



Locally Advanced Lung Cancer: Is It Time to Take Cardiac Protection Seriously in Radiation Planning?

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During the past couple of years, interest has been substantial in the potential cardiac toxicity associated with radiation therapy (RT) for locally advanced (LA) non-small cell lung cancer (NSCLC). The publication of the seminal RTOG (Radiation Therapy Oncology Group) 0617 randomized trial included an intriguing association of RT heart doses with overall survival (OS) on a secondary multivariable analysis (1). This was followed by subsequent publications suggesting the importance of intensity modulated RT (IMRT) planning and cancer center volume on outcomes (2, 3). All 3 factors work together in a rather confounding way to suggest that the planning technique, normal tissue doses (specifically, the heart doses), and overall expertise in either treatment or supportive care are critical in lung cancer outcomes. Couple this observation with data from other disease sites regarding the potential effect of cardiac RT doses on patient outcomes and the stage is set for broad clinical investigation into the topic (4-6). We highlight 4 representative recent clinical investigations both supporting and raising into question the importance of the RT dose to the heart, given the continued guarded outcomes for these patients.

Guberina et al. Heart dose exposure as prognostic marker after radiotherapy for resectable stage IIIA/B non-small-cell lung cancer: Secondary analysis of a randomized trial. *Ann Oncol* 2017. (7)

Summary: The ESPATUE trial was a European randomized trial comparing trimodality therapy and dual modality therapy in patients with stage IIIA(N2) or stage IIIB NSCLC, published in 2015 (8). The ESPATUE treatment regimen delivered 3 cycles of cisplatin/paclitaxel induction chemotherapy followed by neoadjuvant accelerated,

hyperfractionated chemo-RT (45 Gy in 1.5 Gy twice-daily fractions with concurrent cisplatin/vinorelbine). Patients with resectable disease thereafter were randomized to further chemo-RT to a risk-adapted total dose of 65 to 71 Gy or surgery. The trial found no differences in OS or progression-free survival between the 2 arms, with both arms achieving 40% to 45% OS at 5 years.

The goal of the secondary analysis by Guberina et al (7) was to use the ESPATUE data set to validate the findings of RTOG 0617 trial (1), in which multivariable analysis suggested that the heart volume receiving 5 Gy (V5) was an independent prognostic factor for survival. This secondary analysis used RT data from 155 of the patients enrolled in the ESPATUE trial. To assess the risk of a type II error, because that sample size was smaller than that in RTOG 0617, the investigators conducted a detailed power analysis using Monte Carlo simulation and considered various levels of baseline cardiac risk. The power calculation confirmed that this secondary analysis would have $\geq 80\%$ power to detect an effect of heart V5 on survival of the magnitude found in RTOG 0617.

The relationship between heart V5 and survival was assessed using univariable and multivariable modeling, including a model containing covariates similar to the multivariable model used in RTOG 0617. No relationship was found between heart V5 and OS. The hazard ratio for death was 1.005 (95% confidence interval 0.995-1.015) per 1% increase in heart V5 ($P = .30$).

Comment: Reports from randomized controlled trials commonly include exploratory analyses. These post hoc analyses can include examinations of treatment effects in subgroups that were not predefined or the evaluation of prognostic factors that had not been prespecified. Such analyses should be considered hypothesis generating but,

nonetheless, often have an oversized impact on clinical practice.

Examples of clinical practice that have been influenced by post hoc analyses include the use of trimodality therapy for patients with LA-NSCLC who undergo lobectomy (based on an unplanned analysis of the Intergroup 0139 trial) and the use of margin positivity and extracapsular extension to select patients for concurrent chemo-RT after resection of head and neck cancer (based on an unplanned pooled analysis of 2 randomized trials) (9, 10).

One challenge with the evaluation of dosimetric variables as prognostic factors is that the likelihood of a type I error is high. If the dose to the heart is thought to be related to survival, several variables could be tested, including the volume of whole heart receiving certain doses (eg, V5, V10), the dose to percentages of the whole heart (eg, D5, D10), and/or the mean heart dose. Also, similar analyses could be performed for substructures (eg, V5 for the left ventricle, right ventricle, each atrium). The findings reported by Guberina et al (7) support those from another study that was also unable to validate the same relationship (11). Taken together, the results from these 2 studies suggest that the relationship between heart V5 and OS does not hold true in external data sets. We are left to conclude that this hypothesis generated by RTOG 0617 (that heart V5 influences OS) was not borne out.

Dess et al. Cardiac events after radiation therapy: Combined analysis of prospective multicenter trials for locally advanced non–small-cell lung cancer. *J Clin Oncol* 2017. (12)

Summary: From 2004 to 2013, 4 consecutive prospective trials evaluating dose-escalated, hypofractionated thoracic RT were performed at the University of Michigan and the Anne Arbor Veterans Affairs hospital. A secondary analysis performed by Dess et al (12) sought to determine the incidence of cardiac events after thoracic RT in this patient cohort and the relationship to the cardiac RT dose parameters, including the mean dose, V5, V30, and V50. A total of 125 eligible patients with unresectable stage II/III NSCLC were identified, 27% of whom had pre-existing cardiac disease. Patients with small cell lung cancer or those who had undergone stereotactic body RT (SBRT) were excluded. All patients received concurrent chemotherapy, if tolerated. Almost all patients (97%) underwent 3-dimensional (3D) conformal RT, rather than IMRT planning.

With a median follow-up of 51 months for the surviving patients, 19 patients had developed a grade ≥ 3 cardiac event at a median of 11 months, predominantly acute coronary syndrome events ($n=5$) or newly diagnosed congestive heart failure ($n=5$), including 3 grade 5 events. The 2-year cumulative incidence of grade ≥ 3 cardiac events was 11%. The mean heart dose was significantly associated with an increased rate of cardiac events

($P=.01$), with a hazard ratio of 1.07/1 Gy. The findings for V5 and V30 were similar, and all cardiac dose metrics were closely associated. Using Fine and Gray competing risk regression, a mean heart dose of 5 Gy and 12 Gy for patients with pre-existing cardiac disease and 23 Gy and 29 Gy for patients without pre-existing cardiac disease were associated with a 10% and 15% risk of grade ≥ 3 cardiac events, respectively. Both disease progression and grade ≥ 3 cardiac events were associated with an increased risk of death, although disease progression was far more common (71 vs 19 events). Although the occurrence of cardiac events did predict OS, no clear association between any cardiac dose parameter and survival was identified.

Comment: Exploratory multivariable analyses from RTOG 0617 suggested cardiac V5 and V30 are strong, independent, and relatively early predictors of OS (1). However, reports from RTOG 0617 did not include analyses of specific cardiac events or cardiac toxicity, and questions remain regarding whether these findings could be due to chance in a post hoc, exploratory analysis that evaluated multiple dosimetric endpoints or whether the cardiac dose could be a surrogate for an increased mediastinal disease burden (13). Dess et al (12) specifically analyzed cardiac events after dose-escalated thoracic RT, identifying an association between the heart mean dose, V5, and V30 and the risk of high-grade cardiac toxicity in their secondary analysis of the 4 prospective trials. Competing risk analysis found that, although both patients with and without pre-existing cardiac disease had an increased risk of cardiac events after thoracic RT, the risk was markedly greater for those with pre-existing cardiac disease. However, their analysis does not find an association between any cardiac dose parameter and survival, perhaps owing to the relatively modest patient numbers (12). An association between the occurrence of cardiac events and survival was noted; thus, perhaps with a larger sample, they could have shown a survival difference. Concurrently, the investigators appropriately stressed the much greater risk of disease recurrence and associated death from lung cancer, highlighting the challenges inherent to RT for locally advanced lung cancer. With the high rates of recurrence and poor survival and competing critical structures to avoid, it remains critical that physicians avoid underdoing target volumes for heart sparing, and judiciously use advanced technologies when appropriate to limit the cardiac dose to as low as reasonably achievable (12).

Speirs et al. Heart dose is an independent dosimetry predictor of overall survival in locally advanced non-small cell lung cancer. *J Thorac Oncol* 2016. (14)

Summary: In an effort to consider factors that could account for the worse OS for the patients in the dose-escalated arm of RTOG 0617, Speirs et al (14) performed a comprehensive retrospective study of multiple patient

parameters focusing on the heart dose. They reviewed the data from 416 patients with LA-NSCLC treated at a single institution between 2001 and 2015. Any patient with “pre-existing cardiac morbidities” that remained stable were not included in the cardiac toxicity group. Of the 416 patients, 60% had undergone 3D planning and 40% IMRT planning. The RT doses ranged from 50 to 84.9 Gy (median 66.0). As the investigators pointed out, IMRT use became more frequent after 2010, positron emission tomography/computed tomography was more frequently used to assess the mediastinum, and a shift had occurred away from induction and adjuvant chemotherapy toward concurrent chemotherapy; thus, treatment had changed with the available technology. Of the 416 patients, the disease was recontoured for 333 to examine the dose-volume histograms for the study in accordance with the secondary analysis of RTOG 0617 (1). The median follow-up was 14.5 months, with a median OS duration of 16.8 months, generally low by current standards. The factors related to worse OS included heart V50, heart volume, lung V5, bilateral lymph node involvement, and lack of concurrent chemotherapy. Also, heart V50 values $<25\%$ versus $\geq 25\%$ were associated with 1-year OS rates of 70.2% versus 46.8% and 2-year rates of 45.9% versus 26.7%, respectively ($P = .0001$). The median heart V50 was significantly greater (20.8% vs 13.9%) for patients with Common Terminology Criteria for Adverse Events-defined adverse events of grade ≥ 1 . The conclusion of their study was that the heart dose is associated with OS and cardiac events related to chemotherapy and RT.

Comment: The delivery of RT is always a balancing act of the dose to the tumor versus the dose to the normal tissues but, moreover, a dilemma of the dose to specific normal tissues, given the same tumor target coverage goal. Speirs et al (14) showed an association between heart V50 values and OS. This can be challenging to balance with the other normal tissue dose constraints. To accomplish this, there is reason to hope that improved dose delivery is relevant. As shown in the study by Speirs et al (14), IMRT resulted in lower pneumonitis rates ($P = .0001$) and cardiac toxicities ($P = .001$). The median heart V50 values were significantly greater (24.7% vs 10.2%) in the 3D-conformal RT arm than in the IMRT arm.

However, simply improving the technique to achieve a dose of 60 Gy is not likely to be enough to improve outcomes. With significant local failure rates in LA-NSCLC, biologically equivalent doses of >100 Gy biologically effective dose to the primary lung cancer mass and involved nodes should be our goal. This target dose was clearly established in multiple SBRT trials in an effort to gain $>90\%$ local control (15). Doses to LA-NSCLC of 60 to 74 Gy do not begin to approach the biologically effective dose level we need to achieve this goal. Multiple approaches to improve local control and cut toxicity risks are being studied to dose escalate RT for LA-NSCLC that might mean that an increased cardiac risk might not be the

“price of doing business.” Preliminary results on individualized dose escalation using positron emission tomography/computed tomography restaging of patients partway through the primary course of RT according to the tumor response have been reported (16). A similar multi-institutional study, RTOG 1106/ACRIN (American College of Radiology Imaging Network) 6697 has closed and is awaiting analysis. Finally, data concerning SBRT to dose intensify the high-risk areas in LA-NSCLC after conventional chemo-RT could improve local control; however, larger studies to examine the impact on survival need to be completed (17, 18).

Wang et al. Cardiac toxicity after radiotherapy for stage III non-small cell lung cancer: Pooled analysis of dose-escalation trials delivering 70 to 90 Gy. *J Clin Oncol* 2017. (19)

Summary: Similar to the report by Speirs et al (14), Wang et al (19) reviewed the data for patients treated at their institution with dose-escalated RT for locally advanced lung cancer. They were able to limit their analysis to only patients treated in a series of prospective clinical trials, largely investigator-initiated institutional trials but also including data from patients treated in CALGB (Cancer and Leukemia Group B) 30105 at their institution. They analyzed the outcomes of 112 patients treated in 6 trials over the span of 13 years. The primary outcome of the study was symptomatic cardiac events. Cardiac risk was quantified by noting the presence of baseline coronary artery disease and calculating the World Health Organization/International Society of Hypertension score. Of the 112 patients, 26 had ≥ 1 cardiac events. On univariable analysis, the heart RT doses and baseline risks were associated with cardiac events. When accounting for the baseline risk on multivariable analysis, the heart doses remained significant. They showed a sharp difference in the 2-year competing risk-adjusted event rates for mean heart doses <20 and >20 Gy (7% and 21%, respectively).

Comment: The possible usable outcome from their study (19) and arguably the study by Speirs et al (14) are the dosimetry parameters that could guide our clinical practice regarding the heart dose. It would be reasonable to use parameters from both reports to frame dosimetry goals, although ideally these would be externally validated. For example, a V50 of $<25\%$ and a mean heart dose of <20 Gy would seem reasonable and achievable.

Overall, considering the available evidence, the relationship between the heart dose and OS in patients with LA-NSCLC has not been clearly proved. The specific heart dosimetric variables that were associated with OS in RTOG 0617 have failed validation. Also, although additional studies have suggested other candidate variables, these themselves require validation. The relationship between the heart dose and cardiac mortality, however, has been much more consistent.

We have data showing that outcomes can be associated with the esophageal dose, lung dose, spinal cord dose, and cardiac dose (20, 21). However, we lack information regarding how to balance the dose of RT to one normal tissue or another.

For example, if we limit the dose to the heart—implying less dose traversing the mediastinum—at what point will the dose to the lung begin to affect the pulmonary outcomes? Will it be a function of the size of the low- or intermediate-dose path or will it be related to the amount of exposure within the high-dose path? The presence of baseline medical comorbidities (eg, chronic obstructive pulmonary disease vs cardiac disease) could change the priority of one constraint over another given a specific scenario. In patients with a specific cardiac dysfunction, it might be beneficial to spare one part of the heart over another, depending on the type of baseline cardiac disease. From a practical standpoint, it would be reasonable to try and minimize the heart dose now and not think of it as convenient path to drive the dose through to minimize dose to the lungs.

Finally, we are likely to see 2 additional modalities of treatment play a role in this. Particle therapies have some unproved promise to meaningfully spare normal tissue in the thorax (22). The RTOG 1308 trial, with its focus on survival improvement based on a decrease in toxicity might provide some better answers if it can be completed. The field of immuno-oncology with its potential to improve long-term survival and change both the utility of RT and the toxicity profile is only in its infancy (23). We look forward to the integration of these new modalities into treatment and additional clinical investigation to better determine the normal tissue limits of therapy.

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