Letter to the Editor

Adjuvant therapy for resected pN2 non-small cell lung cancer: sequence is not all that matters

Kristine E. Kokeny, Samual Francis, Randa Tao, Ying J. Hitchcock

Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

Correspondence to: Kristine E. Kokeny, MD. Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA. Email: Kristine.Kokeny@hci.utah.edu.

Provenance: This is an invited article commissioned by the Section Editor Mong-Wei Lin (Division of Thoracic Surgery, Department of Surgery, National Taiwan University Hospital and Taiwan University College of Medicine, Taipei).

Response to: Zhao ZR, Ng CS. Tri-modality treatment in N2 stage IIIa non-small cell lung cancer: proper sequence remains unknown. J Thorac Dis 2018;10:S1096-8.

Submitted May 07, 2018. Accepted for publication May 17, 2018.

doi: 10.21037/jtd.2018.05.152

View this article at: http://dx.doi.org/10.21037/jtd.2018.05.152

We appreciate the comments from Zhao and Ng (1) regarding our recent National Cancer Database (NCDB) study comparing survival outcomes after postoperative adjuvant concurrent chemoradiotherapy (CRT) versus sequential chemotherapy followed by postoperative radiotherapy (C→PORT) for locally advanced or incompletely resected non-small cell lung cancer (NSCLC). Patients with pN2 locally advanced NSCLC (LA-NSCLC) fall within two distinct groups; those with ipsilateral mediastinal lymph node involvement recognized at initial radiologic and invasive staging, and those found after thoracotomy to have pN2 disease. When pN2 disease is found at initial staging, therapeutic approaches vary; accepted treatment options include preoperative chemotherapy or preoperative CRT for non-bulky (<3 cm) mediastinal nodal disease. Definitive CRT is also an option based on a phase III randomized trial that showed adding surgery does not improve overall survival (OS) (2).

For completely resected LA-NSCLC and pN2 disease, as Zhao and Ng note, PORT remains controversial. They cite the PORT Meta-analysis Trialists Group study published in 1998 (3) showing PORT *decreased* OS for early stage completely resected NSCLC. This decrement in OS was statistically significant for patients with stage I and II disease. For pN2 disease, survival was slightly better with PORT but was not statistically significant. Findings were similar on updated reports that included two additional trials and updated statistical analyses (4). Critics have cited various flaws in the 1998 meta-analysis, many not addressed in the updates. For example, patients were treated many decades ago without CT-based treatment planning and with outdated techniques including large fraction sizes, total dose, and treatment fields. Many had N0 disease. In response, several studies have found PORT in the modern era is associated with improved OS for pN2 disease, though these studies are limited by their retrospective nature (5-7).

It is hoped that the Phase III randomized Lung Adjuvant Radiotherapy Trial (LungART) will answer the question whether PORT, using modern conventionally fractionated 3D conformal radiotherapy, is beneficial in completely resected pN2 LA-NSCLC. This trial has many strengths. It utilizes contouring guidelines to ensure coverage of nodal regions at risk based on primary tumor location. A validation study (8) showed that application of these guidelines minimized inter-clinician target volume variation and improved consistency of normal tissue dose-volume histogram profiles. Radiation dose to the heart was an important predictor of survival in NRG Oncology clinical trial RTOG 0617. It is notable that the LungART Trial requires heart V35 <30%, in keeping with tighter cardiac dose constraints now in use in ongoing trials of concurrent CRT for inoperable LA-NSCLC (9), and in contrast to lenient heart constraints (V60 <33%, V45 <66%, and V40 <100%) used historically. In addition to the primary outcome of disease-free survival, secondary outcomes in the LungART trial include OS, failure patterns, and

cardiopulmonary toxicity. Yearly echocardiogram and pulmonary function tests are required to determine if treatment-related toxicity contributes to intercurrent death in patients receiving PORT.

Since all patients in our NCDB analysis received radiation, our study did not help answer the important question whether PORT affects survival for patients undergoing surgical resection for NSCLC. However, until results of LungART are available, it is reasonable to consider PORT for completely resected pN2 NSCLC, given the high risk of both local and distant failure. For resected stage II and III NSCLC, adjuvant chemotherapy has been shown in multiple randomized trials to improve OS (7,10) and is considered standard of care. There are no randomized trials comparing postoperative CRT to C→PORT for completely resected pN2 NSCLC, or for R1 or R2 resection regardless of nodal status. When PORT is given for completely resected pN2 NSCLC, our study showed better survival when radiation is given sequentially after postoperative chemotherapy. The reason for this is uncertain, but may be due to increased normal tissue toxicity with CRT, or that increased side effects of CRT interfere with delivery of chemotherapy. For completely resected pN2 disease, we included only patients receiving radiation doses of 45–54 Gray (Gy) in conventional 1.8 or 2.0 Gy fractionation. It was not possible to control for other radiation quality factors such as target definition, field size, or normal tissue doses. In the NCDB, prognostic factors such as lymph node extracapsular extension are not available, nor are details such as extent of mediastinal surgery. In addition, cause of death is not specified, so it is not possible to determine if the worse OS in the CRT group was due to increased intercurrent death or higher lung cancer mortality.

Despite these limitations, after propensity score analysis to account for imbalances in comorbidities, patient demographics, and tumor characteristics between treatment groups, C→PORT still showed statistically better OS compared to CRT in completely resected pN2 NSCLC. After propensity score matching in patients undergoing R1 or R2 resection, there was no survival difference between treatment groups. There was a trend toward better OS with C→PORT, though this was not statistically significant and should be viewed with caution given the small number of patients.

Our study did not address the role of PORT in patients with proven N2 disease on initial staging evaluation who receive neoadjuvant chemotherapy. Whether these patients benefit from PORT, or whether delivery of PORT should depend on the pathologic response to neoadjuvant chemotherapy is uncertain. It is also unclear how immunotherapy and targeted agents for patients with genetic alterations may change the landscape of adjuvant therapy in resected LA-NSCLC. Targeted agents and immunotherapy have led to significant improvements in progression-free and OS in patients with metastatic and unresectable LA-NSCLC. Ongoing trials are evaluating these agents in the management of patients with earlier stage disease. If, or how, these drugs change patterns of failure in resected LA-NSCLC remains to be seen. If the effect is to decrease systemic relapse, then the impact of local failure and the importance of local control and role of PORT could increase. In the meantime, it is imperative to show in a randomized trial that PORT can be delivered safely and that the toxicity of treatment does not outweigh the benefit.

Acknowledgements

The authors would like to thank Michelle Denney for her assistance with editing and formatting.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Zhao ZR, Ng CS. Tri-modality treatment in N2 stage IIIa non-small cell lung cancer: proper sequence remains unknown. J Thorac Dis 2018;10:S1096-8.
2. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-86.
3. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. Lancet 1998;352:257-63.
4. Burdett S, Rydzewska L, Tierney J, et al. Postoperative radiotherapy for non-small cell lung cancer. Cochrane Database Syst Rev 2016;10:CD002142.
5. Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results

database. J Clin Oncol 2006;24:2998-3006.
6. 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.
7. Douillard JY, Rosell R, De Lena M, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys 2008;72:695-701.
8. Spoelstra FO, Senan S, Le Péchoux C, et al. Variations in target volume definition for postoperative radiotherapy in stage III non-small-cell lung cancer: analysis of an international contouring study. Int J Radiat Oncol Biol Phys 2010;76:1106-13.
9. Liao Z, Bradley J, Choi N et al. RTOG 1308: Phase III randomized trial comparing overall survival after photon versus proton chemotherapy for inoperable stage II-IIIB NSCLC. Available online: https://www.nrgoncology.org/Clinical-Trials/Protocol-Table
10. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-60.

Cite this article as: Kokeny KE, Francis S, Tao R, Hitchcock YJ. Adjuvant therapy for resected pN2 non-small cell lung cancer: sequence is not all that matters. J Thorac Dis 2018;10(Suppl 17):S2097-S2099. doi: 10.21037/jtd.2018.05.152

