Editorial

The optimal sequencing of postoperative chemotherapy and radiation therapy in patients with locally advanced or incompletely resected non-small cell lung cancer

Michael J. Weyant

Division of Cardiothoracic Surgery, Department of Surgery, University of Colorado School of Medicine, Aurora, CO, USA

Correspondence to: Michael J. Weyant, MD, FACS. Professor of Surgery, Division of Cardiothoracic Surgery, Department of Surgery, University of Colorado School of Medicine, 12631 East 17th Avenue, MS C310, Aurora, CO 80045, USA. Email: michael.weyant@ucdenver.edu.

Provenance: This is an invited Editorial commissioned by the Section Editor Dr. Jie Dai (Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China).

Comment on: Francis S, Orton A, Stoddard G, *et al.* Sequencing of Postoperative Radiotherapy and Chemotherapy for Locally Advanced or Incompletely Resected Non-Small-Cell Lung Cancer. J Clin Oncol 2018;36:333-41.

Submitted Apr 03, 2018. Accepted for publication Apr 09, 2018.
doi: 10.21037/jtd.2018.04.82
View this article at: http://dx.doi.org/10.21037/jtd.2018.04.82

The National Comprehensive Cancer Network (NCCN) provide specific, evidence based guidelines for the treatment of non-small cell lung cancer (NSCLC) of any stage at presentation (1). Those patients who are suspected or proven to have N2 lymph node involvement are suggested to have either neoadjuvant chemotherapy with or without radiation therapy followed by surgery, or definitive chemoradiation therapy alone. Those patients who are suspected of having disease that will result in R1 or R2 resections (unresectable) are suggested to have combined chemoradiotherapy (1). These guidelines would imply that if discussions of adjuvant treatment of N2 disease are underway that the N2 disease was found incidentally after surgery and not found by preoperative mediastinal staging methods. Similarly, R1–2 resections are not usually a planned or desired result after a surgical attempt at cure of NSCLC. It is helpful to put these two distinct clinical entities in perspective of incidence and survival impact.

Although these recommendations appear clear cut, the real life recommendations are quite patient specific. For example, at a very recent tumor board discussion at our institution, medical oncologists and radiation oncologists continued to struggle with the decision of whether to give adjuvant radiotherapy and if so, in what timing of the two therapies. It is likely this controversy exists due to the lingering perception of older trials of postoperative radiation therapy (PORT) showing some downside to giving PORT (2). In these trials, the lack of benefit of PORT was felt to be due to competing cardiac and pulmonary toxicity from radiotherapy with high noncancer death rates (2). More recently, however, data has been published that suggests improved survival in stage IIIA (N2) patients treated with PORT and chemotherapy (3). Francis *et al.* performed a review of the National Cancer Database (NCDB) in an effort to determine whether there is a path of treatment that is superior and should be recommended as the sole standard of care (4).

This study, which was published in Dec. 2017, queries the NCDB and identifies 747 patients who are treated in the adjuvant setting who had been found to have N2 disease with R0 resections (cohort 1) after surgery, and 277 patients who had positive margins (R1–2) after resection regardless of nodal status (cohort 2). Each of these cohorts was stratified into groups of patients who had either combined adjuvant chemoradiotherapy (CRT) or sequential chemotherapy followed by radiation therapy (C-PORT). The main findings of the study suggested that patients who had completely resected tumors and N2 disease survived longer if the adjuvant therapy was sequential (C-PORT) instead of combined (CRT). The groups with R1–2 resections showed no benefit to the type of sequencing of therapy used.

The benefit of this study is that it helps to provide guidance regarding a specific clinical question. The authors mention the current controversy over whether CRT or

C-PORT is better due to the preference of CRT in the setting of unresectable disease (5) and suggest this should not be applied to the clinical scenarios illustrated in this study. It is worth noting that the clinical problem addressed in the study represents a small percentage of patients with nonmetastatic lung cancer. The authors note that only 1,458 patients had RO resections, surgery with lobectomy or pneumonectomy, pathologic N2 disease, postoperative chemotherapy, and postoperative radiotherapy. Only half of these patients had standard dose radiation therapy. This represents only 0.2% of patients in the database having nonmetastatic disease. The number is smaller still if the group with standard radiation dosing is separated out. These small numbers are likely a reflection of the preference to treat patients with locally advanced disease with neoadjuvant therapy. Defranchi *et al.* report the rate of incidentally found N2 disease to be 6% in clinical T1 lesions and the overall rate of incidentally found N2 disease has been reported to range from 6–18% (6,7).

The two cohorts studied here are distinctly different and warrant separate discussion. The patients who had an R0 resection and subsequently got adjuvant treatment because pathologic N2 disease is found is a unique group. To be placed in this category, patient would have to have had (I) a negative PET scan in the mediastinum; (II) negative invasive mediastinal staging efforts; or (III) surgical resection without consideration of staging of any kind. Scenario three is the least likely and given scenarios 1 and 2 are most likely, the burden of N2 disease is likely to be smaller. It would have been interesting to know which patients had any preoperative invasive mediastinal staging such as endobronchial ultrasound or mediastinoscopy.

The authors note that in cohort two, most patients had microscopically positive margins rather than residual gross tumor. There was a nonstatistical improvement in the C-PORT arm that might have been due to small numbers. Given the lack of superiority of either treatment paradigm the authors postulate that it may be due to a diminishing return due to the potential toxicity of the therapy. The overall reported rate of positive margins after resection is 4.7% and has a clear negative impact on survival (8).

Importantly, it is helpful to discuss some of the shortcomings of the study in the context of limitations of using the NCDB as a platform to answer specific therapeutic questions such as proposed by Francis *et al.* One result mentioned in the manuscript is that patients in cohort 1 (IIIA, N2) with higher levels of comorbidities were more likely to receive combined chemoradiotherapy and not sequential chemoradiotherapy despite the thought that CRT is more toxic and patients treated with CRT demonstrated worse overall survival. Although this data suggest superiority of a particular treatment arm we may not be seeing the entire picture. For example the NCDB only references comorbidities in three groups—0, 1 or ≥2 (9). Many potentially important health-associated factors are not captured by the NCDB including body mass index, smoking status, or performance status, some of which may determine the success of these particular treatment groups. Additionally, it is difficult to truly know which patients received concurrent or sequential treatment because the NCDB only records a start date for chemotherapy but not an end date or number of cycles (9).

Overall, the study by Francis *et al.* has provided valuable insight into the choices that are made regarding adjuvant treatment of lung cancer patients in very specific groups. Regardless of the limitations of studies generated from the NCDB, this publication provides enough data to suggest that a prospective randomized trial addressing this issue will be of clinical value.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology. NCCN Evudence blocks: Non-small cell lung cancer, version 9. 2017. Available online: https://www.nccn.org
2. PORT Meta-Analysis Trialists Group: Post- operative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. Lancet 1998;352:257-63.
3. Robinson CG, Patel AP, Bradley JD, et al. Postoperative radiotherapy for pathologic N2 non-small-cell lung cancer treated with adjuvant chemotherapy: a review of the National Cancer Data Base. J Clin Oncol 2015;33:870-6.
4. Francis S, Orton A, Stoddard G, et al. Sequencing of Postoperative Radiotherapy and Chemotherapy for Locally Advanced or Incompletely Resected Non-Small-

Cell Lung Cancer. J Clin Oncol 2018;36:333-41.
5. Aupérin A, Le Péchoux C, Rolland E, et al. Meta–analysis of concomitant vs. sequential radiochemotherapy in locally advanced non-small cell lung cancer. J Clin Oncol 2010;28:2181-90.
6. Defranchi SA, Cassivi SD, Nichols FC, et al. N2 disease in T1 non-small cell lung cancer. Ann Thorac Surg 2009;88:924-8.
7. Lee DH, Kim JB, Keum DY, et al. Long term survival of patients with unsuspected n2 disease in non-small cell lung cancer. Korean J Thorac Cardiovasc Surg 2013;46:49-55.
8. Osarogiagbon RU, Lin CC, Smeltzer MP, et al. Prevalence, Prognostic Implications, and Survival Modulators of Incompletely Resected Non–Small Cell Lung Cancer in the U.S. National Cancer Data Base. J Thorac Oncol 2016;11:e5-16.
9. Boffa DJ, Rosen JE, Mallin K, et al. Using the National Cancer Database for Outcomes Research: A Review. JAMA Oncol 2017;3:1722-8.

Cite this article as: Weyant MJ. The optimal sequencing of postoperative chemotherapy and radiation therapy in patients with locally advanced or incompletely resected non-small cell lung cancer. J Thorac Dis 2018;10(Suppl 17):S1971-S1973. doi: 10.21037/jtd.2018.04.82

