Year in Review: Top Papers in Interventional Oncology

Eric Wehrenberg-Klee, MD, and Suvranu "Shoey" Ganguli, MD, FSIR, provide an overview of the most significant interventional oncology articles published in the recent literature, with summaries on the impact that each has had on the field.

Institutional Decision to Adopt Y90 as Primary Treatment for Hepatocellular Carcinoma Informed by a 1,000-Patient 15-Year Experience

Salem R, Gabr A, Riaz A, et al. Hepatology. 2018;68:1429–1440.

SUMMARY/TAKEAWAY POINTS

This study reviews the toxicities and overall survival (OS) outcomes in a 1,000-patient cohort acquired over a 15-year period using yttrium-90 (Y-90) radioembolization for hepatocellular carcinoma (HCC). Between December 1, 2003, and March 31, 2017, 1,000 patients with HCC were treated with radioembolization as part of a prospective cohort study. Outcomes were stratified by baseline Child-Pugh (CP) class, United Network for Organ Sharing (UNOS), and Barcelona Clinic Liver Cancer (BCLC) staging systems.

Five hundred six (51%) patients were CP A, 450 (45%) were CP B, and 44 (4%) were CP C. Two hundred sixty-three (26%) patients were BCLC A, 152 (15%) were BCLC B, 541 (54%) were BCLC C, and 44 (4%) were BCLC D. Three hundred sixty-eight (37%) were UNOS T1/T2, 169 (17%) were T3, 147 (15%) were T4a, 223 (22%) were T4b, and 93 (9%) were N/M. In patients classified as CP A, censored OS was 47.3, 25, and 15 months for BCLC A, BCLC B, and BCLC C, respectively. In patients classified as CP B, censored OS for BCLC A was 27 months, BCLC B was 15 months, and BCLC C was 8 months. Forty-nine (5%) and 110 (11%) patients developed grade 3/4 albumin and bilirubin toxicities, respectively.

WHY THIS ARTICLE IS IMPORTANT

This is the largest single-center prospective cohort of Y-90 to date with a sample size and follow-up that, according to the authors, permits meaningful analyses that compensate for heterogeneity of lesion size and liver function. The study provides detailed data regarding Y-90 toxicity and survival outcomes by liver function and tumor burden, which may serve as benchmarks to compare with future studies. Other conclusions from the data set include that Y-90 for HCC allows for fewer treatments, better quality of life, and longer time to progression when compared with transarterial chemoembolization.

Impact of Combined Selective Internal Radiation Therapy and Sorafenib on Survival in Advanced Hepatocellular Carcinoma

Ricke J, Klumpen HJ, Amthauer H, et al. J Hepatol. Published online August 14, 2019.

SUMMARY/TAKEAWAY POINTS

Four hundred twenty-four patients were randomized: 216 patients were randomized to SIRT plus sorafenib and 208 to sorafenib alone. Median OS was 12.1 months (95% confidence interval [CI], 10.6–14.6 months) in the SIRT plus sorafenib arm and 11.5 months (95% CI, 9.8–13.9 months) in the sorafenib arm (hazard ratio [HR], 1.01; 95% CI, 0.81–1.25). In the per-protocol group, median OS was 14 months (95% CI, 10.95–16.40 months) in the SIRT plus sorafenib arm (n = 114) and 11.1 months in the

sorafenib arm (n = 174) (HR, 0.86; 95% CI, 9.7–13.9 months; *P* = .2515). Subgroup analyses of the per-protocol population suggested a survival benefit for younger patients (< 65 years) and noncirrhotics receiving SIRT plus sorafenib.

WHY THIS ARTICLE IS IMPORTANT

This large, randomized, multicenter study attempts to answer a combination treatment question for advanced HCC. From the data, the addition of Y-90 to sorafenib does not statistically significantly improve OS for locally advanced HCC in both the intention-to-treat and per-protocol analyses. The study's ability to demonstrate a survival benefit was compromised by the 47% of patients who did not receive SIRT per intention to treat or were excluded from the analysis due to protocol deviations. Although the subgroup analyses were not powered to answer these questions, they suggest a survival benefit for younger patients and noncirrhotics. The potential benefit in noncirrhotics brings up an important issue in current Y-90 clinical practice, which is proper and optimal patient selection.

Radioembolization With 90Y Glass Microspheres for Hepatocellular Carcinoma: Significance of Pretreatment 11C-Acetate and 18F-FDG PET/CT and Posttreatment 90Y PET/CT in Individualized Dose Prescription

Ho CL, Chen S, Cheung SK, et al. Eur J Nucl Med Mol Imaging. 2018;45:2110–2121.

SUMMARY/TAKEAWAY POINTS

This study aimed to establish a clinical methodology to allow for individualized Y-90 dosing. Prior to treatment, patients underwent imaging with both 11C-acetate and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT to define differentiation of their HCC. Subsequently, patients underwent standard of care pretreatment technetium-99m macroaggregated albumin (MAA) single-photon emission CT/CT to assess the tumor-to-nontumor (T/N) ratio via MAA. After patients received Y-90, they also underwent Y-90 PET/CT for T/N Y-90 to quantify the dose delivered. Tumor response was assessed on 2-month follow-up PET/CT.

Sixty-two patients were prospectively enrolled in this study. Tumors were defined as well-differentiated (> 70% 11C-acetate tumor avidity), poorly differentiated (> 70% 18F-FDG avid tumor), or moderate (avid for both tracers but not meeting the previous criteria). Correlation between tumor differentiation, Y-90 PET-assessed dose delivery, and response found that patients with well-differentiated tumors responded (complete responses or partial response) at 152 Gy, with moderately differentiated tumors at 174 Gy and poorly differentiated tumors at 262 Gy, with a sensitivity and specificity of 89.2% and 88%, respectively. If all patients were grouped, a tumor dose of 170 Gy was necessary to achieve response, with a 70% sensitivity and 76% specificity. T/N MAA correlated closely with a posttreatment Y-90 PET (r = 0.918). T/N MAA, with values normalized to a maximum tolerated liver dose of 70 Gy, suggests that response will be achieved in the well-differentiated group with a T/N MAA of 2.0, moderately differentiated at 2.3, and poorly differentiated at 3.5.

WHY THIS ARTICLE IS IMPORTANT

This study contributes to the growing data advancing how Y-90 radioembolization dosimetry is performed. It is the first study to stratify Y-90 dose response across different HCC subgroups based on tumor metabolic profiles and correlate those doses with T/N MAA. Although 11C-acetate imaging is not clinically feasible at most institutions, 18F-FDG PET could be readily incorporated into the workup of patients undergoing Y-90 radioembolization. Identifying poorly differentiated tumors for which a T/N MAA of 3.5 is necessary for response can help us titrate dosing and identify patients who would benefit from other therapies if such a T/N MAA cannot be achieved.

Immune Activation Underlies a Sustained Clinical Response to Yttrium-90 Radioembolisation in Hepatocellular Carcinoma

Chew V, Lee YH, Pan L, et al. Gut. 2019;68:335–346.

SUMMARY/TAKEAWAY POINTS

This study analyzes tumor tissue and blood samples from a cohort of patients with HCC to assess the immune response to Y-90 radioembolization. Multiparameter immune analysis, including next-generation sequencing and time-of-flight mass cytometry, was used to identify immune biomarkers predictive of response or nonresponse to Y-90 radioembolization. The study included 41 patients who underwent surgical resection with or without previous Y-90 radioembolization with tumor and

blood analysis, as well as another cohort of 31 similarly treated patients whose blood was analyzed at multiple time points.

The authors found that Y-90 radioembolization activates the local immune response with increased activated natural killer and CD8+ T cells and increases expression of multiple innate and adaptive immune response genes in post–Y-90 radioembolization tumors, including genes that promote CD8+ T cell chemotaxis to the tumor. Patients with a sustained response (ie, those with no evidence of progression at 6 months after Y-90 radioembolization) demonstrated increased tumor necrosis factor–α expression with specific T cell subsets at 1 and 3 months after therapy. Peripheral blood analysis found that a higher percentage of T cells expressing the checkpoints programmed cell death protein 1 (PD-1) and TIM-3 and the homing receptor CCR5 and CXCR6 were predictive of a sustained response before therapy and at 3 months after Y-90 radioembolization. By contrast, patients with no or transient response to Y-90 radioembolization showed increased regulatory T cells and nonspecific CD8+ T cells.

WHY THIS ARTICLE IS IMPORTANT

As immunotherapy changes the landscape of cancer treatment, the role that interventional techniques may play in the future and whether they can synergize with new therapies such as checkpoint inhibitors is an area of intense interest. This article shows that Y-90 radioembolization strongly activates the immune system, supporting the role of Y-90 radioembolization and immunotherapy combination regimens. Furthermore, the authors identified both pre- and posttreatment biomarkers of response that could be used to identify patients who will derive sustained benefit from Y-90 radioembolization, as well as identify possible pathways for turning nonresponders into responders through therapeutic targeting of immune checkpoints.

Irreversible Electroporation Reverses Resistance to Immune Checkpoint Blockade in Pancreatic Cancer

Zhao J, Wen X, Tian L. Nat Commun. 2019;10:899.

SUMMARY/TAKEAWAY POINTS

In a mouse model of pancreatic cancer, the investigators demonstrated that the addition of irreversible electroporation (IRE) to anti-PD-1 immune checkpoint blockade promotes an antitumoral immune response and significantly prolongs survival. In a single-tumor pancreatic cancer model, the authors demonstrated that the addition of IRE led to significantly longer survival, with 36% of dual-treated mice alive at the end of the study. This improved response was closely correlated with an antitumoral immune response, with increased percentages of activated CD8+ T cells within treated tumors. The authors found that IRE induces immunostimulatory necrotic cell death and causes the release of danger-associated molecular patterns known to stimulate the innate immune response. Furthermore, they demonstrated that IRE modulates tumor stroma that may promote lymphocyte infiltration. IRE plus PD-1 inhibition was found to be superior to radiation plus PD-1 inhibition in *KRAS* mice with spontaneous pancreatic tumors, showing significant differences in survival and intratumoral immune response.

WHY THIS ARTICLE IS IMPORTANT

As with Y-90, advancing our understanding of the immune-stimulating properties of interventional oncology techniques is critical, as the landscape of cancer treatment is altered by new immunotherapies. In this study, the authors demonstrated the ability of IRE to increase the response to PD-1 inhibitors in a murine model of pancreatic cancer—a challenging malignancy with a dismal prognosis that has been resistant to immunotherapy. The authors suggest that IRE both activates the tumor-specific immune response and alters pancreatic tumor stroma, which have been significant barriers to multiple therapeutic modalities. ■

Eric Wehrenberg-Klee, MD
Division of Interventional Radiology
Massachusetts General Hospital
Instructor of Radiology
Harvard Medical School
Boston, Massachusetts
ewehrenberg-klee@partners.org
Disclosures: Cofounder and consultant to CytoSite Bio; research funding from and consultant to BTG plc.

Suvranu "Shoey" Ganguli, MD, FSIR
Division of Interventional Radiology
Co-Director, Center for Image Guided Cancer Therapy
Massachusetts General Hospital
Associate Professor of Radiology
Harvard Medical School
Boston, Massachusetts
sganguli@mgh.harvard.edu
Disclosures: Consultant to Sirtex Medical Inc., Boston Scientific Corporation, Medtronic, BTG plc, and Boston Biomedical Associates.