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NCCN Guidelines Panel: Hepatobiliary Cancer

We thank the panel for adopting the 2019 SIO hepatobiliary task force recommendations.

On behalf of the Society of Interventional Oncology, we respectfully request the NCCN Guidelines Panel for Hepatobiliary Cancer review the enclosed recommendations:

Specific Change 1: Reorganize panel HCC E (1) (Principles of Locoregional Therapy) IIB (Arterially directed therapies) such that radioembolization receives its own paragraph with dosimetry recommendations, similarly provided for external beam radiation therapy on panel E(2).

Rationale: Radioembolization is a form of radiation therapy and warrants dosimetry recommendations present in all other forms of radiotherapy within the NCCN guidelines.

Specific Change 2: Per the recent DOSISPHERE (NCT02582034, https://ascopubs.org/doi/10.1200/JCO.2017.35.4_suppl.482) randomized phase II trial of standard vs. personalized dosimetry in advanced HCC (accepted for publication in *Lancet Gastroenterology*), we recommend treatment with a tumor threshold dose if >205 Gy if feasible. In this trial, the median overall survival was 26.7m (CI 95%:13.5-NR) versus 6.0m (CI 95%:3.8-14.9) for patients who received a tumor dose \geq 205 Gy vs. 120+/-20 Gy respectively, p=0.0106, HR=0.336 (95%CI:0.154-0.735), p=0.0063. The mean tumor size in this study was 10.5 cm and portal vein invasion was present in 70% of patients.

Rationale: Randomized evidence in support of a survival benefit when utilizing a tumor dose threshold that has been previously validated retrospectively with multiple studies

References:

DOI: 10.1200/JCO.2017.35.4_suppl.482 *Journal of Clinical Oncology* 35, no. 4_suppl (February 01, 2017) 482-482

Garin E, Rolland Y, Pracht M, et al. High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with ⁹⁰Y-loaded glass microsphere radioembolization. *Liver Int.* 2017;37(1):101-110. doi:10.1111/liv.13220

Kappadath SC, Mikell J, Balagopal A, Baladandayuthapani V, Kaseb A, Mahvash A. Hepatocellular Carcinoma Tumor Dose Response After ⁹⁰Y-radioembolization With Glass Microspheres Using ⁹⁰Y-SPECT/CT-Based Voxel Dosimetry. *Int J Radiat Oncol Biol Phys.* 2018 Oct 1;102(2):451-461. doi: 10.1016/j.ijrobp.2018.05.062. Epub 2018 Jun 2. PMID: 30191875.

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Chan KT, Alessio AM, Johnson GE, Vaidya S, Kwan SW, Monsky W, Wilson AE, Lewis DH, Padia SA. Prospective Trial Using Internal Pair-Production Positron Emission Tomography to Establish the Yttrium-90 Radioembolization Dose Required for Response of Hepatocellular Carcinoma. *Int J Radiat Oncol Biol Phys*. 2018 Jun 1;101(2):358-365. doi: 10.1016/j.ijrobp.2018.01.116. Epub 2018 Feb 9. PMID: 29559288.

Specific Change 3: Per the recently released multicenter retrospective Legacy Study results, presented at CIRSE 2020 (<https://programme.2020summit.cirse.org/login?redirect=%2Fcirse2020%2Fcirs%2Fyttrium-90-glass-microspheres-in-the-treatment-of-hepatocellular-carcinoma-the-legacy-study>), we recommend that patients with preserved liver function who are treated with radioembolization for solitary hepatocellular carcinoma involving 2 hepatic segments or less receive a dose of >400 Gy. The primary endpoint of this study was met demonstrating a 72.2% objective response rate and a 76.1% duration of response of greater than 6 months. We also recommend that when treating with radioembolization, normal liver should be spared when feasible.

Rationale: Radioembolization to small volumes of liver with ablative intent has demonstrated safety and improved efficacy over palliative lobar doses.

Specific Change 4: Modification to panel INTRA-1 to include concurrent systemic therapy with arterial directed therapy. Per the recent MISPHEC (NCT01912053), open-label multicenter phase II trial, we recommend the addition of gemcitabine and cisplatin to radioembolization for the first line treatment of unresectable intrahepatic cholangiocarcinoma. This trial demonstrated an overall response rate of 56%, a median progression free survival of 6 months, and an overall survival of 22 months. Patients who were downstaged to resection (n = 9, 22%) demonstrated a postoperative 24-month PFS and OS of 66.7% and 88.9%, respectively. Adverse events were predominantly confined to patients with cirrhosis and bilobar disease.

Rationale: Patients can receive both radioembolization and standard of care systemic therapy for the first line treatment of unresectable intrahepatic cholangiocarcinoma.

References:

Edeline J, Toucheffeu Y, Guiu B, Farge O, Tougeron D, Baumgaertner I, Ayav A, Campillo-Gimenez B, Beuzit L, Pracht M, Lièvre A, Le Sourd S, Boudjema K, Rolland Y, Boucher E, Garin E. Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial. *JAMA Oncol*. 2019 Oct 31;6(1):51-9. doi: 10.1001/jamaoncol.2019.3702. Epub ahead of print. PMID: 31670746; PMCID: PMC6824230.

Specific Change 5: Revise section IIC of panel HCC E(2) to state “external beam radiation therapy” rather than “radiation therapy.”

Rationale: Similar to changes that were made to HCC panels 4,5, and 6, panel E(2) should specify that recommendations are for external beam radiation therapy.

Thank you for your consideration of these recommendations.

Sincerely,

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