Editorial

The more and the heavier may not always be an answer

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Non-small cell lung cancer (NSCLC), especially locally advanced NSCLC, is difficult to treat. As patients with locally advanced NSCLC present no evidence of systemic spread, cure is suggested as the treatment goal. However, treatment outcomes are often unsatisfactory. Furthermore, this stage includes heterogeneous combinations of disease, ranging from T4 (invasion to heart, great vessel, or vertebrae) disease to mediastinal nodal invasions (N2 or N3). However, there is no doubt that locally advanced NSCLC should be treated with curative intent, using both local and systemic modalities.

Then, how should we manage patients with locally-advanced NSCLC by means of systemic and local control? As noted above, no definitive answer currently exists. Whether to perform surgery or radiotherapy as the local modality and whether chemotherapy should precede local therapy remain debated. Moreover, locally advanced NSCLC is more difficult to treat than other cancers because the patient's functions are often impaired by the treatment. Therefore, we need to give special attention not only to short-term treatment-related toxicities but also to long-term systemic effects.

In cases where complete local control is unlikely to be achieved by surgery alone, such as resected locally advanced NSCLC or incompletely resected NSCLC, the optimal way to integrate chemotherapy and radiotherapy for adjuvant treatment remains unknown. Adjuvant chemotherapy has been shown to improve overall survival in several clinical trials (1). Postoperative radiotherapy (PORT) has also gained positive agreement for patients with pN2 disease or incomplete resection (2-4). However, although both therapies have been proven effective respectively, each treatment requires considerable time to deliver. Hence, it is difficult to deliver both treatments within an appropriate period after surgery. Therefore, ideal sequence of postoperative chemotherapy and RT remains controversial.

Postoperative concurrent chemoradiotherapy (CCRT) has been proposed as an alternative approach (5); however, two problems exist with this method. First, postoperative CCRT, after removal of the gross tumor, is associated with high toxicity. As such, the risk of adverse events may outweigh the potential benefits. Especially in patients with lung cancer, systemic performance is mostly affected by lung function. Therefore, treatment-related toxicities should be considered as the first priority. Even in early-stage lung cancer, the diffusion lung capacity for carbon monoxide (DLCO) and respiratory co-morbidities are associated with long-term prognosis (6,7). We should avoid treatments

that are likely to significantly impair patient performance. Second, the role of chemotherapy in CCRT is known as a radio-sensitizer rather than as a systemic controller (8). The use of dose-reduced chemotherapy, to obviate the excessive toxicity that is associated with full-dose chemotherapy or radiotherapy, could potentiate the local control effect without impacting the systemic control of systemically overt metastatic lesions.

In the February 2018 issue of the *Journal of Clinical Oncology*, Francis and coworkers (9) discussed this controversial issue, based on relatively recent practical experiences using the National Cancer Database, between 2006 and 2012. It is very difficult to carry out reliable prospective studies, which require patient recruitment and effective treatment qualities. However, considering that this study used a modern radiotherapeutic-technique, it would be reasonable to modify or maintain treatment strategies based on the results of this study. In patients with complete resected (R0) NSCLC and pN2 disease, results of the propensity matching analysis in this study revealed that the postoperative CCRT was ineffective and associated with worse survival outcomes. Meanwhile, for patients with positive resection margins (mainly R1 resection), there were no statistically significant differences between sequential chemotherapy followed by PORT and CCRT. CCRT is generally associated with higher therapeutic toxicity than individual treatment modalities. Although this study did not demonstrate the risk of CCRT, this therapy should not be applied unless there is a benefit. In other words, after potentially hazardous surgery which regarded as a potentially hazardous procedure, CCRT is considered inappropriate.

Then what is the preferred sequence of chemotherapy and PORT? Some groups suggesting that chemotherapy should be used first argue that systemic control should be the main treatment, because recurrence patterns are mostly systemic. Other groups suggesting radiotherapy should be used first argue that completeness of local control is critically associated with recurrence free survival, and local tumor regrowth eventually causes systemic metastasis. Unfortunately, no studies have provided a clear answer to this question so far. However, from recent findings from liquid biopsy, circulating tumor cells (CTC) and cell-free DNA (cfDNA) are expected to be the potential surrogate markers for treatment decisions (10-12). For example, if CTC or cfDNA are detected after surgery, we can assume that chemotherapy could be performed first. If not, radiotherapy would be the first choice, or no adjuvant treatment needs to be performed.

In patients with macroscopically positive resection margins, there is no convincing evidence that CCRT is more beneficial than sequential approaches. Re-operation and the completion of local control is most desirable in this setting; however, such procedures are almost impossible to accomplish in clinical practice. Although there is no definite answer, on the basis of personal experience from surgical treatments for stage IIIa (N2) disease (13,14), macroscopically positive surgical margins should be regarded as non-surgical, and CCRT is more appropriate, whenever possible. Considering that sufficient chemotherapy or radiotherapy doses cannot be delivered immediately after surgery, reckless surgery where complete resection is unlikely should be avoided.

This study could not establish firm treatment guidelines for locally advanced lung cancer. However, regardless of the direction and degree of improvement, real-world clinical experience is very important, and generation of a national data system has contributed greatly to this improvement. It would also be very useful if national data from the US, Europe, and Asia are globally compiled and analyzed together. Moreover, if we know recurrence dynamics and patterns, which represent treatment failure mechanisms, we will acquire deeper insight into the proper ways to overcome the limitations of current therapies.

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Footnote

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