Reply to A.V. Louie et al

I read with interest the comments by Louie et al1 regarding our report describing the results of a randomized trial of sublobar resection (SR) with or without brachytherapy for stage I lung cancer. Their comments addressed three areas to which I would like to respond. First, they discussed the value of lymph node staging in high-risk patients undergoing surgery and requested information about the adequacy of staging nodal disease in our study. This was in fact reported in an earlier analysis. Among 210 evaluable patients for whom data were available for that secondary analysis, 64% underwent a video-assisted thoracoscopic surgery (VATS) resection and 36% an open resection. Segmentectomy was only performed in 27% of patients and wedge resection in 73%. There were no differences between the degree of nodal evaluation among patients treated with VATS or thoracotomy. However, significant differences were observed between patients who underwent a segmental or wedge resection in terms of nodal upstaging (9% vs 1%) and number of lymph node stations sampled (three vs one), respectively. Considering that only credentialed surgeons participated in the study, we were disappointed to see that 41% of patients treated with wedge resection had no lymph node sampling at all, compared with 2% of those treated with segmentectomy. It should be emphasized that the type of lymph node dissection performed was not mandated in the study, because this was deemed a high-risk operable population.

A second point raised in their comments was the impact of treatment-related mortality and morbidity in high-risk patients treated with SR, which the authors perhaps use as an argument in favor of stereotactic ablative radiotherapy (SABR). Probably the most influential multicenter trial in North America for SABR in high-risk stage lung cancer is RTOG (Radiation Therapy Oncology Group) 0236.4 This study involved 55 patients deemed medically inoperable. Conversely, in Z4032, eligible patients were those deemed high risk for lobectomy but still considered operable. It is noteworthy that in an analysis of selection criteria for these two National Cancer Institute studies of stage I lung cancer, pretreatment forced expired volume in 1 second (61.3% vs 53.8%) and carbon monoxide diffusing capacity (61.6% vs 43.7%) were superior for SABR patients compared with those undergoing surgery.5 This demonstrates that patients are not comparable between clinical trials. There was no treatment-related mortality after SABR in RTOG 0236, but 30- and 90-day mortality rates were also low, at 1.4% and 2.7%, after SR in Z4032.5,6 Not unexpectedly, grade ≥ 3 adverse events occurred in a lower percentage of SABR patients compared with those undergoing SR (16.3% vs 30.6%) when these two studies are compared. It is reasonable to consider these numbers when counseling patients.

Third, in the conclusion of their letter, Louie et al1 argue that SABR should be considered a primary modality for high-risk patients. I strongly disagree with this statement. A number of studies now support the role of SABR as the gold standard for medically inoperable patients, but this does not translate to SABR being considered the primary modality for high-risk operable patients currently treated with SR. Long-term follow-up results from RTOG 0236 were recently reported at the 2014 American Society for Radiation Oncology meeting. Median follow-up was 4 years and is now similar to the median follow-up of 4.49 years reported in Z4032. Overall survival at 5 years was only 40% after SABR compared with 61.1% and 56.7% after SR for the two arms studied in Z4032. Although it can be argued that patients are not similar between these two studies, this speaks to the need for a prospective randomized trial to compare SABR and SR in high-risk operable patients. Z4099 was a randomized trial that addressed this very question.8 Unfortunately, this trial closed because of poor accrual, with the biggest impediment being the unwillingness of patients to be randomly assigned to two disparate therapies. The investigators have addressed this in a redesign of the trial, using random assignment of a site rather than random assignment of the patient. This should be more palatable to patients, because they will know at the time of consent to the study which treatment they will receive. It is hoped that this redesigned study will be opened by the RTOG Foundation in the next few months. It is imperative such a study be undertaken to truly answer the question of SABR as a viable alternative to patients currently treated with SR.

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REFERENCES


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AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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