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CORRESPONDENCE

Correspondence on Rajyaguru et al

TO THE EDITOR: In their recent article in *Journal of Clinical Oncology*, Rajyaguru et al[1] report on a retrospective comparison of two local ablative methods (stereotactic body radiotherapy [SBRT] and radiofrequency ablation [RFA]) for the management of localized hepatocellular carcinoma (HCC) using the National Cancer Database. The authors find that overall survival is better in the RFA than in the SBRT cohort, even when some parameters are matched. For the comparison of effectiveness of local ablative methods, prospective randomized studies are still missing, and hence, retrospective analyses of large databases such as the study by Rajyaguru et al are relevant as the best evidence at hand. This study is specifically impressive because it reports data on almost 4,000 patients. However, although some limitations are discussed by the authors, several major limitations remain unaddressed, which we would like to highlight.

First, the major weakness of the study design is that information on the liver function of patients is missing (ie, Child-Turcotte-Pugh [CTP] score, which is the predominant prognostic factor, because a majority of patients die as a result of liver failure and portal hypertension). Moreover, data on Barcelona Clinic Liver Cancer stage and presence of portal vein invasion are also missing. The authors attempt to compensate for missing CTP score by providing the Ishak fibrosis score, although this information is available for few patients (SBRT, 16%; RFA, 29%). However, the prognostic value of the Ishak score is low compared with that of CTP score,[2] and comorbidity scores also cannot compensate for missing CTP score. Finally, clinical TNM stage I and II data are assumed to represent exclusively T stage, ignoring N stage, and not to represent prognostic stage groups I or II. Therefore, the authors' matched pair analysis explores only minor prognostic variables and thus cannot achieve properly matched patient cohorts. We suspect that the difference in survival reported is a result of selection bias, mainly resulting from imbalanced CTP scores and Barcelona Clinic Liver Cancer stages.

Second, this analysis excludes patients receiving any form of adjuvant or neoadjuvant therapy or other forms of local ablative therapies. This is intriguing, because the typical course of the disease almost inadvertently requires further treatment, as discussed by the authors. This exclusion raises important uncertainties about patient selection, because it does not reflect common practice.

Third, regarding patient numbers, there is a major imbalance between the two treatment arms (SBRT, n = 296 *v* RFA, n = 3,684), which underlines the risk of a major selection bias. One has to assume that only patients who were not candidates for other treatment options were referred for SBRT. Interestingly, patients receiving RFA were more likely to have private insurance, and they were younger compared with patients receiving SBRT. Both of these factors would have a direct impact on survival.

Fourth, much of the authors' discussion focuses on local control (LC) after RFA and SBRT, and interestingly, the authors state that LC in HCC may not translate into improved progression-free or overall survival. Unfortunately, no data on LC are reported in this analysis to prove this hypothesis, which would, if true, favor neither RFA nor SBRT. However, SBRT and RFA are local ablative therapies, and multiple recent publications conclude that even though SBRT shows an advantage for larger tumors, both techniques result in the same LC rates.[3,4]

Fifth, the data presented originate from the years between 2003 and 2014. SBRT at that time (2003 to 2010) was in the early phase of development and optimization (ie, there was no standardized technique or radiation dose for liver tumors). In contrast, there are now widely accepted guidelines[5] and reports that advanced technologies for liver SBRT and the use of sufficiently high radiation doses are significantly associated with improved outcomes, perhaps even exceeding those achievable with RFA,[3,6] with low toxicity[7] and good quality of life.[8] Proper knowledge of SBRT details regarding prescription dose, motion management, and image guidance as well as their correlation with LC is therefore of paramount importance in interpreting these outcome data.

In summary, Rajyaguru et al[1] report rather surprising differences in survival between RFA and SBRT. A closer look at their work reveals that a number of highly important prognosis factors for patients with HCC are not taken into consideration in the statistical analysis. Therefore, we would like to emphasize these weaknesses and suggest that physicians treating HCC contribute to prospective randomized trials that compare the two methods.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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