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Organization:

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On behalf of the Society of Interventional Oncology, we respectfully request the NCCN Colon and Rectal Cancer Guideline panel review the enclosed data for inclusion in the management of metastatic colon and rectal cancers.

Specific Change 1: In “Principles of Surgery, Criteria for Resectability of Metastases and Locoregional Therapies within Surgery” add yttrium-90 radioembolization radiation lobectomy to portal vein embolization and staged liver resection as options to induce future liver remnant hypertrophy when hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume.

Rationale: Unilobar Y-90 radioembolization to the tumor-bearing hepatic lobe results in hypertrophy of the contralateral lobe (future liver remnant) in the range of 26 to 47% between 44 days and 9 months. This compares favorably to portal vein embolization, but provides the additional advantages of treating the hepatic disease and obtaining tumor control in the interval to hypertrophy, as well as possibly facilitating R0 surgical resection by causing retraction of the hepatic tumor(s) away from critical structures.

References:

Teo JY, Allen JC Jr, Ng DC, et al. A systematic review of contralateral liver lobe hypertrophy after unilobar selective internal radiation therapy with Y90. HPB (Oxford). 2016;18(1):7-12
Vouche M, Lewandowski RJ, Atassi R, et al. Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. J Hepatol. 2013;59(5):1029-1036
Melstrom LG, Eng OS, Raoof M, et al. Is hepatectomy safe following Yttrium-90 therapy? A multi-institutional international experience. HPB (Oxford). 2019;21(11):1520-1526

Specific Change 2: mFOLFOX + bevacizumab + DEBIRI may be considered as first line therapy for patients with liver-limited metastases.

Rationale: In a randomized trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastases, there was significantly more downsizing to resection in the FOLFOX-DEBIRI arm versus the FOLFOX/bevacizumab arm and there was significantly improved progression-free survival in the treatment arm.

Reference:

Martin RC 2nd, Scoggins CR, Schreeder M, et al. Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis. Cancer. 2015;121(20):3649-3658

Specific Change 3: Consider the addition of a footnote or other statement to appear within the algorithms of COL-D and REC-F addressing the consideration of locoregional therapies for highly selected patients who have developed chemotherapy-resistant/-refractory disease with predominant hepatic metastases.

Rationale: The algorithms of COL-D and REC-F make it appear that regorafenib or trifluridine + tipiracil are the only therapeutic options for patients who have developed chemotherapy-resistant/-refractory metastases, with the consideration of locoregional therapies figuring only as a secondary discussion, even though according to the current guidelines, “consensus amongst panel members is that arterially directed catheter therapy and, in particular, yttrium-90 microsphere selective internal radiation is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.”

Specific Change 4: For COL-5 and COL-10, consider modifying comment “aa” to indicate while resection is preferred over locally ablative procedures, for unresectable patients, the preferred therapy is image-guided ablation, assuming it is technically feasible.

Rationale: Thermal ablation (RFA or microwave) provides the best local control rates for small (< 3 cm) colorectal liver metastasis when compared to other non-surgical local therapies. Image-guided ablation should be prioritized as the first choice of loco-regional therapy for unresectable patients.

References:

Solbiati L, Ahmed M, Cova L, Ierace T, Brioschi M, Goldberg SN. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. *Radiology*. 2012;265(3):958-968.

Odisio BC, Yamashita S, Huang SY, et al. Impact of Prior Hepatectomy History on Local Tumor Progression after Percutaneous Ablation of Colorectal Liver Metastases. *J Vasc Interv Radiol*. 2018;29(3):395-403 e391.

Shady W, Petre EN, Gonen M, et al. Percutaneous Radiofrequency Ablation of Colorectal Cancer Liver Metastases: Factors Affecting Outcomes--A 10-year Experience at a Single Center. *Radiology*. 2016;278(2):601-611.

Calandri M, Yamashita S, Gazzera C, et al. Ablation of colorectal liver metastasis: Interaction of ablation margins and RAS mutation profiling on local tumour progression-free survival. *Eur Radiol*. 2018;28(7):2727-2734.

Specific Change 5: In COL C2, consider adding the following:

“Combination of systemic therapy with image-guided thermal ablation leads to improved overall survival for patients who are not resectable,” and consider modifying the comment about conformal external beam radiation to:

“Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of clinical trial and should not be used indiscriminately in patients whose tumors are potentially surgically resectable or ablatable.”

Rationale: In a randomized phase II trial, patients who received radiofrequency ablation in addition to systemic therapy showed statistically significant improvement in overall survival compared to patients treated with chemotherapy alone. Based on current evidence, image-guided thermal ablation should be preferred over conformal external beam radiation therapy.

Reference:

Ruers T, Van Coevorden F, Punt CJ, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. *J Natl Cancer Inst*. 2017;109(9).

Specific Change 6: In “Principles of Imaging,” consider updating the last bullet point under “Monitoring”, which currently states “PET/CT is not indicated. For monitoring of patients having undergone locoregional therapies, including thermal ablation or radioembolization, PET/CT may be beneficial.

Rationale: For patients who had received thermal ablation, follow up PET/CT was shown to be equivalent to contrast-enhanced CT in 67% of patients yet superior in 27% of patients. PET/CT was superior in demonstrating extrahepatic disease in 50%, local hepatic recurrence at the site of ablation in 50%, new hepatic disease in 27%, and excluding of extrahepatic disease in 0.5%.

For patients who have received Y-90 radioembolization, PET/CT can provide response assessment but has also been shown to predict overall survival.

References:

Sahin DA, Agcaoglu O, Chretien C, et al., The utility of PET/CT in the management of patients with colorectal liver metastases undergoing laparoscopic radiofrequency thermal ablation. *Ann Surg Oncol*. 2012;19(3):850-855

Shady W, Kishore S, Gavane S, et al. Metabolic tumor volume and total lesion glycolysis on FDG-PET/CT can predict overall survival after (90)Y radioembolization of colorectal liver metastases: A comparison with SUVmax, SUVpeak, and RECIST 1.0. *Eur J Radiol*. 2016;85(6):1224-1231

Edalat F, Camacho JC, Kokabi N, Kendi AT, Galt JR, Kim HS. Standardized Added Metabolic Activity Predicts Survival After Intra-arterial Resin-Based 90Y Radioembolization Therapy in Unresectable Chemorefractory Metastatic Colorectal Cancer to the Liver. *Clin Nucl Med*. 2016;41(2):e76-e81

Sabet A, Meyer C, Aouf A, et al. Early post-treatment FDG PET predicts survival after 90Y microsphere radioembolization in liver-dominant metastatic colorectal cancer. *Eur J Nucl Med Mol Imaging*. 2015;42(3):370-376

We would like to thank the NCCN panel members for their time and effort in reviewing this submission.