15] M.C. Niekel, S. Bipat, J. Stoker, Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment, *Radiology* 257 (2010) 674–684.
- [16] M. Scharitzer, A. Ba-Salamah, H. Ringl, C. Kolblinger, T. Grunberger, M. Weber, et al., Preoperative evaluation of colorectal liver metastases: comparison between gadoteric acid-enhanced 3.0-T MRI and contrast-enhanced MDCT with histopathological correlation, *Eur. Radiol.* 23 (8) (2013) 2187–2196.
- [17] D. Barimani, J.H. Kauppila, C. Stuessen, E. Sparrelid, Imaging in disappearing colorectal liver metastases and their accuracy: a systematic review, *World J. Surg. Oncol.* 18 (264) (2020).
- [18] D.A. Kooby, Y. Fong, A. Suriawinata, M. Gonen, P.J. Allen, D.S. Klimstra, et al., Impact of steatosis on perioperative outcome following hepatic resection, *J. Gastrointest. Surg.* 7 (8) (2003) 1034–1044.
- [19] B. Nordlinger, H. Sorbye, B. Glimelius, G.J. Poston, P.M. Schlag, P. Rugier, et al., Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial, *Lancet* 371 (9617) (2008) 1007–1016.
- [20] H. Nakano, E. Oussoultzoglou, E. Rosso, S. Casnedi, M.P. Chenard-Neu, P. Dufour, et al., Sinusoidal injury increases morbidity after major hepatectomy in patients with colorectal liver metastases receiving preoperative chemotherapy, *Ann. Surg.* 247 (1) (2008) 118–124.