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SSAT SUMMARY

Innovation and Future Perspectives in the Treatment of Colorectal Liver Metastases

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Abstract

Technological advances and investigation into tumor biology have enhanced treatments of patients with colorectal liver metastases (CLM). This article briefly summarizes paradigm shifts in treatments of this disease in the following 4 sections. (1) Small metastases: The treatment of multiple and small CLM has evolved from anatomic resection to parenchyma-sparing hepatectomy. Survival after parenchyma-sparing hepatectomy was similar to or better than anatomic resection. The use of preoperative chemotherapy may cause tumor disappearance. However, the use of fiducial markers may aid in intraoperative localization. Post-resection completion ablation is a new useful treatment concept. It was defined as percutaneous ablation under cross-sectional imaging guidance to eradicate CLM which were intentionally unresected during latest surgery. (2) Bilateral (bilobar) metastases: Two-stage hepatectomy (TSH) is a well-established approach for treating multiple bilateral CLM. The use of hybrid operating room accelerates this sequence because it allows first-stage hepatectomy, portal vein embolization, and computed tomography in one hospitalization. This accelerated TSH sequence enables the second-stage hepatectomy within 4 weeks compared to 8 weeks using conventional TSH sequence. (3) Synchronous lung metastases: For patients with synchronous liver and lung metastases, simultaneous surgical approach is feasible. Specifically, a transdiaphragmatic approach enables simultaneous resection of liver and lung metastases via one abdominal incision. (4) Multiple mutation: Somatic gene mutation testing is increasingly used to evaluate tumor biology. Mutations in TP53, RAS, and SMAD4 affect prognosis through three different signaling pathways of colorectal carcinogenesis. This information can be used to change clinical decision-making regarding surveillance intensity and treatments for liver recurrence.

Keywords Colorectal liver metastasis · Liver resection · Postoperative completion ablation · Synchronous lung metastases · Somatic gene mutation

Introduction

In recent years, a combination of technological advances and more widespread investigation into tumor biology have enhanced the treatment of patients with colorectal liver metastases (CLM). The following section provides examples of the paradigm shifts in treatment of this disease process based on these developments.

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Small Metastases

First, the treatment of multiple and small CLM has evolved from predominately anatomic resections such as major hepatectomy or extended hemi-hepatectomy to parenchymal-sparing approaches for both unilateral and bilateral lesions. Our group previously reported that parenchymal-sparing hepatectomy (PSH) for solitary lesions < 3 cm in diameter does not increase recurrence and has been associated with better survival, as it improves salvage ability in cases of liver recurrence.[1] A meta-analysis regarding anatomical vs. non-anatomical resection showed that surgical margins, overall survival, and disease-free survival did not differ significantly between two groups.[2] The EORTC trial showed decreased risk of progression-free survival in patients undergoing perioperative chemotherapy compared with patients undergoing upfront surgery[3] although there was no difference on overall

survival.[4] Preoperative chemotherapy is commonly used in patients who are not eligible for upfront surgery. For the treatment of small metastases, the use of preoperative chemotherapy may increase the risk of disappearance of the metastases. We recommend the use of fiducial markers, which can be placed in interventional radiology prior to chemotherapy.[5] The indications for the fiducial placements include lesions < 2 cm in greatest diameter and > 1 cm deep in the liver parenchyma.[5] For such metastases, fiducial marker placement may aid in intraoperative localization during PSH.

The dissemination of PSH has renewed interest in the use of ablation during resection of CLM. Historically, the use of radiofrequency ablation for CLM was associated with higher risk of local recurrence.[6] Recent studies have shown an association between local recurrence and the ablation margin as determined by cross-sectional axial and coronal imaging.[7] Optimal identification and definition of the ablation margin can be determined using three-dimensional evaluation via computed tomography, resulting in lower rates of local recurrence following ablation. In a recent study using this technique, the local tumor progression-free survival rate at 3 years was significantly higher when an ablation margin > 1 cm was achieved (79%) compared with an ablation margin ≤ 1 cm (56%, $P = 0.012$).[8] The local tumor progression-free survival rate at 3 years is also dependent on tumor size and was higher for lesions < 2 cm in greatest diameter than for lesions ≥ 2 cm (64% vs. 40%, $P = 0.020$).[9] Most recently, we have reported the usefulness of post-resection completion ablation. This new sequential treatment concept was defined as the use of image-guided percutaneous ablation within 180 days from liver resection to eradicate known CLM which were intentionally unresected during latest surgery.[10] *RAS* mutation status has been shown to have an impact on outcomes regardless of the chosen local therapy.[11] Studies reported association of surgical margin and ablation margin with *RAS* mutation status.[8, 9, 12–14] For ablation, *RAS*-mutant patients have earlier local tumor progression, irrespective of tumor size.[9] An ongoing randomized controlled trial to compare thermal ablation and liver resection for CLM (the COLLISION trial) will add clinical evidences for this topic.[15] A study by Brudvik et al. found that *RAS*-mutant patients were more likely to have positive and narrower margins after liver resection.[14] In this study, the rate of margin positivity was higher in patients with *RAS* mutation than in patients with wild-type *RAS* (11.4% vs. 5.4%, $P = 0.007$). For patients who later presented with liver-first recurrence, the width of the resection margin was significantly smaller in patients with *RAS* mutation than in patients with wild-type *RAS* (4 mm vs. 7 mm, $P = 0.031$). Further studies will be needed to determine whether higher positive margin rates are associated with higher rates of local recurrence in patients with *RAS* mutation.

Bilateral (Bilobar) Metastases

The two-stage hepatectomy (TSH) technique has been used as the preferred approach in patients with multiple bilateral CLM in whom PSH cannot be performed.[16] During first-stage hepatectomy, partial hepatectomies (most commonly of the left liver) are performed to clear the future liver remnant. This is traditionally followed by portal vein embolization in interventional radiology 1–3 weeks after the first-stage hepatectomy. After approximately 3–4 weeks, the patient undergoes a second-stage major hepatectomy. The use of a hybrid operating room equipped for both interventional radiologists and surgeons allows the first-stage hepatectomy and portal vein embolization to be performed on the operating room table under the same anesthesia. The two imaging components, a robotic C-arm and multi-slice computed tomography, are available on rails. With this type of equipment, patients are able to sequentially undergo a first-stage hepatectomy, a right portal vein embolization (plus segment 4 portal vein), and a high-resolution contrast-enhanced computed tomography of the liver immediately after the two procedures (three encounters in one). In this accelerated TSH sequence, the second-stage major hepatectomy can be performed within 4 weeks, thus saving 3–4 weeks compared with the typical 7–8 weeks waiting time from first- to second-stage hepatectomy.[17] It should be noted that this approach needs a hybrid operating room and cannot be utilized in all centers. An alternative approach may be as follows: a first-stage hepatectomy followed by a portal vein embolization during the same hospitalization in radiology rooms. Similar to ablation, the outcome of TSH is highly associated with *RAS* mutation status, with a median survival of 102 months for *RAS* wild-type patients vs. 34 months for *RAS*-mutant patients. Approximately 30% of patients undergoing TSH are candidates for re-resection of hepatic and/or extrahepatic recurrences. Likewise, overall survival in patients undergoing re-resection for recurrence after two-stage hepatectomy is better in *RAS* wild-type patients compared with *RAS*-mutant patients ($P = 0.019$).[18]

Synchronous Lung Metastases

Increasingly, colorectal cancer patients present with advanced disease including synchronous liver and lung metastases. For these patients, we recommend the consideration of a simultaneous approach if possible, using one abdominal incision to first resect the liver metastases, followed by a transdiaphragmatic approach for resection of the lung metastases. This approach is best suited for patients with peripheral lung lesions, and in many cases avoids a thoracic incision while still allowing for manual palpation and inspection of the lung. When compared with similar patients who underwent the conventional approach to synchronous liver and lung metastases (liver resection followed by

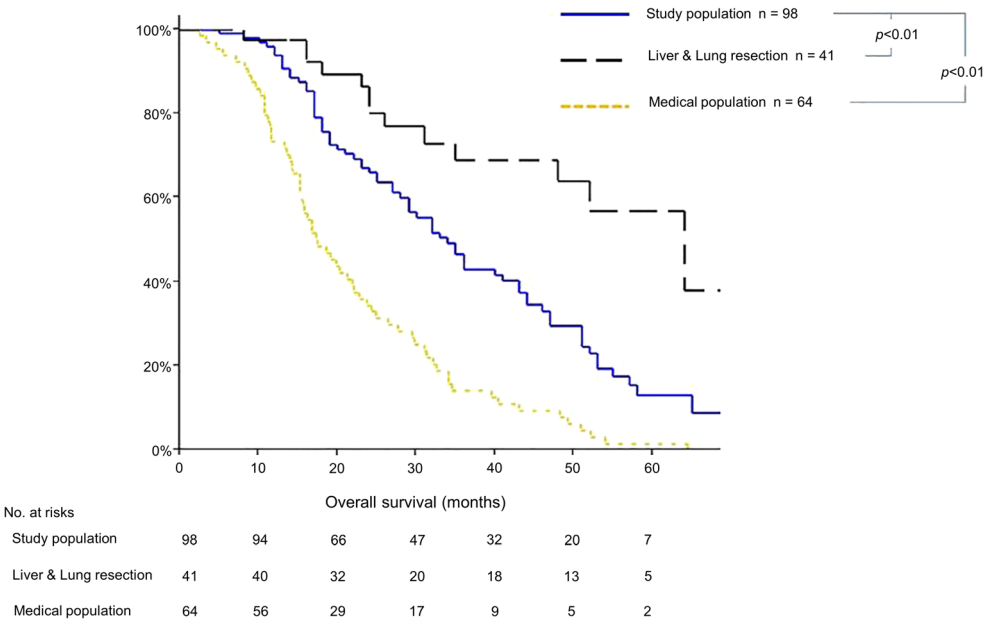

Fig. 1 Comparison of overall survival among patients with synchronous colorectal liver and lung metastases. Adapted from Mise Y, Kopetz S, Mehran RJ, Aloia TA, Conrad C, Brudvik KW, Taggart MW, Vauthey JN. Ann Surg Oncol. 2015;22:1585–92. Used with permission

staged wedge resection via video-assisted or open thoracic surgery followed by liver resection), patients who underwent the combined approach had shorter overall length of hospital stay and reduced operative blood loss with similar rates of lung-related morbidity and lung resection surgical margin positivity.[19]

Another commonly encountered scenario involves patients presenting with resectable liver metastases and innumerable, thus unresectable, lung metastases. In such patients, the natural history of metastatic colorectal cancer is determined by the progression of liver metastases rather than lung metastases. These patients rarely develop shortness of breath or other pulmonary symptoms. Further, lung metastases can be controlled with alternate chemotherapy regimens (i.e. combined fluorouracil + bevacizumab). A recent study about patients with synchronous liver and lung metastases compared resection of liver metastases only (without resection of lung metastases) vs. resection of liver and lung metastases vs. palliative chemotherapy. The patients undergoing resection of liver metastases only had an intermediate survival between patients undergoing resection of both liver and lung metastases and patients undergoing palliative chemotherapy (Fig. 1).[20] The intermediate survival in patients undergoing resection of CLM without resection of lung metastases may be attributable to patient selection or resection of CLM. In patients undergoing CLM resection only, wild-type *RAS* is associated with improved survival.[20] A randomized controlled study

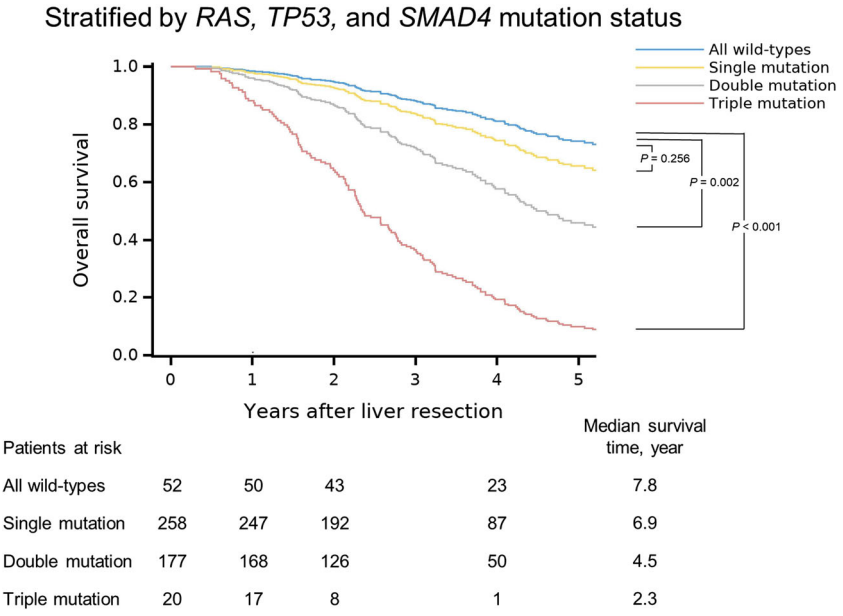

Fig. 2 Overall survival by *RAS*, *TP53*, and *SMAD4* mutation status. Overall survival curves after adjustment for *BRAF* mutation status, largest liver metastasis diameter, and surgical margin status. Based on Kawaguchi Y, Kopetz S, Newhook TE, De Bellis M, Chun YS, Tzeng CD, Aloia TA, Vauthey JN. Clin Cancer Res. 2019 Jun 20. pii: clincanres.0863.2019. https://doi.org/10.1158/1078-0432.CCR-19-0863. [Epub ahead of print]. Used with permission

(LUNA, liver resection with unresectable pulmonary nodules for colorectal adenocarcinoma; NCT02738606) is ongoing to objectively determine the benefit of liver resection only.[21]

Multiple Mutations

Somatic gene mutation testing is being increasingly used to evaluate the biology of colorectal cancer in patients undergoing resection of CLM.[11] The most common somatic mutation in metastatic colorectal cancer is *TP53*.[22] The second most common mutation is *RAS* occurring in 45–50% of the patients. As such, *TP*53 and *RAS* co-mutations are common in patients undergoing CLM resection. Recent data has shown that *TP*53 and *RAS* co-mutations are associated with worse OS and RFS compared with patients with a single or no mutation.[22, 23] Additionally, the tumor suppressor gene *SMAD4*, mutated in 15–20% of CLM patients, is independently associated with worse prognosis in patients undergoing CLM resection.[24, 25] Taken together, mutations in *TP53*, *RAS*, and *SMAD4* affect prognosis through three different signaling pathways of colorectal carcinogenesis (the P53 pathway, the mitogen-activated protein kinase pathway, and transforming growth factor-β pathway).[24] Our recent study indicated that a "triple mutation" in *TP53*, *RAS*, and *SMAD4* was associated with worse overall and recurrence-free survival in CLM patients compared with double mutations in any two of the three genes (Fig. 2).[24] This finding can be used to tailor the surveillance frequency after CLM resection and change decisions of treatments for liver recurrence. Multiple mutation status may be useful for risk stratification for future clinical trials.

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