Reply to Yang et al and De Bari et al

It is with great interest that we read the thoughtful commentaries by Yang et al¹ and De Bari et al,² and we thank the authors for furthering the discussion of optimizing care for patients with hepatocellular carcinoma (HCC).

A central issue in the management of HCC is how to best assess treatment response. As noted, several different assessment schemes are available including the original Response Evaluation Criteria in Solid Tumors (RECIST), which primarily assess tumor size and growth; modified RECIST, which also account for tumor necrosis; and the criteria used by the European Association for the Study of the Liver. Each criterion has its own merits, and tumor responses in each could be obscured by treatment modalities that cloud the accurate assessment of liver tumors. At the initiation of our study,³ we chose the response criteria that most closely represented our clinical practice. Clinically, our multidisciplinary liver tumor board primarily uses the growth of tumors to define progression, and thus, we chose to use the classic RECIST criteria in our study. It should be noted that tumors that we defined as local failures on this study were nearly uniformly in concordance with clinical assessments, which also include arterial enhancement. In addition to matching our clinical practice, the decision to monitor tumor responses with the RECIST criteria matches the standard assessment used on the largest prospective trials of HCC and the current standard used by the Radiation Therapy Oncology Group/ NRG Oncology.⁴

Given the difficulties of imaging-based HCC treatment assessment, analysis of pathologic responses at the time of transplantation can be especially informative. Although few patients underwent transplantation in our study, pathologic complete response rates were similar in patients treated with radiofrequency ablation (RFA) and stereotactic body radiotherapy (SBRT; 44% v 33%, respectively). These rates are similar to those seen in contemporary studies.^{5,6} Since our study was published, a randomized trial comparing transarterial chemoembolization and proton-based hypofractionated radiation has been published.⁷ For patients proceeding to transplantation, pathologic complete response rates were numerically (but not significantly) increased for radiotherapy compared with transarterial chemoembolization (25% v 10%, respectively).

In summary, we believe that using the RECIST criteria to evaluate tumor response in our study was appropriate and closely correlated with clinically defined treatment failure. Within the limitations of our retrospective study, SBRT outperformed RFA as tumor size increased. These results are entirely consistent with the large body of literature documenting increased failure rates with

RFA as HCC size increases. Rather than suggesting that SBRT replace RFA for the treatment of HCC, we believe that these data show that SBRT is an excellent alternative for when an HCC is too large (ie, > 2 cm) to be effectively ablated by RFA. We are in the process of opening a clinical trial comparing RFA with SBRT to test the results of this study in both larger and smaller HCCs. Given the difficulties of imaging-based treatment response for HCC, one of the goals of this trial will be to assess the pathologic treatment response of both modalities at the time of transplantation. This trial will also address the differences in follow-up between the two modalities seen in our current study and allow for the prospective determination of acute toxicity rates. Of note, in the current study, there was no association between the development of acute toxicity and tumor size for either RFA or SBRT.

Daniel R. Wahl, Yebin Tao, Matthew Schipper, Theodore S. Lawrence, and Mary Feng

University of Michigan Medical Center, Ann Arbor, MI

ACKNOWLEDGMENT

Supported in part by Grant No. P01 CA59827 from the National Institutes of Health and by the Taubman Institute.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

REFERENCES

1. Yang JF, Lo CH, Huang WY: Is stereotactic body radiotherapy better than radiofrequency ablation for the treatment of hepatocellular carcinoma? *J Clin Oncol* 34:2797, 2016
2. De Bari B, Ozsahin M, Bize P, et al: Can stereotactic body radiotherapy really be considered the preferred treatment in large hepatocellular carcinoma? *J Clin Oncol* 34:2798-2799, 2016
3. Wahl DR, Stenmark MH, Tao Y, et al: Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. *J Clin Oncol* 34:452-459, 2015
4. Bujold A, Massey CA, Kim JJ, et al: Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. *J Clin Oncol* 31:1631-1639, 2013
5. O'Connor JK, Trotter J, Davis GL, et al: Long-term outcomes of stereotactic body radiation therapy in the treatment of hepatocellular cancer as a bridge to transplantation. *Liver Transpl* 18:949-954, 2012
6. Facciuto ME, Singh MK, Rochon C, et al: Stereotactic body radiation therapy in hepatocellular carcinoma and cirrhosis: Evaluation of radiological and pathological response. *J Surg Oncol* 105:692-698, 2012
7. Bush DA, Smith JC, Slater JD, et al: Randomized clinical trial comparing proton beam radiation therapy with transarterial chemoembolization for hepatocellular carcinoma: Results of an interim analysis. *Int J Radiat Oncol Biol Phys* 95:477-482, 2016

DOI: 10.1200/JCO.2016.67.7492; published online ahead of print at www.jco.org on June 20, 2016.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Reply to Yang et al and De Bari et al

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Daniel R. Wahl

No relationship to disclose

Yebin Tao

No relationship to disclose

Matthew Schipper

Consulting or Advisory Role: Armune Bioscience

Theodore S. Lawrence

No relationship to disclose

Mary Feng

Honoraria: Medivation/Astellas (I), Genome Dx (I), Nanostring (I)

Consulting or Advisory Role: Genome Dx (I), Nanostring (I), Myriad (I), Varian (I)

Speakers' Bureau: Medivation/Astellas (I)

Research Funding: Celgene (I), Varian

Patents, Royalties, Other Intellectual Property: PFS Genomics for Radiotype Dx, Patent Pending (I)

Travel, Accommodations, Expenses: Varian (I), Genome Dx (I)