Editorial

Optimal sequencing of postoperative radiotherapy and chemotherapy in IIIA-N2 non-small cell lung cancer

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Lee *et al.* questioned the optimal sequencing of postoperative radiotherapy (PORT) and postoperative chemotherapy (POCT) after surgery for patients with IIIA-N2 non-small cell lung cancer (NSCLC) which was left untested in a prospective randomized setting (1); and performed the PORT-first strategy with an institutional multidisciplinary consensus, based on their hypothesis that the PORT-first strategy possibly being more effective in locoregional control than the PORT after POCT without compromising proven overall survival benefit of POCT. Their study is a documentation of retrospective experience revealing a PORT-first strategy with POCT in eligible (43/105) and without POCT in medically (30/105) or protocolly (23/105) ineligible and refusing (8/105) patients. Lee *et al.* pointed out that their overall survival results of 40.2% was comparable with the literature (2,3) and their survival results of 61.3% in the patients with POCT was superior than previous series (2-5). Lee *et al.* deserves appreciation for drawing attention to the sequencing of adjuvant treatment in IIIA-N2 NSCLC to claim the possible benefit of PORT-first strategy.

Even after a radical resection, a high locoregional recurrence almost up to 40% was reported after adjuvant chemotherapy (4,6-9), and the common decision such as The American College of Radiology in their multidisciplinary Appropriateness Criteria was to encourage PORT for N2 NSCLC patients to improve locoregional control (10). One of the concerns in retrospective series presenting PORT such as in this manuscript is the variability of PORT target volume definition, especially in a wide range of years treated by different physicians, such as documented by different cohorts (11,12). The objective evaluation of PORT reveals a significant survival benefit for N2 disease independent from chemotherapy, while a local regional control assistance in patients with N1 disease who do not receive chemotherapy (4,13-17). It would not be wrong to note the major problem in all older trials with deaths due to radiotherapy technical weaknesses which avoided local regional control effect turning out into a survival benefit (15). The phase 3 trial of "The Lung Adjuvant Radiotherapy (Lung ART)" enrolling N2 disease into PORT with modern and standardized techniques is expected to shed light on the gray zone in a prospective manner (12,18,19).

The role of PORT seems to traverse a long way from Lung Cancer Study Group trial in 1980 revealing important decrease in local recurrence from 41% to 3% without survival benefit in 5 years (13); to a warning to withhold PORT by Groupe d'Etude et de Traitement des Cancers Bronchiques based on high numbers of death following PORT (31% *vs.* 8%) (15). Trodella *et al.* on the other side randomized stage I NSCLC patients to receive PORT or not and concluded a significant disease free benefit with a trend for survival benefit (17). The subgroup analysis of ANITA, trial investigating the benefit of adjuvant vinorelbine by Douillard *et al.*, highlighted the significant survival benefit of PORT for N2 disease independent from chemotherapy in addition to survival benefit for N1 who did not receive chemotherapy (4). Besides, SEER data outlined a major survival gain for N2 patients with PORT (20). A recent meta-analysis, in stage IIIA-N2 NSCLC patients, acknowledged that modern PORT could improve the

5-year OS by 13% (21). A 2015 analysis of the National Cancer Data Base documented that PORT increased survival in pN2 patients (5). It is also evident that modern PORT claims additional survival advantage despite adjuvant chemotherapy (22).

PORT has also been discussed regarding the cohort who is gaining the benefit most; Matsuguma *et al.* claimed PORT to serve more in case of more than single station mediastinal nodal involvement (23), Saji *et al.* pointed out the poor prognostic group with less than ten nodes dissected and four or more nodes positive (24). SEER data could also documented the major improvement of survival in N2 group in addition to more than 50% involvement of nodes dissected (25). Lopez Guerra *et al.* analyzed retrospective MD Anderson Cancer Center series of 1,402 stage I–III (N0–N1) NSCLC patients who did not receive PORT to define local regional risk factors and documented 9% local regional recurrence which provoked decrement in survival (26); where multivariate analysis pointed out the surgical procedure (single/multiple wedge + segmentectomy × lobectomy + bilobectomy + pneumonectomy), tumor size larger than 2.7 cm and visceral pleura invasion to be independent risk factors for local recurrence; N1, visceral pleura invasion, and lymphovascular invasion (LVI) to be independent risk factors for regional recurrence (26). As there is a common consensus for PORT in treating close/positive surgical margins or N2 nodal involvement, multidisciplinary individualized decision for PORT is required based on number and station of N1 involvement, LVI, visceral pleura invasion and extracapsular invasion (26,27). Hui *et al.* recently emphasized a subgroup of proper candidates among resected IIIA-N2 NSCLC population in whom PORT significantly improved the OS as the ones having three or more of the five factors of SI (smoking index: number of cigarettes smoked per day × number of cigarette-years) ≤400, cN2, pT3, SCC, and ≥4 positive nodes (28). Details of the cohort by Lee *et al.* needs to be analyzed for the percent of the patients who were expected to get benefit most.

There are points to be extracted from their cohort to enlighten the comparison. The ratio of patients staged with PET-CT before surgery would be helpful hint to understand the cohort treated; besides the follow up of the patients treated in this cohort seems a little loose to be able to capture locoregional and systemic failure with simple chest radiography or chest CT or optional annual PET-CT. As the types of surgical resection were detailed as lobectomy & bilobectomy or pneumonectomy in their patients, quantification of regional lymph node involvement have not been detailed in this paper to reveal the patients' risk load. As the authors mentioned that no routine preoperative pathological evaluation for mediastinal disease performed and surgical resection decision was based on clinically N0–1 or single station minimal N2 disease, surgical data whether the dissection was formal or selective and postoperative data for the number of dissected nodes, positive N1 nodes/station and positive N2 nodes/stations were lacking in the manuscript. Besides, it would be great to know the related pathological details of the cohort to reveal the accurate R0 complete resection rates in both treatments (29), not only microscopically confirmed free resection margins, but also a systematic nodal dissection and the ratio of extracapsular tumor extension in nodes removed. All the patients except two were defined as clear surgical margins and though there was an enormous difference (2 patients with positive margins, one on each arm; and 101 negative margin patients, 42 on PORT-first plus POCT and 61 PORT alone), the authors analyzed the resection status both univariately and multivariately, instead of exclusing these two patients.

As duration between the surgery and initiation date of POCT seemed to impact survival in colorectal and breast cancer patients, one of the most important questions about timing of PORT is whether postponing POCT might affect survival. In other tumor sites such as head and neck or breast cancer, the delay to initiate PORT has been presented to have a negative impact on outcome (30-33), while the data for lung cancer for this correlation is not reported much (34,35). A recent Canadian data documented 1,032 cases treated with POCT with a median time to adjuvant chemotherapy (TTAC) of 8 weeks where 35% of the cohort received POCT more than 10 weeks after surgery. Booth *et al.* have appreciated no association between TTAC and overall survival (OR =1.00, 95% CI =0.99–1.00) (36). In the lack of prospective data to clarify the TTAC, data by Lee *et al.* could also be defined as another cohort, though there is not a direct comparison, to point out the mild delay for POCT might not cause any sacrifice in overall survival.

The histology might have an influence on locoregional failure as adenocarcinoma and squamous cell carcinoma, due to the fact that squamous cell was pointed out to be a poor prognostic factor for survival (37); however the prognostic significance of the histology is yet to be defined in fully resected pN2 NSCLC (2). As the histology seemed to be evenly distributed here for both PORT & POCT and POCT alone groups, histology might not affect the

outcome in this cohort.

As a summary, optimal sequencing of PORT and POCT after surgery for patients with IIIA-N2 NSCLC is a candidate topic to be discussed and studied prospectively, however for now, PORT-first strategy sounds to be feasible and triggering related research where Lee *et al.* provided a first-hand retrospective valuable information to initiate the discussion.

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Footnote

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References

1. 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.
2. Dai H, Hui Z, Ji W, et al. Postoperative radiotherapy for resected pathological stage IIIA-N2 non-small cell lung cancer: a retrospective study of 221 cases from a single institution. Oncologist 2011;16:641-50.
3. Zou B, Xu Y, Li T, et al. A multicenter retrospective analysis of survival outcome following postoperative chemoradiotherapy in non-small-cell lung cancer patients with N2 nodal disease. Int J Radiat Oncol Biol Phys 2010;77:321-8.
4. 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.
5. Mikell JL, Gillespie TW, Hall WA, et al. Postoperative radiotherapy is associated with better survival in non-small cell lung cancer with involved N2 lymph nodes: results of an analysis of the National Cancer Data Base. J Thorac Oncol 2015;10:462-71.
6. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589-97.
7. 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.
8. NSCLC Meta-analyses Collaborative Group, Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-77.
9. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-27.
10. Gopal RS, Dubey S, Rosenzweig KE, et al. ACR Appropriateness Criteria® on Induction and Adjuvant Therapy for Stage N2 Non-Small-Cell Lung Cancer: expert panel on radiation oncology-lung. Int J Radiat Oncol Biol Phys 2010;78:969-74.
11. Uno T, Sumi M, Kihara A, et al. Postoperative radiotherapy for non-small-cell lung cancer: results of the 1999-2001 patterns of care study nationwide process survey in Japan. Lung Cancer 2007;56:357-62.
12. 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.
13. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. The Lung Cancer Study Group. N Engl J Med 1986;315:1377-81.
14. Mayer R, Smolle-Juettner FM, Szolar D, et al. Postoperative radiotherapy in radically resected non-small cell lung cancer. Chest 1997;112:954-9.
15. Dautzenberg B, Arriagada R, Chammard AB, et al. A controlled study of postoperative radiotherapy for patients with completely resected nonsmall cell lung carcinoma. Groupe d'Etude et de Traitement des Cancers

Bronchiques. Cancer 1999;86:265-73.
16. Feng QF, Wang M, Wang LJ, et al. A study of postoperative radiotherapy in patients with non-small-cell lung cancer: a randomized trial. Int J Radiat Oncol Biol Phys 2000;47:925-9.
17. Trodella L, Granone P, Valente S, et al. Adjuvant radiotherapy in non-small cell lung cancer with pathological stage I: definitive results of a phase III randomized trial. Radiother Oncol 2002;62:11-9.
18. Le Péchoux C, Dunant A, Pignon JP, et al. Need for a new trial to evaluate adjuvant postoperative radiotherapy in non-small-cell lung cancer patients with N2 mediastinal involvement. J Clin Oncol 2007;25:e10-1.
19. Le Péchoux C. Role of postoperative radiotherapy in resected non-small cell lung cancer: a reassessment based on new data. Oncologist 2011;16:672-81.
20. 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.
21. Billiet C, Decaluwé H, Peeters S, et al. Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: a meta-analysis. Radiother Oncol 2014;110:3-8.
22. 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.
23. Matsuguma H, Nakahara R, Ishikawa Y, et al. Postoperative radiotherapy for patients with completely resected pathological stage IIIA-N2 non-small cell lung cancer: focusing on an effect of the number of mediastinal lymph node stations involved. Interact Cardiovasc Thorac Surg 2008;7:573-7.
24. Saji H, Tsuboi M, Yoshida K, et al. Prognostic impact of number of resected and involved lymph nodes at complete resection on survival in non-small cell lung cancer. J Thorac Oncol 2011;6:1865-71.
25. Urban D, Bar J, Solomon B, et al. Lymph node ratio may predict the benefit of postoperative radiotherapy in non-small-cell lung cancer. J Thorac Oncol 2013;8:940-6.
26. Lopez Guerra JL, Gomez DR, Lin SH, et al. Risk factors for local and regional recurrence in patients with resected N0-N1 non-small-cell lung cancer, with implications for patient selection for adjuvant radiation therapy. Ann Oncol 2013;24:67-74.
27. Gomez DR, Komaki R. Postoperative radiation therapy for non-small cell lung cancer and thymic malignancies. Cancers (Basel) 2012;4:307-22.
28. Hui Z, Dai H, Liang J, et al. Selection of proper candidates with resected pathological stage IIIA-N2 non-small cell lung cancer for postoperative radiotherapy. Thorac Cancer 2015;6:346-53.
29. Rami-Porta R, Wittekind C, Goldstraw P, et al. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005;49:25-33.
30. Huang J, Barbera L, Brouwers M, et al. Does delay in starting treatment affect the outcomes of radiotherapy? A systematic review. J Clin Oncol 2003;21:555-63.
31. Bütof R, Baumann M. Time in radiation oncology - keep it short! Radiother Oncol 2013;106:271-5.
32. Chen Z, King W, Pearcey R, et al. The relationship between waiting time for radiotherapy and clinical outcomes: a systematic review of the literature. Radiother Oncol 2008;87:3-16.
33. Froud PJ, Mates D, Jackson JS, et al. Effect of time interval between breast-conserving surgery and radiation therapy on ipsilateral breast recurrence. Int J Radiat Oncol Biol Phys 2000;46:363-72.
34. Bütof R, Kirchner K, Appold S, et al. Potential clinical predictors of outcome after postoperative radiotherapy of non-small cell lung cancer. Strahlenther Onkol 2014;190:263-9.
35. Würschmidt F, Bünemann H, Ehnert M, et al. Is the time interval between surgery and radiotherapy important in operable nonsmall cell lung cancer? A retrospective analysis of 340 cases. Int J Radiat Oncol Biol Phys 1997;39:553-9.
36. Booth CM, Shepherd FA, Peng Y, et al. Time to adjuvant chemotherapy and survival in non-small cell lung cancer: a population-based study. Cancer 2013;119:1243-50.
37. Asamura H, Goya T, Koshiishi Y, et al. A Japanese Lung Cancer Registry study: prognosis of 13,010 resected lung cancers. J Thorac Oncol 2008;3:46-52.

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