Our thanks to Drs. Giuliani and Bezjak for a thoughtful commentary on a controversial topic. Upon synthesizing the discussion points, we reframed the debate into four discrete questions, which we will address in this rebuttal.

**Are the imaging features used to predict recurrence, namely the CT high-risk features (HRFs), any good?**

Drs. Giuliani and Bezjak stress that studies reporting LRs require pathologic correlation to ensure that LR is correctly diagnosed. We agree. Both the Peulen and Huang studies, included LRs that had confirmation of recurrence (1,2). In the Peulen HRF validation study, while it is true that only 13 of 53 LRs were confirmed by biopsy, only those 13 were included in their analyses (1). We cannot require biopsies of patients without recurrence, since such procedures are often not clinically indicated and are associated with risk. Regarding their clinical utility, HRFs have excellent reported sensitivities of 92% (1,2) and specificities of 85% (1) and 92% (2). We conclude that HRFs perform well enough for clinical practice.

**If imaging is highly suggestive of LR and biopsy is unsafe, is salvage treatment contraindicated?**

If salvage treatment is contraindicated, the only remaining options are best-supportive care and/or palliative interventions, with inevitable morbidity and mortality from progression. There is ample precedent for treating without pathology. Treatment of primary lung cancers when biopsy is unavailable is well-established in surgical guidelines when the risk of cancer is high (3) and similarly, many SBRT series do not require biopsy in all patients (4).

When biopsies are unsafe, salvage surgery may be unsafe as well. However, salvage SBRT (or treatment with other radiation fractionations) remains a possibility. Hearn et al. retrospectively identified 10 medically inoperable patients with isolated LRs ≤5 cm, who tolerated salvage SBRT with no grade 3–5 toxicities (5). Another series examined grade 3–5 toxicities after salvage SBRT in 29 patients with LRs (32 tumors: 21 peripheral, 11 central). Toxicities were dependent on tumor location: treatment of central tumors was associated with grade 4 (n=2) and grade 5 (n=3) toxicities. Peripheral tumors, however, had no grade 4–5 toxicities (6). These findings support the use of cautious...
salvage SBRT in carefully selected patients. We conclude that in patients with imaging findings highly suggestive of LR, but unable to tolerate biopsy, salvage treatment can be more appropriate than palliation alone.

**If imaging is highly suggestive of LR and biopsy was done but is non-diagnostic, is salvage treatment also contraindicated?**

When clinical and radiologic suspicions are high, clinicians may be dissatisfied by a negative biopsy. Consider a hypothetical scenario: several HRFs are present, including bulging margins, cranio-caudal growth, and sequential enlargement. A PET scan reveals a SUV$_{max}$ of 10. A biopsy returns as non-diagnostic. Is it best to repeat the biopsy, treat, or do nothing? Nishimura et al. presented two cases of LR that proceeded to salvage SBRT without pathology. In one case, the biopsy was unsuccessful, and in the second, the tumor board recommended against biopsy given the strong suspicion for LR and patient comorbidities (7). We, like Nishimura et al., conclude that salvage treatment is not contraindicated by a non-diagnostic biopsy. At times, we may be forced to act using the best available evidence when our gold standard (i.e., pathology) fails us.

**If imaging is highly suggestive of LR and biopsy is safe, is biopsy necessary?**

This is the most controversial of the four questions. Biopsies are imperfect and come with risks of complications (8), non-diagnostic samples (9) and treatment delays. A rule of ‘biopsy for all’ should not be enforced without careful consideration. As Drs. Giuliani and Bezjak correctly indicate, biopsies in this patient population are at risk for false positives, even 14 months after treatment (10). Furthermore, in a case from their own institution, a patient with LR required 11 needle passes over three different biopsy attempts before a pathological diagnosis was obtained (11).

In conclusion, our differing viewpoints ultimately share common ground. We all agree that there are unclear rules for when imaging is sufficient to guide salvage therapy. Biopsies remain the gold standard in diagnosing LR and should be obtained when feasible. However, we contend that a pathologic diagnosis is not always possible—even with a biopsy attempt. Accepting that a validated, evidence-based approach using HRFs can be sufficient to inform salvage treatment in a multidisciplinary setting, grants clinicians the flexibility to provide appropriate care tailored to a patient’s specific situation.

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**Footnote**

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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