Commentary

Optimal sequencing of adjuvant chemotherapy and radiation therapy in resected non-small cell lung cancer with pathological N2 disease

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Abstract: The individual role of adjuvant chemotherapy and radiation therapy in the setting of pathological N2 non-small cell lung cancer (NSCLC) has been extensively investigated in the clinical trial literature. However, high-level clinical trial information regarding the optimal sequencing of these two therapies is currently lacking in the medical literature. This commentary will explore issues regarding postoperative radiotherapy sequencing in the context of new published information in the medical literature.

Keywords: Non-small cell lung cancer (NSCLC); adjuvant; chemotherapy; radiation; sequencing

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An impressive clinical trial record exists in the investigation of the clinical benefits and risks related to the utilization of post-operative radiation therapy (PORT) in resected localized and locally-advanced non-small cell lung cancer (NSCLC). These trials generally demonstrated that local control can be improved with the application of PORT; however, the impact on overall survival was less certain. In response to this uncertainty, the PORT Meta-analysis Trialists Group published an individual patient meta-analysis on this important topic in 1998 (1). This report identified a statistically significant reduction in survival with the application of PORT to all nodal (N0–N2) groups. In the most recent update of the meta-analysis, PORT was associated with an 18% relative increase in the risk of death (i.e., hazard ratio: 1.18) (2).

The negative effect of PORT on survival was particularly pronounced in N0–N1 patient subgroup (1,2). In patients with N2 disease, there was no statistically significant reduction (or improvement) in survival, but a significant improvement in local recurrence rate (absolute 24%) was observed (1,2). Subsequent to the publication of this meta-analysis, utilization rate of PORT for resected NSCLC was substantially reduced. In a 2006 Surveillance, Epidemiology, and End Results (SEER) Program analysis, utilization of PORT for all nodal (N0, N1 and N2) declined by an absolute 4%, 32%, and 28% from 1992 (6 years before the PORT publication) to 2002 (4 years after the PORT publication) (3). It is important to note that the PORT meta-analysis has been criticized due to the use of older two-dimensional radiation techniques which may have led to additional toxicities no longer seen in a modern treatment population (4,5).

Recently, the American Society of Radiation Oncology (ASTRO) issued guidance for the indication and radiation treatment of PORT in resected NSCLC (6,7). This guideline document recommended against the routine utilization of PORT in completely resected (R0 resection) N0–1 NSCLC. However, the use of PORT in incompletely resected (i.e., R1: positive margin/microscopic residual cancer or R2: gross residual primary or nodal disease) for any N status patient was felt to be potentially appropriate to improve local control. In terms of R0 resected N2 disease, the guideline stated that the application of PORT in this patient population is reasonable in order to primarily improve local control. Specifically in relation of adjuvant chemotherapy, the guideline document recommended that PORT should be given sequentially (not concurrently) with

any chemotherapy as not to interfere with standard of care treatment. The use of adjuvant chemotherapy has been shown to be associated with a 5–15% absolute improvement in overall survival (8,9). Given the lack of proven survival benefit with PORT for N2 disease, the recommendation was structured this way out of concern regarding any potential toxicity associated with concurrent treatment that could lead to treatment breaks or chemotherapy de-intensification.

Recently, multiple publication have demonstrated that there may be a small but significant survival benefit with the application of PORT for completely resected N2 disease (10-15). In 2006, Lally *et al*. described a SEER analysis where an improvement of survival was demonstrated in the N2 patient subset with a hazard ratio of 0.855 (95% confidence interval: 0.762 to 0.959, P=0.0077) (10). This finding was confirmed in a secondary analysis of the Adjuvant Navelbine International Trialist Association (ANITA) trial in which the N2 subgroup of patients treated with adjuvant chemotherapy benefited from the addition of PORT (median survival improved to 47.4 months from 23.8 months) (11). A series of three recent National Cancer Database analyses (12-14) have all consistently shown survival benefits of adjuvant radiation for N2 NSCLC. Additionally, a fourth National Cancer Database analysis confirmed the survival benefits in N0–2 patients with incompletely resected disease (15). None of these papers specifically directly assessed the issue of sequencing of radiation treatment in terms of adjuvant chemotherapy.

Recently in the *International Journal of Radiation Oncology, Biology, and Physics*, Lee *et al*. presented an analysis entitled "Radiation Therapy-First Strategy After Surgery With or Without Adjuvant Chemotherapy in Stage IIIA-N2 Non-Small Cell Lung Cancer" (16). The objective of this manuscript was to investigate the issue of radiation sequencing as this institution has an institutional policy to deliver PORT prior to adjuvant chemotherapy. The authors argue that utilizing this sequencing approach may have clinical benefits if the overall tumor burden may be higher in the locoregional space rather than the systemic micrometastatic disease space. They hypothesized that this may improve locoregional control without significantly affecting overall survival.

This investigation retrospectively identified a total of 105 post-operative patients with stage IIIA (N2) NSCLC who received PORT first with (n=43, 41%) or without (n=62, 59%) subsequent post-operative adjuvant chemotherapy (POCT). Adjuvant radiotherapy with three dimension conformal radiotherapy techniques was delivered to a total dose of 50.4 to 60.0 Gy (at 1.8–2.0 Gy/day with potential of 66 Gy in margin positive cases). In terms of POCT, 4–6 cycles of platinum-based chemotherapy was initiated 3–4 weeks after completion of PORT in patients receiving such therapy. All patients were routinely followed according to a pre-existing schedule including chest X-rays, computed tomography and PET-CT.

In terms of the PORT prior to POCT and PORT alone groups, the authors described some differences in the two groups in terms of better performance status, higher forced expiratory volume in one second, and lower comorbidity index statistically favoring the PORT prior to POCT group. Additionally, the PORT prior to POCT was radiated to a higher mean dose (56.6 *vs*. 52.2 Gy, P<0.001). There were no significant differences in locoregional failure, distant metastases or both conjoint failures between the two study groups. However, the authors reported an improvement in 5-year survival favoring the PORT prior to POCT group (61.3% *vs*. 29.2%, P<0.001). In a multivariable analysis, the addition of POCT and lack of pneumonectomy were associated with improved survival.

The authors of this report did not directly test the hypothesis of a PORT first being either equivalent or superior to a PORT last treatment strategy. They did report on the 5-year survival of the PORT prior to POCT and did compare that to historical controls to indirectly conclude that this strategy may be appropriate and can lead to optimal outcomes. Unfortunately, such comparisons are hypothesis generating at best and should not change practice patterns unless confirmed ideally with a prospective randomized controlled trial. In particular, the favorable survival may in part be due to patient selection as disclosed by the authors in their comparative analysis of the PORT prior to POCT versus PORT alone cohorts. Another significant limitation of this work was the lack of descriptive toxicity, chemotherapy de-intensification/delay data to gauge any potential deleterious effects of the PORT first approach.

Overall this study should be considered a first step in the investigation of this question. Ideally prospective data should be acquired to investigate this sequencing question to either show equivalence (or superiority) of this approach in terms of important clinical outcomes such as survival, local control, and toxicity. The European Organization for Research and Treatment of Cancer (EORTC) Lung Adjuvant Radiotherapy Trial (Lung ART) trial is an ongoing randomized trial enrolling patients with completed resected N2 NSCLC assessing adjuvant PORT versus no PORT therapy. The use of POCT as well as sequence (pre PORT

or post PORT) will be a stratification variable for the clinical trial. Potentially, this trial may provide an important secondary analysis assessing this question of treatment sequencing and may be the basis of a future controlled trial if important clinical outcome differences are observed related to treatment sequence.

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Footnote

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