Editorial

Targeted surgical therapy for lung cancer

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Provenance: This is an invited Editorial commissioned by the Section Editor Feichao Bao (Department of Thoracic Surgery, The First Affiliated Hospital, Zhejiang University, Hangzhou, China).

Comment on: Hattori A, Matsunaga T, Takamochi K, Oh S, Suzuki K. Significance of Lymphadenectomy in Part-Solid Lung Adenocarcinoma: Propensity Score Matched Analysis. Ann Thorac Surg 2018;106:989-97.

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Oncologists and precision medicine teams have become the stars of lung cancer treatment. As our understanding of the heterogeneity of the molecular drivers and of the immune landscape of individual patient's tumors becomes more nuanced, it is now clearer that a one-size-fits-all approach for the treatment of advanced lung cancer makes little sense. Instead, treatment is based upon histology, driver mutations, and immune markers. With that foundation, practice-changing trials of targeted therapies are being reported at a dizzying pace.

Similarly, although not as appreciated, surgical therapy for early-stage lung cancer, has also become more targeted. Expert surgeons now more frequently, utilize minimally invasive techniques, and sublobar resections for lung preservation (1-6). Although the surgical community eagerly awaits the publication of survival results from modern trials evaluating sublobar resection versus lobectomy (JCOG0802 and CALGB 140503), it is safe to assume that those trials may yield just as many questions as answers. Rather than a one-size-fits-all approach of sublobar resection or lobectomy for individual cancers, it seems much more likely that surgeons will continue to evaluate, and carefully select patients for each type of procedure. Our ability to do so has been greatly facilitated by the increased resolution of computed tomography scans that have enabled nodule classification, and pathologic prediction and of positron emission tomography (PET) scans that have enabled identification of gross nodal disease and highly metabolic tumors at risk for micrometastatic nodal disease. Additionally, histological classification, when determined preoperatively, can help predict the outcome of a sublobar resection (7-11). Indeed, such nuances are the basis of surgical targeted therapy.

The thoracic surgery group from the Juntendo University, in Japan, have been leaders in describing the targeted surgical treatment of early-stage lung cancer, publishing numerous manuscripts about their experience in selecting patients for a sublobar resection (7-9,12,13). In their most recent publication in the "*Annals of Thoracic Surgery*", they take this concept further, by exploring the role of targeted lymphadenectomy (14). The authors evaluated 462 patients with clinical stage I radiological part-solid adenocarcinomas, who had undergone either a systematic lobe-specific mediastinal lymph node dissection (m-LND) or hilar lymph node only dissection (h-LND). Among these patients, the authors propensity matched 92 pairs of patients for a detailed analysis. Notably, nodal metastases were only present in 4.9% of the solid dominant lesions, and could be predicted by high carcinoembryonic antigen levels (>3.0 ng/mL) and by high SUVmax on PET (>2.8). Only nine patients (1.9%) in the entire cohort, had pathologic N2 disease. Given this low rate of nodal positivity, it is perhaps not surprising that there was no difference in survival between patients who had m-LND or h-LND. Overall survival in the entire cohort at the 5 year mark was 94% for m-LND and 93% for h-LND (P=0.585) and locoregional recurrence was less than 2% for both groups. Survival in propensity matched pairs was essentially identical.

In what context should we put these results? Do the

results reported by Hattori *et al.* indicate we should discourage surgeons from routinely undertaking the laborious task of a mediastinal node dissection? The answer is a resounding "no", but the reasons why are perhaps subtle. Although it is compelling to pool and compare all of these cases together, it is remarkable how much *a priori* surgical judgment actually went into the selection of which operative techniques were used in these patients, both regarding the extent of resection, and the extent of lymph node dissection. That judgment, in essence the ability of expert surgeons to perform a targeted surgical resection and lymph node dissection, can never be accounted for in retrospective reviews, even among propensity matched groups which are unable to account for differences in treatment allocation, particularly in the patients with early stage lung cancer with competing risk factors (15).

For example, the surgeons had elected to perform a segmentectomy in 28% of cases, and a hilar node only lymph node dissection in 32% of patients. I would argue, that within these selected groups, the rate of nodal disease and recurrence were so low, and survival was so exceptional, precisely *because* the surgeons chose the right patients for each procedure, based upon a careful clinical and radiologic assessment of their tumors. Propensity-score matching can account for many factors, but it can never match groups for surgical judgment. It should also be noted that patients in the current study who underwent a "lesser" lymph node dissection (h-LND) still received an excellent oncologic operation with meticulous, anatomic dissection, and a higher number of lymph nodes resected (4.7 4.0 nodes) than in many US and European studies. Additionally, the authors routinely relied upon intraoperative frozen sections for the real-time, pathological assessment of lymph nodes to guide their choices, regarding the extent of the resection and lymphadenectomy. I therefore think that we need to be careful to ensure that the authors' statement, "extent of lymph nodal dissection was not associated with oncological outcome of clinical-stage I radiological part-solid lung adenocarcinoma" is not applied across the board to all tumors or to all patients.

Certainly, that philosophy should not be the mantra of all surgeons in an era in which too few patients are already undergoing comprehensive lymph node evaluation, particularly during sublobar resection (16). My concern is that surgeons will use this data to infer that lymph node dissection is not important at all for these early stage lung cancers. Clearly, that is not what an in depth look at the approach of the group from Juntendo University shows. Rather, we as thoracic surgeons should perform a detailed lymphadenectomy as part of lobar and sublobar resections, and insist that pathologists carefully examine these nodes. Our ability to optimally stage patients, and to obtain exquisite local and regional control, even with sublobar resection, is what will distinguish surgical from other competing methods of local therapy, such as stereotactic radiation therapy (SABR or SBRT) and radiofrequency ablation (RFA). A large balance of evidence now suggests that a more extensive lymphadenectomy is associated with improvements in survival following NSCLC resection, even for SLR (16-20). It remains undetermined whether this is strictly due to improvements in staging, or whether there is an actual oncological benefit due to the improved locoregional control limiting future recurrences. A provocative paper in *Science* earlier this year demonstrated that lymph node metastases themselves have the ability to generate systemic metastases, providing some evidence for the latter hypothesis (21).

Ultimately surgeons, just like medical oncologists, must recognize that a one-size-fits-all approach to lung cancer makes little sense. Advances in preoperative radiographic and molecular characterization, now allow experienced surgeons to select patients for targeted sublobar resection, either segmentectomy or wedge resection. This will continue to be the case no matter the results of the randomized trials JCOG0802 and CALGB 140503. Indeed, our ability to treat high risk patients safely, and compete favorably with local ablative techniques depends upon proper patient selection for sublobar resection. Certainly there are also tumors in which the expected rate of lymph node metastases are low, that a lymphadenectomy could probably be skipped. However, it should be pointed out that, more extended lymph node dissection has not been associated with increases in perioperative complications (22,23). Given that fact, surgeons should strongly consider performing at least a lobe-specific sampling of the hilar and mediastinal lymph node stations, even for the low-risk part solid tumors described by Hattori *et al.* It is of particular interest, that other ablative techniques that do not address the locoregional lymph nodes, such as stereotactic radiation, suffer from high rates of delayed locoregional and systemic recurrences. For example, in two trials of operable patients undergoing stereotactic radiation, despite excellent "in-field" control, 46% of patients recurred in RTOG 0618 at 4 years and 42% of patients recurred in JCOG 0403 at 5 years (24,25). Although this may be the result of under-staging prior to enrollment, one would expect recurrences

simply related to inadequate staging to occur earlier in the time course after stereotactic radiation. Rather, it may be that treatment failure at the primary site or that untreated micrometastatic disease in nearby lymph nodes facilitates a later systemic recurrence. Given the previous paper mentioned that demonstrated the ability of lymph node metastases themselves to systemically metastasize, I would argue that lymphadenectomy remains critical, to ensure excellent survival outcomes for patients with presumed early stage lung cancer (21). I am certain that Hattori and colleagues feel the same way. Indeed, their excellent results demonstrate the remarkable survival that can be achieved in patients undergoing a thoughtful, targeted surgical therapy for early stage lung cancer.

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Footnote

Conflicts of Interest: The author reports personal/spousal financial relationships with AstraZeneca, Merck, Pfizer, and PPD and is a Board member of the Lung Cancer Research Foundation.

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