Editorial Commentary

Revealing age and gender as determinants of survival after pulmonary segmentectomy should represent just the beginning of more discovery

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Comment on: Hattori A, Suzuki K, Takamochi K, *et al.* Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer with radiologically pure-solid appearance in Japan (JCOG0802/WJOG4607L): a post-hoc supplemental analysis of a multicentre, open-label, phase 3 trial. Lancet Respir Med 2024;12:105-16.

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The debate regarding the relative efficacy of segmentectomy versus lobectomy in the treatment of early-stage non-small cell lung cancer (NSCLC) ostensibly reached a conclusion recently with the results of the JCOG0802/WJOG4607L trial. While the objective was to establish non-inferiority of segmentectomy over lobectomy, superiority was revealed in the former over the latter (1). As with all quality trials, when conclusions are drawn, more questions are raised, typically requiring a deeper dive into the granular aspects of the study's findings. In the post hoc analysis conducted by Hattori *et al.* published in *The Lancet Respiratory Medicine*, valuable insights from the available long-term data of the randomized, controlled phase III trial JCOG0802/WJOG4607L are offered (2). However, perhaps equally important, their analysis can serve as a lead point to ask whether other factors, yet to be delineated definitively, can impact or augment the findings of their study.

Hattori *et al.* performed a post hoc analysis of the JCOG0802/WJOG4607L non-inferiority randomized, controlled trial, comparing overall survival, relapse-free survival, recurrence patterns, mortality, and causes of death between segmentectomy and lobectomy in patients with predominantly pure-solid NSCLC (defined as a consolidation-to-tumor ratio =1). The analysis included 553 patients with radiologically confirmed pure-solid NSCLC, equally divided between those who underwent segmentectomy or lobectomy, between August 2009 and October 2014 in Japan. Although the data cutoff of June 13, 2020 provided a median follow-up time of 7.3 years, the authors noted that survival data beyond 5 years remains immature. The minimum follow-up time was 5 years. The two groups were relatively well-matched, and the five-year overall survival rate was significantly higher in the segmentectomy group compared to the lobectomy group (92.4% *vs.* 86.1%, P=0.033), while the five-year relapse-free survival rates were comparable between the groups (82.0% *vs.* 81.7%, P=0.94) (2).

Notably, locoregional recurrence was significantly higher in the segmentectomy group compared to the lobectomy group (16% *vs.* 8%, P=0.0021). Five-year relapse-free survival was significantly lower for segmentectomy *vs.* lobectomy in patients younger than 70 (84.4% *vs.* 87.4%, P=0.049) and in female patients (82.2% *vs.* 94.2%, P=0.047). Conversely, for patients over 70 years, segmentectomy

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showed improved overall five-year survival compared to lobectomy (85.6% *vs.* 77.1%, P=0.13), a trend also seen in male patients (92.1% *vs.* 80.5%, P=0.0085). Interestingly, non-lung cancer-related deaths (e.g., respiratory disease, other cancers) were more common in the lobectomy group, although this difference did not achieve statistical significance (P=0.19) (2).

The Lung Cancer Study Group's 1995 report initially suggested that sublobar resection was inferior to lobectomy for T1N0 NSCLC. However, subsequent trials, including the recent CALGB 140503, have indicated that segmentectomy is non-inferior, with seven-year data demonstrating comparable overall survival (3,4). Despite this, the optimal treatment strategy remains debated, particularly as recent evidence shows that tumors with visceral pleural invasion yield similar survival and short-term outcomes with either surgical approach (5). Furthermore, other high-risk features such as lymphovascular invasion have yet to be identified as other tumor-related characteristics that could attenuate the benefits of segmentectomies. Although *Tab. S10* presents these characteristics, it does not provide any additional information regarding potential differences between the surgical arms. In fact, the surgical issue of margins and what is deemed to be adequate or perhaps even advantageous or disadvantageous requires better delineation. Last and certainly not least, the initial eligibility for the JCOG0802/WJOG4607L trial was predicated on the radiographic characteristics of the nodules as seen on imaging. The trial also required a subsequent two-step registration process with intraoperative histological confirmation of NSCLC before continuing with the protocol. Hattori *et al.* attempted to prove that radiological features are important to understanding how specific subsets of patients among a larger cohorts may not benefit from a sublobar approach. This perspective is very important as it can affect how thoracic surgeons approach a malignant appearing nodule in a forward-thinking manner. However, the translation of these characteristics into actual tumor histology as identified on final pathology, and how this aligns with or challenges the findings from the JCOG0802/WJOG4607L trial, has not yet been clearly defined in greater detail. The question arises as to how the histological characteristics of pure- *vs.* part-solid nodules influence initial imaging and subsequent surgical approaches, given their significant clinicopathologic differences. These distinctions, which have been shown to have implications for overall prognosis, can guide decisions between segmentectomy and lobectomy (1-2,6). Additionally, the relationship between imaging and pathology is imperative to examine with greater specificity due to an inherent level of operator dependence when initially describing tumor appearance on thin-slice computerized tomography scans. Moreover, large tertiary healthcare centers often conduct multidisciplinary discussions, known as "Tumor Boards", involving radiologists, oncologists, and thoracic surgeons and several other professionals with expertise in their subspecialties, to collaboratively interpret imaging findings. Owing to the protocolized nature of this as well as any clinical trial, it is unclear the depth to which discussions were pursued regarding the other tumor findings for the patients initially enrolled in the JCOG0802/WJOG4607L trial at the participating centers (1,2). Given the potentially limitless variability in each NSCLC that presents, the question that is raised then is, "Can a definitive treatment paradigm truly be established based solely on the described imaging appearance?". Understanding that treatment decisions are rarely made on a singular diagnostic modality and that there is not a clearly superior decision-facilitating instrument, the answer, for the time being, is probably. Nevertheless, studies such as that by Hattori *et al.* add additional dimension to the decision-making process that are essential for investigating specific subpopulations within treated cohorts and represent a starting point.

Of note, in this post hoc analysis, two key factors differentiating the non-inferiority outcomes between segmentectomy and lobectomy were age and sex. Younger patients and females showed lower relapse-free survival with segmentectomy, likely due to higher locoregional recurrence and fewer deaths from other causes, compared to lobectomy. The authors suggest that females, who have a higher prevalence of *EGFR* mutations, may be more susceptible to recurrence. Conversely, older male patients, often burdened with more comorbidities and higher smoking rates, exhibited greater relapse-free survival, potentially due to increased mortality from non-cancer-related causes. This parallels the recent literature indicating that lobectomy in older males carries a higher mortality risk within five years, with overall survival favoring segmentectomies in this population (2,7).

Additionally, the difference in outcomes between males and females is highlighted in a recent study that found that women are less likely to be diagnosed with advanced lung cancer than men, contributing to higher five-year mortality rates in males, irrespective of age or histology (8). While the segmentectomy group showed higher overall survival among older male patients, their causes of death were more likely related to lung cancer compared to the lobectomy group. This raises questions as to why similar age groups and sexes show different causes of death depending on the type of surgery. One hypothesis offered by the authors is that the physiological stress of lobectomy contributes to higher mortality from other causes. However, this is contrary to what was shown by Suzuki *et al.*, who found similar rates of intraoperative and postoperative complications (grade >2) between complex segmentectomies and lobectomies, with air leaks being more significantly associated with the segmentectomy arm (9).

Accurately determining causes of death, especially in patients with multiple comorbidities, can be a complex challenge. The interplay of various health factors makes it difficult to pinpoint a singular cause, leading to potential misattributions or oversights. Differentiating specific causes of mortality, such as those attributable to lung cancer (whether primary or recurrent) versus cardiovascular or cerebrovascular diseases, presents a significant challenge. Although overall survival in segmentectomy patients was positively influenced by the elderly male cohort, these individuals often present with multiple comorbidities and concomitant significant diseases, leading to increased perioperative mortality and higher surgical risk (7). This issue complicates the ability to draw definitive conclusions concerning true causes of death, especially given the non-significant differences observed between the lobectomy and segmentectomy groups (P=0.19).

Thus, considering the factors of age and sex, it seems reasonable to recommend segmentectomy for males over 70 years and lobectomy for females under 70 years. However, the decision becomes more complex for females over 70 years or males under 70 years. Alternatively, can a male patient at 69 years and 11 months be meaningfully distinguished from one at 70 years and 1 month? If the answer is yes, then is that magnitude of difference similar to justify a lobectomy in a female patient who is 70 years and 1 month? With all other variables being equal, what is the optimal approach then for a female who is younger than 70 years? It is crucial to consider these questions, as recent studies have shown that women under the age of 65 years experience significantly improved survival rates following general lung surgical resection, with a rapid decline thereafter. This decline is thought to coincide with the diminishing effects of protective biological factors, which may taper off as women approach a fully postmenopausal state. However, these findings should be interpreted with caution, as advancing age is naturally associated with increased comorbidities (10,11). The authors of the present study suggest that the increased overall survival observed in women under 70 years, despite lower relapse-free survival in the segmentectomy group, may partly be due to the effects of adjuvant chemotherapy. However, the study by Sandler *et al.* contradicts these findings, reporting that adjuvant therapy did not significantly improve survival in women aged 65–72 years with medical comorbidities; the benefit was observed in all women younger than 65 years (10). Furthermore, in the present study, patients were aged between 61 and 73 years; however, it is unclear whether the age distribution was skewed toward the younger or older end of this range. This ambiguity further complicates the decision-making process regarding the use of a 70-year age cutoff. Therefore, it is critical to base age-related treatment decisions on a solid biological foundation rather than a subjective age determination. These types of questions require greater investigation especially when age and gender findings such as those which are presented by Hattori *et al.* are put forth.

It must be emphasized that post-trial follow-up studies in the form of post-hoc analyses, such as the one by Hattori *et al.*, introduce a heightened risk of selection bias and subsequent confirmation bias. A significant factor is the lack of randomization among included subjects, which may artificially skew the results (12). Although the authors acknowledge the limitations of post-hoc analysis, they do not clearly explain how they adjusted their study design to mitigate these risks (e.g., through propensity-score matching). Likewise, this renders the conclusions reached less clinically relevant as the patient populations surgeons are often presented with may not align with those utilized in this study.

The authors recognize several of these drawbacks, including the small sample size which may diminish the statistical power of their findings. The study further notes that the data, derived primarily from a Japanese cohort, may not be generalizable to other populations. However, these findings underscore the necessity for personalized treatment strategies in resectable NSCLC, tailored to factors such as age, gender, and tumor histology. As we anticipate the forthcoming 10-year follow-up data, further discourse is warranted on the physiological impacts of each surgical technique and the survival outcomes associated with radiologically pure-solid versus part-solid NSCLC. Additional post hoc analyses from this data set and possibly other larger series on several other characteristics, some of which were aforementioned, during this time, most assuredly will add greater robustness to this discourse. It would be remiss not to mention the recent post-hoc analysis of the CALGB 140503 randomized controlled trial by Altorki *et al.*, which also supported the non-inferiority of sublobar resection compared to lobectomy. Notably, the authors did not differentiate tumors by radiologic appearance nor account for variations in outcomes by age or sex (13). Subsequent post-hoc analysis of this dataset similar to what was done by Hattori *et al.* could help determine whether the aforementioned trends hold or diverge significantly. Furthermore, in the modern era of next generation sequencing, it also is possible that reflex testing for early-stage disease, the utility of which has been questioned in practice by some clinicians for not having a purpose in a stage of disease that would not require any additional therapy, may find a meaningful purpose. Similarly, with the advent of artificial intelligence models, the operator dependence in distinguishing radiologic appearance may be greatly reduced, enabling quicker and more accurate diagnostic decisions. Combing radiographic features, including radiomic data and comprehensive biomarker testing acquired earlier in the planning process combined with artificial intelligence could enhance the precision of risk stratification, guiding the choice between lobectomy and sublobar resection more effectively and accurately (14). However, in taking the first step in trying to seek answers to the question of "who stands to benefit more from segmentectomy?", Hattori *et al.* have exposed more that is unknown and opened up the forum to explore several other factors associated with improved outcomes.

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