Editorial

Sequencing postoperative radiotherapy and adjuvant chemotherapy in non-small cell lung cancer: unanswered questions on the not evidence-based approach

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Abstract: This editorial comments on the study by Lee *et al.* which reported on the use of postoperative radiotherapy (PORT) as first strategy after resection of stage IIIA-pN2 non-small cell lung cancer (NSCLC). After completion of PORT, 41% of patients received postoperative chemotherapy (POCT). The five-year overall survival (OS) was significantly higher in patients treated with PORT and POCT than in patients treated with PORT alone. Authors concluded that PORT used as first postoperative strategy does not compromise a benefit of POCT and its implementation should be further studied. We discuss the pros and cons of using PORT before POCT for stage IIIA-pN2 NSCLC. Some radiobiological data support earlier use of PORT, however, caution should be paid to not to unnecessarily delay or omit POCT because of its demonstrated survival benefit. Concurrent postoperative radio-chemotherapy could be an attractive approach, but we still have very limited clinical data on its use in this indication.

Keywords: Non-small cell lung cancer (NSCLC); postoperative radiotherapy (PORT); postoperative chemotherapy (POCT)

Submitted Apr 13, 2016. Accepted for publication Apr 21, 2016.
doi: 10.21037/jtd.2016.05.76
View this article at: http://dx.doi.org/10.21037/jtd.2016.05.76

Based on the results of the meta-analyses (1,2), postoperative chemotherapy (POCT) is a standard approach for patients with resected stage II–III non-small cell lung cancer (NSCLC). Confirmed survival benefit of POCT highlights the problem of up to 40–60% of loco-regional recurrence rate (1-3). Postoperative radiotherapy (PORT) could reduce the rate of loco-regional recurrence (3,4). However, a value of PORT for NSCLC is still an open question. According to the results of the meta-analysis, PORT decreased the overall survival (OS) at 2 years from 55% to 48% (P=0.001). This deleterious effect was the most pronounced in patients with a complete resection and no mediastinal involvement (pN0–N1), whereas for stage III patients neither detrimental nor beneficial effect on survival was found (4). The updates of this meta-analysis confirmed these results (5,6). Despite the lack of high quality evidence for the use of PORT, we can see its growing use in pN2 patients. Results of the PORT meta-analyses have been criticized due to the heterogeneity of included trials and the use of inadequate radiotherapy techniques and schedules. Modern series of PORT show promising results with very low toxicity (3,7-9). Population-based studies support the use of PORT also with adjuvant chemotherapy for pN2 patients, in contrast to pN0 and pN1 patients in whom PORT was associated with reduction of survival (10-12).

In the commented study, Lee *et al.* (13) retrospectively analyzed 105 patients with postoperative stage IIIA (pN2) NSCLC who received PORT as first treatment-strategy with or without subsequent POCT. Three-dimensional conformal radiotherapy started within four to six weeks

after surgical resection (44–45 Gy for a bronchial stump, involved mediastinal nodal stations, and its next draining stations and a boost up to 50.4–60 Gy for a bronchial stump and involved nodal stations). POCT (4–6 cycles of platinum-based chemotherapy administered 3 to 4 weeks after the completion of PORT) was given for 43 patients (41%). Thirty patients (48.4%) did not receive POCT because of comorbidities, 23 patients (37.1%) because of institutional policy, 8 patients (12.9%) because of refusal of treatment, and one patient (1.6%) because of old age. There were no significant differences in loco-regional and distant failure between the groups with and without POCT. The 5-year OS was significantly higher in the group with POCT than in group without POCT: 61.3% *vs.* 29.2%, respectively, P<0.001. There was no significant difference in the loco-regional recurrence free survival between the groups. The authors concluded that the PORT-first strategy after surgery for stage IIIA (pN2) NSCLC patients did not compromise the clinical outcomes, and that the OS benefit of POCT given after PORT was observed. Since the OS was superior to that obtained in the historical series in which PORT was applied after POCT (3,9,12), the authors suggested that the use of PORT before rather than after POCT may have contributed to this improvement. Such conclusions obviously have their limitations, also acknowledged by the authors. The main limitation of the presented study is its retrospective nature and—in consequence—an imbalance in the main prognostic factors between the presented groups. Patients in the POCT arm were younger, showed significantly better performance status and had lower comorbidity index, which could impact the obtained result. Homogenous treatment protocol was probably provided for all cases, but the total radiation dose actually administered in the POCT group was higher. PORT was probably interrupted in some no-POCT patients due to clinically important reasons. One may presume that the patients who died or progressed during PORT did not receive POCT, which actually has a well-documented impact on the patients' outcome, whereas PORT given in the first instance is still controversial. As a result of the listed limitations the selection bias can be observed, especially in the context of the low rate of patients receiving POCT (41% only). Additionally, the interpretation of the results of this study must be very careful, because of the small size of the analyzed groups. Finally, the short follow-up time with a median of 30 months (range, 3–123 months) is of note in the context of 5 years results presented in the article; the mature data of this study may differ from the presented one.

Weak evidence supporting PORT in NSCLC despite its quite common use in pN2 disease is a reason for most controversies surrounding the ways of PORT delivery, namely the schedule, target delineation and sequencing in relation to chemotherapy. The commented article reported the results of the use of PORT before POCT. As the literature on the use of PORT before POCT is scarce, findings from this study are of value as potentially hypothesis-generating. We did not identify any other studies directly evaluating the PORT-first strategy. It appears that the PORT-first strategy could be a reasonable option in R1 patients since the risk of local failure with microscopic positive resection margin is greater, so prompt local treatment may lead to improvement of results through preventing dissemination of microscopic disease. However, the PORT-supporting studies focused mostly on R0 patients. Another reason for PORT-first strategy seems to be the lower response rate to chemotherapy than to radiotherapy in terms of loco-regional control. Thus, delaying the effective treatment through favoring an inefficient one may lead to worse treatment results. The main reason against the PORT-first strategy is the fact that this is not the standard (which is POCT). Starting adjuvant treatment with radiotherapy may lead to delaying or even not performing POCT, due to radiotherapy toxicity. In studies supporting the use of PORT, this treatment was given after completion of chemotherapy (3,9). Also the current guidelines consistently recommend delivering PORT sequentially after completion of POCT, in order not to interfere with a well-established standard of care, which is adjuvant chemotherapy (14). The risk of metastatic disease after surgery remains dominant, and systemic recurrence is generally incurable, so the loco-regional control achieved with PORT can only translate into a survival benefit when distant micrometastatic disease is controlled by effective chemotherapy. On the other hand, to cure the patient, loco-regional control must be achieved. Thus, PORT and POCT are not competitors, but are complementary, so their integration may be critical and the main considerations should include their timing and sequencing.

Animal models suggest that removal of the primary tumor may accelerate the growth of metastases or residual tumors due to conversion of cancer cells in G0 phase into proliferation (15). As these kinetic changes have a rapid onset but appear to be transient (i.e., "stimulated" cells return to the non-proliferating population after few divisions), it provides a substantial theoretical rationale to initiate adjuvant therapy as soon as possible after surgery.

Cells in G0 phase are unresponsive to conventional chemotherapy and irradiation, because they are not proliferating, so the cellular processes targeted by most anticancer agent and ionizing radiation are not active. That short period of time when they enter cell cycle again, and become more vulnerable to the cytostatics and radiotherapy, should not be overlooked. However, there are no data to provide insight into the optimal sequence of adjuvant treatment methods: whether PORT is most effective given concurrently with, before, or after adjuvant chemotherapy. Lee *et al*. (13) hypothesized that the PORT-first strategy may be more effective in terms of loco-regional control without compromising OS, since the tumor burden in the mediastinum can be higher than that of systemic micrometastases. Indeed, microscopic spread of tumor throughout the mediastinal lymphatic network makes a curative "en bloc" resection unrealistic. Given the limited loco-regional effectiveness of chemotherapy, mediastinal irradiation is the only practical mean of treating the mediastinal lymph nodes. From a radiobiological standpoint, delaying the initiation of radiotherapy decreases the probability of eradicating a tumor as the quantitative relationship exists between probability of cure and the burden of clonogenic cells it contains. The amount of tumor cells depends on the tumor burden left after surgery and the number of divisions they underwent before start of radiotherapy. Moreover, there is clinical evidence, that after chemotherapy the median doubling time of lung cancer is shorter than that seen for untreated tumors, which suggests accelerated repopulation (16). It is also important to notice that the optimal time of initiating POCT for NSCLC is not established, and there are even some data that delayed time to adjuvant chemotherapy is not associated with inferior survival in NSCLC (17). On the other hand, N stage has never been proven prospectively to be associated with loco-regional relapse, and N2 disease—although used as a selection factor for the consideration of PORT—is rather related to the risk of distant recurrence (18). Preventing loco-regional relapse in patients who are more likely to develop metastatic disease would not be meaningful in terms of OS.

Breast cancer is an example of malignancy, in which an improvement in loco-regional control with post-mastectomy radiotherapy did not translate into a survival benefit until more effective systemic treatment became available (19). Delaying radiotherapy in order to give 12 weeks of chemotherapy does not compromise outcome, however, in the setting of positive or close margins a delay in initiating radiotherapy may be detrimental (20). Re-excision, which is the best solution in such breast cancer patients, is not applicable in case of close or positive margin in resected lung cancer. Thus starting PORT in close proximity to surgery may be appropriate in this scenario. Again, breast cancer provides an analogous model of benefit/risk balance between PORT and adjuvant chemotherapy. In early studies increased risk of cardiovascular death offset the benefit regarding cancer-specific survival yielding no OS gain from radiotherapy. With more modern radiotherapy techniques, post-mastectomy irradiation was found to improve OS (19). The same is probably true for NSCLC, as the therapeutic ratio for PORT may be improved with modern techniques.

A possible way of early postoperative delivery of PORT is to use the concurrent POCT and PORT. In a definitive treatment, the concurrent radio-chemotherapy has been proven to be superior to radiotherapy alone (21), as well as to sequential radio-chemotherapy (22). To the best of our knowledge, there was no comparison of postoperative concurrent radio-chemotherapy with postoperative sequential radio-chemotherapy. Keller *et al*. (23) compared concurrent postoperative radio-chemotherapy with PORT alone and showed no difference in survival between these two groups. Recurrence rate and the median time to recurrence were also similar in the two groups. The meta-analysis of six studies on 5.172 stage IIIA N2 NSCLC cases demonstrated that postoperative radio-chemotherapy had a greater OS benefit than POCT alone, but no significant difference in disease free survival (24). Among the included studies there was only one that evaluated the role of concurrent postoperative radio-chemotherapy (25). The results of this study showed that concurrent postoperative radio-chemotherapy increased both loco-regional and distant free survival rate compared with POCT alone, but not the OS rate. Treatment was relatively well tolerated: 13.6% of patients in the group of postoperative radio-chemotherapy suffered from grade 3 and 4 acute radiation esophagitis, there were similar and tolerable hematologic toxicities rates in both groups. It seems that concurrent postoperative radio-chemotherapy could be a possible (with respect to toxicity) and effective solution.

To conclude, a proper sequencing of PORT and POCT in patients after complete resection of stage IIIA-pN2 NSCLC is not established. Current recommendations that PORT should follow POCT (as in breast cancer), may be challenged by the findings from Lee *et al*. (13) study, that demonstrated an effective use of PORT as first postoperative strategy. Controlled studies dealing with

the problem of sequencing PORT and POCT in NSCLC patients are needed, even though the use of PORT in pN2 patients is still not a strongly evidence-based approach.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Wenyong Tan (Department of Oncology, Shenzhen People's Hospital, Shenzhen, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Lee HW, Noh OK, Oh YT, *et al*. Radiation Therapy-First Strategy After Surgery With or Without Adjuvant Chemotherapy in Stage IIIA-N2 Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2016;94:621-7.

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Cite this article as: Kepka L, Socha J, Rucinska M, Wasilewska-Tesluk E, Komosinska K. Sequencing postoperative radiotherapy and adjuvant chemotherapy in non-small cell lung cancer: unanswered questions on the not evidence-based approach. J Thorac Dis 2016;8(7):1381-1385. doi: 10.21037/jtd.2016.05.76

