Editorial

Post-operative radiation therapy in locally advanced non-small cell lung cancer and the impact of sequential versus concurrent chemotherapy

Mark R. Waddle[1], Stephen Ko[1], Margaret M. Johnson[2], Yanyan Lou[3], Robert C. Miller[1], Anna C. Harrell[1], Daniel M. Trifiletti[1]

[1]Department of Radiation Oncology, [2]Division of Pulmonary Medicine, [3]Department of Hematology and Oncology, Mayo Clinic, Jacksonville, Florida, USA

Correspondence to: Daniel M. Trifiletti, MD. Department of Radiation Oncology, Mayo Clinic, 4500 San Pablo Road South, Jacksonville, FL 32224, USA. Email: trifiletti.daniel@mayo.edu.

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Background

Lung cancer is the second most common cancer and the leading cause of death from cancer in the United States (1). Despite the adoption of lung cancer screening, most patients present with locally advanced or advanced disease which is associated with poor survival (1). In an attempt to improve survival multimodality therapy including surgery, chemotherapy, and/or radiation therapy is commonly utilized in locally advanced non-small cell lung cancer (NSCLC). For patients who are surgical candidates and have T1–3 disease (tumors ≤7 cm that do not invade the mediastinum, diaphragm, heart, great vessels, carina, trachea, esophagus, recurrent laryngeal nerve, or spine) and have only ipsilateral pulmonary or hilar nodes (N1) the optimal treatment is surgery followed by chemotherapy (2). However, patients found to have pathologically involved ipsilateral mediastinal lymph nodes (pN2) at the time of surgery, or have microscopically (R1) or grossly (R2) positive margins, have unacceptably high rates of local-regional recurrence at 40–60% (3). Although the optimal adjuvant treatment for these patients is uncertain, post-operative radiation therapy (PORT) with either concurrent or sequentially chemotherapy is typically recommended.

Evidence for the use of PORT in resectable locally advanced NSCLC

Several historic studies demonstrated improved local control and a trend towards improved disease free survival in patients with pN2 disease who receive PORT following resection of NSCLC, but no statistically significant survival improvement was found (4-6). In fact, a large meta-analysis of 2,128 patients from 9 randomized trials found that PORT was detrimental to survival in patients with pN0 and pN1 disease, but did trend towards improved survival in those with pN2 disease (7). Further, a large database study of the Surveillance, Epidemiology, and End Results (SEER) database showed similar findings in a subset of 7,456 patients treated from 1988–2002. In this study, Lally *et al.* showed that PORT had no impact on survival in the overall group of patients, but, as opposed to the PORT meta-analysis, found that patients with pN2 disease receiving PORT had a statistically significant improved survival. In this cohort, PORT also was associated with negative impact on survival for patients with pN0–pN1 disease (8).

Because of persistent uncertainty surrounding the optimal adjuvant treatment of NSCLC, the Adjuvant Navelbine International Trialist Association (ANITA)

trial, an open label phase III study, was initiated that randomized stage I–IIIA patients to receive either cisplatin and vinorelbine versus observation after surgery (9). PORT was then recommended in a sequential manner for patients with pathologic node positive disease but this was neither randomized, nor mandatory. This study again confirmed previous findings that overall, PORT resulted in a shorter median survival and a worse 5-year survival when combined with chemotherapy versus chemotherapy alone. However, on subgroup analysis for patients with pN2 disease, the findings were the opposite: PORT in addition to chemotherapy improved median survival to 47.4 *vs.* 23.8 months with chemotherapy alone and improved 5-year survival to 47.4% *vs.* 34% with chemotherapy alone. These findings were both highly statistically significant and clinically meaningful.

Despite the breadth of data showing impaired survival in pN0 and pN1 and marginal benefit in pN2 resected NSCLC, controversy exists over the results of these trials due to the outdated nature of the radiation therapy techniques. In the large meta-analysis published by the PORT meta-analysis group discussed above, 7 of the 9 trials delivered radiation via now outdated Cobalt-60 equipment with conventional techniques lacking CT scan based planning which has been shown to increase morbidity, and may have resulted in reduced tumor control. Further, although treatment was given via high-energy linear accelerator in ANITA, the majority of treatment was given before the era of highly conformal intensity modulated radiation therapy (IMRT) which greatly reduces the toxicity of radiation therapy in lung cancer (10,11).

More recent investigations utilizing modern radiation therapy techniques for PORT have shown more favorable results. A recent randomized phase III study of patients with pN2 NSCLC evaluated treatment with either adjuvant chemotherapy alone versus concurrent chemotherapy followed by PORT (POCRT) (12). Despite slow accrual and a limited sample size of 140 patients, this study demonstrated improved local and regional control and improved distant disease free survival with POCRT. POCRT was also associated with a higher median survival (40 *vs.* 28 months) and although not statistically significant, the hazard ratio for death in the POCRT of 0.69 trended favorably (P=0.073) (12).

Modern database studies have shown similarly favorable findings with the addition of PORT, presumably from the use of contemporary radiation techniques. A study by Wang *et al.* utilized the National Cancer Database (NCDB) to evaluate survival in patients treated with PORT for positive margins after lobectomy or pneumonectomy for stage II or III NSCLC. PORT was associated with improved overall survival for all patients with pN0–pN2 disease, with a hazard ratio of 0.80, and demonstrates that positive margins are a strong indication for PORT (13). Additionally, an updated meta-analysis published in 2018 for patients with resectable NSCLC and pN2 disease from 8 randomized controlled trials and 8 retrospective series published from 1996–2015 found that with modern techniques, PORT resulted in significantly improved local control and survival. Overall, the hazard ratio of PORT was 0.73 in favor of improved overall survival (P=0.008) and demonstrated an absolute benefit of 8% in 5-year survival. Locoregional recurrence was similarly improved with a hazard ratio of 0.37 (P<0.001). These findings persisted with a restriction of trials to those including induction and/or adjuvant chemotherapy (14).

However, in the absence of level 1, randomized controlled trial data demonstrating improved survival with the addition of PORT, controversy exists in treatment guidelines. The American Society of Clinical Oncology (ASCO) released consensus guidelines in 2017 advising against routine use of PORT in patients with resected Stage IIIA pN2 disease (15). Conversely, the American Society for Radiation Oncology (ASTRO) 2105 guidelines endorsed the use of PORT in patients with pN2 disease or positive margins for improvement of local control based on high level evidence (16).

PORT with chemotherapy in resected locally advanced lung cancer

Another controversy in the adjuvant treatment of patients with resected lung cancer is the timing of and addition of chemotherapy to PORT, and whether chemotherapy should be given concurrently or sequentially. For non-surgical patients treated definitively with chemotherapy and radiation therapy alone, there is clear level one evidence that concurrent chemoradiation results in improved 5-year survival over sequential treatment, an absolute improvement of 6% and relative increase in survival of 60% (17,18). However, it is also clear that concurrent therapy is associated with increased toxicity, and that this toxicity may limit a patient's ability to complete the treatment course.

Sequencing of postoperative radiotherapy and chemotherapy for locally advanced or incompletely resected NSCLC

To address this uncertainty, Francis *et al.*, in the *Journal of Clinical Oncology*, investigated the optimal sequencing of postoperative radiotherapy and chemotherapy for locally advanced or incompletely resected NSCLC (19). In this study, the investigators leveraged the NCDB, a large hospital based observational cohort consisting of approximately 70% of newly diagnosed cases of cancer in the United States.

The analysis included patients with T1–3 disease who underwent lobectomy or pneumonectomy for invasive squamous cell carcinoma (SCC) or adenocarcinoma of the lung diagnosed from 2006–2012. Patients were then divided based on the pathologic nodal involvement and margin status so that patients with pN2 disease and negative margins (R0) made up cohort one and patients with positive margins (R1 & R2) regardless of nodal status (pN0–pN2) made up cohort two. It is important to note that these groups were very carefully selected based on treatment so that only patients with radiation doses from 45–54 Gy in cohort 1 and 45–70 Gy in cohort 2, all given in 1.8 or 2.0 Gy fractions only, were included to select patients that received modern, standard of care radiation therapy. They included no information on radiation therapy modality (conventional, 3D conformal, or IMRT), but did require that radiation was given in a timely manner (<90 days) after chemotherapy or surgery. Further, the timing of chemotherapy was carefully selected to infer whether chemotherapy was given concurrently (chemo ±14 days from the start of RT), or sequentially with radiation (6–18 weeks prior to RT). They included an analysis of several patient characteristics including age, sex, race, treatment facility type, Charlson/Deyo comorbidity score (CCS), tumor grade, histology, tumor size, pathologic T stage, pathologic N stage, and surgery type. For statistical considerations, their primary endpoint was overall survival and they performed univariate and multivariate analysis to report hazard ratios. They subsequently performed a propensity score analysis to account for differences in the baseline patient characteristics.

There are three novel and important findings in this investigation. First, among patients with T2–3 NSCLC treated with a margin clearing lobectomy or pneumonectomy, those found to have pathologic N2 disease had an elevated risk of death with concurrent chemo-radiation therapy (HR =1.45, P<0.01) when compared to sequential chemo-radiation therapy. An increased hazard of death was also identified in patients with one or more comorbidity (HR =1.25, P=0.05). Interestingly, patients with no reported comorbidities had increased risk of death with concurrent chemo-radiation therapy, but in patients with one or more comorbidities, there was no measurable difference. These findings were confirmed on propensity score matching.

Second, they found that the timing of chemotherapy and PORT had no impact on survival in patients with positive margins after surgery for T1–3 disease, regardless of nodal status. It should be noted that 94% of patients in this cohort had microscopic (R1) residual disease, as opposed to gross (R2) residual disease and that this cohort was small, consisting of only 277 patients. Although further limited by sample size (n=128), there was no impact of sequencing of chemotherapy on survival on further propensity matched analysis.

Third, this study reported on the utilization of each chemotherapy sequencing by year over the studied period from 2006–2012 for each cohort. Interestingly, they found a significant increase in the use of sequential chemotherapy for cohort one with an increase from 53% to 63% and a decline in concurrent chemo-radiation therapy from 47% to 37%. For the second cohort the trend was opposite; the use of concurrent chemo-radiation therapy increased from 67% to 81% whereas the use of sequential chemotherapy declined from 33% to 19%.

There are several important limitations of this study that must be considered. First, this is a retrospective study that does not include all factors which may impact survival, and is lacking information on toxicity, local recurrence, and cause of death. Without these endpoints, interpretation of the results becomes limited only to survival which may be influenced by many unknown and uncontrolled for factors. Further, patients were unbalanced between the groups with those receiving concurrent chemo-radiation therapy a having higher levels of comorbidities. Although attempts were made to correct for this, it may not have been possible to correct for the true performance status of these patients. Second, the author's method of selecting patients included inference of timing of radiation therapy and chemotherapy which may not be accurate. The authors also included doses of 45 Gy which is below currently recommended doses for both cohorts of patients, per the National Comprehensive Cancer Network (20). The number of chemotherapy cycles and the type of chemotherapy were unavailable and

greatly limits the generalizability of this data. Additionally, although the initial group of eligible patients was large at 5,503, the final analysis had only 747 in cohort one and 277 in cohort two. When using such a selective group from a much larger population, the investigators risk the inadvertent introduction of selection bias. Finally, the authors made no attempts to adjust survival by treatment year. Since the incidence of sequential chemotherapy has increased over time, it may be that the survival benefit seen from this treatment may be an actual association due to improved chemotherapy, radiation therapy, or improved supportive care that has occurred over time.

Nevertheless, this study provides new insight into an important but currently unknown question regarding the timing of adjuvant chemotherapy with PORT, and should serve to be hypothesis generating for future randomized controlled trials. The ongoing phase III European Organisation for Research and Treatment of Cancer trial EORTC 22055-08053, Radiation Therapy in Treating Patients With Non-Small Cell Lung Cancer That Has Been Completely Removed by Surgery (LUNG ART) seeks to determine if PORT using modern treatment techniques is beneficial in pN2 disease when given sequentially after chemotherapy (21). However, there is no arm available to compare sequential with concurrent chemotherapy. Therefore, until level-one evidence based on a randomized study becomes available for the timing of chemotherapy with PORT, the current study by Francis *et al.* may serve as justification for current practice of sequential chemo-radiation therapy in patients with pN2 disease and justifies either concurrent chemotherapy or sequential chemotherapy for patients with R1 positive margins being treated with adjuvant radiation therapy.

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Footnote

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

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