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Comparing Ablative Modalities for Hepatocellular Carcinoma: Cautions in Interpreting Big Data

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To the Editor

Rajyaguru et al¹ presented “Radiofrequency Ablation Versus Stereotactic Body Radiotherapy for Localized Hepatocellular Carcinoma in Nonsurgically Managed Patients: Analysis of the National Cancer Database” and concluded that their results supported that overall survival after radiofrequency ablation (RFA) was superior to that after stereotactic body radiotherapy (SBRT) in nonsurgically managed stage I to II hepatocellular carcinoma (HCC).

There are several cautions in this interpretation, especially given the inherent considerable imbalance in patient tumor and clinical characteristics for those treated with RFA versus SBRT. Imbalance in the groups could be expected, given that SBRT may be reserved for patients felt to be poor candidates for RFA. The authors sought to address the imbalance in patient characteristics using propensity score–matched analysis to match on known potential confounders. Nevertheless, for key known confounders, it is unclear that the level of detail was adequate for meaningful matching. For example, although patients were matched on a single cross-sectional measurement of tumor size, within the category that was most imbalanced (ie, tumors ≥ 4 cm), it is not clear that the distribution of tumor volume in patients receiving RFA was adequately matched with the distribution of tumor volume in those receiving SBRT. Prior evidence supports that tumor volume is a strong, independent predictor of disease outcomes in HCC,² and therefore, a meaningful difference in unmatched tumor volume could have affected, or indeed biased, the survival risk estimate.

Similar concerns exist for whether the match for Charlson-Deyo comorbidity scores adequately represented a matched distribution of performance status of patients and whether the liver fibrosis variable (missing in 84% of patients receiving SBRT and in 71% of those receiving RFA) adequately reflected a matched distribution of liver function. Although the benefit of retrospective big data analysis allows for larger sample sizes, there is typically a loss of critical detail in the data that can be meaningful in accounting for complex selection biases.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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The related question that follows is whether there are potentially influential unknown (or unaccounted for) confounders. In particular, potential important sources of confounding by indication were not accounted for, including confounding variables that fundamentally determine whether a treatment is indicated. For example, presence of tumor thrombus, a factor that typically selects against RFA, can be an explicit clinical indicator prompting radiation treatment, and predicts worse disease outcomes. Confounders that are unaccounted for, such as this, are particularly influential in the interpretation of results when biasing results away from the null hypothesis.

A final strong caution concerns the utility of the NCDB in interpreting overall survival outcomes. A prior audit demonstrated variation in quality of vital status abstraction in the NCDB; Winchester et al³ warned: “Vital status follow-up from hospital registries has not been systematically reviewed or validated, and it appears that methods to determine vital status vary widely between registries. Many hospital registries do not have access to sources of vital status follow-up available to central registries, including linkage with state vital records and the National Death Index (NDI).”³(p6) Moreover, evidence suggests registry-to-registry variation in the completeness, timeliness, and accuracy of data, as well as cumulative rates of loss to follow-up, from this database. The significant difference in the distributions of era of diagnosis for patients receiving RFA versus SBRT indicates that the underlying populations (registries) from which RFA versus SBRT patient data were drawn may have differed between treatment groups. If there were any systematic differences by era or registry in survival reporting, the difference in survival between RFA and SBRT groups could have been biased, either toward or against the null.

The results reported by Rajyaguru et al¹ are thought provoking, but they underscore the need for continued prospective evaluation of these two treatment modalities to define their optimal indications.

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