

# Year in Review: Top Papers in Interventional Oncology

An overview of the most significant interventional oncology articles published in the recent literature and summaries on their impact on the field.

**BY ERIC WEHRENBURG-KLEE, MD, AND SUVRANU “SHOEY” GANGULI, MD, FSIR**

## Atezolizumab Plus Bevacizumab in Unresectable Hepatocellular Carcinoma

Finn RS, Qin S, Ikeda M, et al. *N Engl J Med*. 2020;382:1894-1905. doi: 10.1056/NEJMoa1915745

### SUMMARY/TAKEAWAY POINTS

This article reports the results of a global, open-label, phase 3 trial for patients with unresectable hepatocellular carcinoma (HCC) (Child-Pugh A) who had not previously received systemic treatment. Patients were randomly assigned 2:1 to either atezolizumab plus bevacizumab or sorafenib. The coprimary endpoints were overall survival (OS) and progression-free survival (PFS). The study included 501 patients; 336 patients were randomized to the atezolizumab/bevacizumab group (intravenously every 3 weeks) and 165 patients were randomized to the sorafenib group (orally twice daily). The hazard ratio for death with atezolizumab/bevacizumab as compared with sorafenib was 0.58 (95% CI, 0.42-0.79;  $P < .001$ ). OS at 12 months was 67.2% (95% CI, 61.3%-73.1%) with atezolizumab/bevacizumab and 54.6% (95% CI, 45.2%-64.0%) with sorafenib. Median PFS was 6.8 months (95% CI, 5.7-8.3 months) versus 4.3 months (95% CI, 4.0-5.6 months) ( $P < .001$ ). Grade 3 or 4 adverse events occurred in 56.5% in the atezolizumab/bevacizumab group and 55.1% in the sorafenib group. Grade 3 or 4 hypertension occurred in 15.2% of patients in the

atezolizumab/bevacizumab group, but other high-grade toxic effects were infrequent.

### WHY THIS ARTICLE IS IMPORTANT

This is not an interventional oncology (IO) paper per se, but it has major implications on the treatment of advanced HCC and will likely overlap with IO approaches. In patients with unresectable HCC, atezolizumab combined with bevacizumab resulted in better OS and PFS outcomes than sorafenib, placing this combination as the new first-line standard of care treatment for advanced HCC. Programmed death-1 (PD-1) inhibitors had shown promising clinical activity as second-line treatment for HCC in phase 1/2 studies, but despite being associated with response rates in the range of 15% to 20%, they did not show improved OS. However, this study did meet that important endpoint. This study also reinforces combination therapy for improved outcomes, combining bevacizumab (vascular endothelial growth factor inhibitor) with the immunotherapy atezolizumab, which targets programmed death-ligand 1. Studies using this new combination with IO treatments are planned and underway.

## Radioembolization Plus Chemotherapy for First-line Treatment of Locally Advanced Intrahepatic Cholangiocarcinoma: A Phase 2 Clinical Trial

Edeline J, Toucheffeu Y, Guieu B, et al. *JAMA Oncol*. 2019;6:51-59. doi: 10.1001/jamaoncol.2019.3702

### SUMMARY/TAKEAWAY POINTS

Forty-one patients with unresectable intrahepatic cholangiocarcinoma (ICC) who had never received

chemotherapy or intra-arterial therapy were included in this study and underwent treatment with first-line cisplatin (25 mg/m<sup>2</sup>) and gemcitabine (1,000 mg/m<sup>2</sup>

reduced to 300 mg/m<sup>2</sup> for the cycles just before and after radioembolization). Yttrium-90 (Y-90) was delivered during cycle 1 of chemotherapy if disease was unilobar and cycles 1 and 3 if disease was bilobar. The primary outcome was response rate at 3 months according to RECIST 1.1 (Response Evaluation Criteria in Solid Tumors, version 1.1), which was 41% with a 98% disease control rate. Median PFS was 14 months (95% CI, 8-17 months), and median OS was 22 months (95% CI, 14-52 months). Seventy-one percent of patients had grade 3 to 4 toxicities, and 22% of patients were downstaged to surgical intervention. After a median of 46 months after surgery, median relapse-free survival had not been reached among these patients.

#### WHY THIS ARTICLE IS IMPORTANT

This study represents the first prospective study of radioembolization with chemotherapy for the treatment of unresectable ICC and as such is an important advancement of the scientific literature in the field. OS compares favorably to the 11.7-month median OS seen with gemcitabine/cisplatin alone in the ABC-02 trial. This trial thus argues strongly for the inclusion of Y-90 as part of treatment for liver-confined or liver-dominant unresectable ICC. The rate of grade 3 to 4 toxicities was high, primarily representing progressive liver failure, especially in patients with preexisting cirrhosis, which suggests that the combination should be avoided in cirrhotic patients and that a sequential approach (chemotherapy then Y-90 or vice versa) rather than a combined approach could mitigate toxicities.

## Multicenter Study of Metastatic Lung Tumors Targeted by Interventional Cryoablation Evaluation (SOLSTICE)

Callstrom MR, Woodrum DA, Nichols FC, et al. *J Thorac Oncol.* 2020;15:1200-1209. doi: 10.1016/j.jtho.2020.02.022.

#### SUMMARY/TAKEAWAY POINTS

In this study, 128 patients with 224 lung metastases were treated with percutaneous cryoablation with 12- and 24-month follow-up. Patients with one to six metastases from extrapulmonary cancer with a maximal diameter of 3.5 cm were enrolled. Patients were excluded if they had uncontrollable primary or metastatic disease outside the lung. Time to progression of index tumor(s), presence of metastatic disease, and OS rates were assessed. Complications were captured for 30 days after the procedure. Recurrence-free response of treated tumor was 85% at 12 months and 77% at 24 months (of assessable tumors). After repeat ablation, local tumor efficacy was 91% at 12 months and 84% at 24 months. OS rates were 97.6% and 86.6% at 12 and 24 months, respectively. The rate of pneumothorax requiring chest tube placement was 26%. There were eight grade 3 complications and one grade 4 event.

#### WHY THIS ARTICLE IS IMPORTANT

These data represent the largest multicenter prospective study of image-guided percutaneous cryoablation for the treatment of lung metastases. Similar efficacy data were reported in the largest study of stereotactic body radiation therapy (SBRT), in which SBRT achieved 85% disease control of pulmonary metastases at 2 years. Although percutaneous cryoablation is associated with a relatively high rate of pneumothorax requiring chest tube placement, the rate of long-term complications is low, and percutaneous cryoablation is associated with a much lower incidence of pain than SBRT, which has a high rate of fracture as treatment sequelae. This study thus helps further establish percutaneous cryoablation as an alternative to SBRT in patients with pulmonary metastases who are poor surgical candidates.

## Assessment of Image-Guided Intratumoral Delivery of Immunotherapeutics in Patients With Cancer

Sheth RA, Murthy R, Hong DS, et al. *JAMA Netw Open.* 2020;3:e207911. doi: 10.1001/jamanetworkopen.2020.7911

#### SUMMARY/TAKEAWAY POINTS

In this case series, MD Anderson Cancer Center presents its 2-year experience with image-guided intratumoral injections. The cohort spanned a range of malignant tumors, injection sites, and immunotherapeutics. The study assessed the technical success and safety of these interventions. During the study period, 85 patients under-

went 498 encounters, and these encounters comprised 327 image-guided intratumoral investigational agent injections in 67 patients in clinical trials. An additional 18 patients with melanoma underwent 113 image-guided talimogene laherparepvec injections (FDA approved). There were no adverse events reported related to the technical component of the procedure. Serious adverse

events, including dyspnea and severe flu-like symptoms, developed within 24 hours of the injection and required hospitalization in three of 327 (2%) investigational agent injections and four of 113 (4%) talimogene laherparepvec injections.

### WHY THIS ARTICLE IS IMPORTANT

Image-guided intratumoral delivery of therapeutics is a growing and promising area for IO. Intravenous drug penetration into tumor tissue can be inadequate due to the tumor microenvironment. Direct, image-guided intratumoral delivery is a compelling approach to overcome these barriers. With advancements in immune-

based cancer therapies, there is increased interest in the delivery of therapeutic agents directly into tumors, either as a primary therapy or in combination with systemic immunotherapy. By successfully delivering a high concentration of immunostimulatory agents into a tumor site, local intratumoral drug delivery has the potential to drive sustained, systemic immune responses. The findings of this case series study suggest that intratumoral injections of immunotherapies were feasible across a range of histologic conditions and target organs. As these clinical trials and therapies increase, the optimal methods and techniques for image-guided intratumoral drug delivery will need to be elucidated and standardized.

## Inflammation Induced by Incomplete Radiofrequency Ablation Accelerates Tumor Progression and Hinders PD-1 Immunotherapy

Shi L, Wang J, Ding N et al. *Nat Commun.* 2019;10:5421. doi: 10.1038/s41467-019-13204-3

### SUMMARY/TAKEAWAY POINTS

This study evaluates the differing immune response of incomplete and complete radiofrequency ablation (RFA) in mouse models of syngeneic colorectal carcinoma. Mice implanted with the murine colorectal tumor lines CT26 or MC38 were treated with incomplete RFA (iRFA), complete RFA, or no treatment. PD-1 inhibition was added to treatment of a group of mice treated with iRFA. The investigators found that iRFA-treated mice had significantly reduced survival relative to untreated mice due to widespread progression of metastases, and the addition of PD-1 inhibition was ineffective at halting metastatic spread or improving survival. To understand the mechanisms behind this worsened survival, the authors studied the genomic and immune profile of the untreated tumors. Mice treated with iRFA had sustained inflammation in residual tumor mediated by tumor necrosis factor- $\alpha$ , which appeared to lead to a sustained infiltrate of myeloid-derived suppressor cells. Furthermore, iRFA-treated tumors showed a decreased infiltrate of CD8+ cells in residual tumor and a smaller percentage of them appeared active. Infiltrate of the suppressive immune cell population is thought to be due to sustained CCL2 expression that is critical for the recruitment of tumor-associated macrophages, and the inclusion of an anti-CCL2 antibody with treatment significantly prolonged survival in iRFA-treated mice.

### WHY THIS ARTICLE IS IMPORTANT

We are increasingly learning that the use of locoregional therapies may increase checkpoint inhibitor efficacy. Although there are encouraging reports of synergy between ablative strategies and checkpoint inhibition, the optimal

ablative technique as well as the appropriate sequencing of therapy are unknown. In this context, it is important to know that iRFA may lead to worsening of disease progression by causing an immunosuppressive-type inflammation within residual tumor. Ways to reduce this immunosuppressive inflammation with CCL2 antagonism are also important to understand. These data will help to improve the future development of clinical trials exploring thermal ablative strategies and checkpoint inhibition. ■

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