Perspective

Dose escalation for unresectable locally advanced non-small cell lung cancer: end of the line?

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Abstract: Radiation Therapy Oncology Group (RTOG) 0617 was a randomized trial that investigated both the impact of radiation dose-escalation and the addition of cetuximab on the treatment of non-small cell lung cancer (NSCLC). The results of RTOG 0617 were surprising, with the dose escalation randomization being closed prematurely due to futility stopping rules, and cetuximab ultimately showing no overall survival benefit. Locally advanced unresectable NSCLC has conventionally been treated with concurrent chemoradiation. Though advances in treatment technology have improved the ability to deliver adequate treatment dose, the foundation for radiotherapy (RT) has remained the same since the 1980s. Since then, progressive studies have sought to establish the safety and efficacy of escalating radiation dose to loco-regional disease. Though RTOG 0617 did not produce the anticipated result, much interest remains in dose escalation and establishing an explanation for the findings of this study. Cetuximab was also not found to provide a survival benefit when applied to an unselected population. However, planned retrospective analysis suggests that those patients with high epidermal growth factor receptor (EGFR) expression may benefit, suggesting that cetuximab should be applied in a targeted fashion. We discuss the results of RTOG 0617 and additional findings from post-hoc analysis that suggest that dose escalation may be limited by normal tissue toxicity. We also present ongoing studies that aim to address potential causes for mortality in the dose escalation arm through adaptive or proton therapy, and are also leveraging additional concurrent systemic agents such as tyrosine kinase inhibitors (TKIs) for EGFR-activating mutations or EML4-ALK rearrangements, and poly (ADP-ribose) polymerase (PARP) inhibitors.

Keywords: Lung cancer; chemoradiotherapy (CRT); dose escalation; intensity modulated radiotherapy (IMRT); cetuximab

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Chemoradiotherapy (CRT) and dose escalation

The radiotherapy (RT) dose for locoregionally advanced non-small cell lung cancer (NSCLC) has been standard since the 1980s. Radiation Therapy Oncology Group (RTOG) 73-01 randomized patients to four different regimens: 40 Gy split course or 40, 50, or 60 Gy continuous courses with 2 Gy per fraction daily treatments (1,2). This study found that in the 2D era, local control and overall survival was superior for those patients receiving 60 Gy, establishing the standard RT dose regimen.

Given uniformly poor outcomes despite 60 Gy thoracic RT, multiple studies established the importance of chemotherapy, first sequentially, then concurrently with RT (3-10). A meta-analysis subsequently concluded that indeed concurrent CRT had superior overall survival in comparison to a sequential regimen (11). This has since remained the foundation of our current treatment for locally advanced lung cancer.

Seeking further improvements in stage III NSCLC outcomes, many tried to leverage technologic improvements

in the planning and delivery of RT. The introduction of computerized tomography (CT) ultimately spawned three-dimensional conformal radiation therapy (3DCRT), which allowed the application of volumetric imaging to define volumes for more complex and conformal treatment planning. This enhanced the ability to deliver higher doses to tumors while limiting doses to normal tissues. Since then, there have been a number of radiation dose escalation studies leading towards the development of the experimental arm in RTOG 0617.

Initial dose escalation with 3DCRT was studied in the setting of RT alone or sequentially following chemotherapy. RTOG 93-11 was a phase I–II dose escalation study with 3DCRT that sought to take advantage of the new technology to dose escalate beyond 60 Gy (12). Patients received sequential chemoradiation with radiation dose up to 90.3 Gy based on lung V20. The 90.3 Gy cohort had two dose-related deaths and 83.8 Gy was deemed the maximum tolerated dose. This small study notably did not show any significant difference in locoregional control with dose escalation. Kong *et al*. published a phase I study of dose escalation at the University of Michigan, treating with doses up to 103 Gy based on effective lung volume, with 18% of patients receiving neoadjuvant chemotherapy (13). In this study, higher doses were associated with improved rates of 5-year survival in this cohort.

In the setting of concurrent chemotherapy, a modified phase I/II trial from North Carolina of 62 patients escalated the RT dose to 74 Gy (14-16). Patients in this study were treated with induction and concurrent carboplatin and paclitaxel. North Central Cancer Therapy Group (NCCTG) 0028, a phase I/II trial, thereafter confirmed the maximum tolerated dose of RT with concurrent carboplatin and paclitaxel at 74 Gy, with too many dose limiting toxicities at 78 Gy (17). RTOG 0117 was a combined phase I/II study which initially was planned to escalate RT dose from 75.25 Gy up to 80.5 Gy with increasing dose per fraction with concurrent carboplatin and paclitaxel (18,19). However, excessive toxicity at 75.25 Gy in 2.15 Gy fractions resulted in the de-escalation to 74 Gy in 2 Gy fractions, further establishing this as the maximum RT dose. CALGB 30105 randomized patients to either paclitaxel or gemcitabine-based induction chemotherapy and concurrent CRT to 74 Gy, closing the carboplatin/gemcitabine arm due to grade 4–5 pulmonary toxicity (20). Given the findings of these studies, 74 Gy was established was the dose-escalated experimental arm for RTOG 0617.

Epidermal growth factor receptor (EGFR) inhibition with CRT

In addition to studying dose escalation, RTOG 0617 also investigated the role of cetuximab in the management of stage III NSCLC. While not the initial intent of the study, the promising results of RTOG 0324, a single arm phase II trial of cetuximab with concurrent chemoradiation with 63 Gy and carboplatin and paclitaxel published by Blumenschein *et al*. reported 2-year survival of 49.3% in patients without selection of patients in regard to EGFR status (21). Notably, survival in this trial was the longest achieved in a study reported by the RTOG. Furthermore, the rationale was supplemented by the results of a randomized study of cetuximab in locoregionally advanced head and neck cancer patients, finding that the addition of cetuximab carried a locoregional control and overall survival benefit over RT alone (22). These promising results of cetuximab, without selection of patients based on EGFR mutational status led to its inclusion in RTOG 0617.

RTOG 0617

RTOG 0617, therefore, was a randomized phase III study that was designed to compare 74 and 60 Gy with concurrent followed by consolidation carboplatin and paclitaxel. It was subsequently amended to address the question of the role of cetuximab concurrently and with consolidation for unresectable stage III NSCLC (23). Patients were thus randomized equally among four arms: 60 or 74 Gy with or without cetuximab. Radiation was delivered in 2 Gy fractions by 3DCRT or intensity modulated radiotherapy (IMRT), with image-guided radiation therapy and planning with positron emission tomography (PET)/CT or 4D CT encouraged. Additionally, compliance with normal tissue dose constraints was encouraged, though not required. Randomization was stratified based on RT technique (3DCRT or IMRT), Zubrod performance status, use of PET in staging, and histology.

RTOG 0617 enrolled 544 patients from 185 institutions, with 464 enrolled while randomization to radiation dose was active, and 514 for cetuximab. The radiation dose randomization was closed prematurely due to futility stopping rules, although enrollment continued for cetuximab randomization. Four-hundred nineteen patients were ultimately analyzed for outcomes. When the results were presented, a surprising survival detriment was found with the 74 Gy arm in comparison to the 60 Gy arm, with

2-year overall survival rates of 45% and 58%, respectively. There was no progression-free survival or local progression differences based on radiation dose randomization.

Furthermore, the addition of cetuximab did not significantly affect overall survival, with 2-year overall survival rates of 52% in the cetuximab and 50% in the non-cetuximab arm. However, with planned retrospective EGFR expression analysis in a subgroup of patients (203 total patients), cetuximab was seen to offer survival benefit with EGFR H-score 200 or higher (high EGFR expression), with median overall survival of 42 months in comparison to 21.2 months (HR 1.72, two-sided log-rank P=0.032). There was a trend towards survival detriment with H-score less than 200 (P=0.056).

What happened?

The premature closing of the dose escalation component was unexpected to some, although to date, radiation dose escalation in the setting of concurrent chemotherapy has not been associated with improved survival (24,25). However, as these results were surprising and counter-intuitive, very thorough analysis was performed. The investigators analyzed the quality of radiation delivered, finding the overall survival difference persistent even when analyzing only those cases with physician review and dosimetric requirements of 95% of the dose covering 90% of the planned treatment volume. This suggests that tighter radiation fields to avoid toxicity were not responsible for underdosing of the target. However, mean lung dose (MLD) and V20 were both significantly higher in the 74 Gy cohort. Of note, more patients completed consolidation chemotherapy in the 60 Gy arm (70%) than the 74 Gy arm (64%), although randomized studies (26,27) and meta-analyses (28) have not shown a benefit to consolidation chemotherapy following concurrent CRT. The interaction between radiation dose and cetuixmab was also non-significant. These results suggest that greater cardiopulmonary toxicity, associated with dose escalation, may have resulted in clinically meaningful differences in survival.

Furthermore, data were recently presented comparing the outcomes of patients treated with either IMRT or 3DCRT on RTOG 0617 at the 2015 World Conference on Lung Cancer and the 2015 American Society for Radiation Oncology (ASTRO) Annual Meeting. Patients treated with IMRT had more advanced disease and larger planning target volumes (PTVs). Despite this, there was a trend towards lower V20s, and significantly lower rates of grade 3+ pneumonitis (29,30). Of note, only lung V20 was predictive of grade 3+ pneumonitis. Additional analyses focused on heart dose, which demonstrated that heart V40 was significantly lower with the use of IMRT (30) and was associated with decreased overall survival. The relationship between heart dose and survival corroborates retrospective findings described by Liao *et al*., which found that lung and heart doses are associated with worse overall survival (31).

These data suggest that potentially the broad application of dose escalation may be detrimental to overall survival, and more stringent planning parameters may be required to derive benefit from its application. In particular, dose delivered to the heart may require close attention, particularly V40, and limits on dose escalation may be required based on the ability to meet stricter heart dose constraints.

While these technical details may explain the limitations in survival with the application of dose escalation, the comparable rates of local control with dose escalation in the context of adequate radiation coverage raise questions on the outlook for the utility of higher radiation doses. This may be attributable to radiographic evaluation of tumor progression versus radiation changes or the lower rate of chemotherapy completion in the dose escalation arm. However, there remains limited prospective data to support the utility of dose escalation, mostly in the setting of RT alone, from the University of Michigan (13). RTOG pooled analysis suggested a locoregional control and survival benefit with higher biological effective dose (BED), but pools data across a significant time period, from 1988 to 2002 which may have potential confounders (32).

Of note, patients treated in the standard treatment arm had much better outcomes than anticipated based on historical data, with 2-year overall survival of 58% and median survival of 28.7 months. The authors speculated that this may be due to staging PET and PET/CT imaging which was acquired for almost all patients (about 90%) in the study. Thus, the potential for stage migration may have played a role in these improved outcomes. Indeed, there have been data using population-based datasets such as the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database, the California Cancer Registry (CCR), and institutional databases (33-35). In each of these studies, the increased use of PET over time was associated with upstaging of disease. Despite stable overall survival from lung cancer, Dinan *et al*. noted improved survival within stage IV patients in the SEER-Medicare cohort (34),

while Chee described the same phenomenon in stage III and IV patients in the CCR population (33). In addition to the benefits of PET in staging, the PET-START trial randomized patients to PET-CT or CT-based radiation planning, finding that patients who had PET-CT-based planning showed a near-significant trend towards an overall survival benefit (36,37).

Additionally, RTOG 0617 did not find a benefit with the use of cetuximab applied in an unselected fashion. This too was unsurprising as cetuximab was not found to improve outcomes in CALGB 30407 (38), which randomized patients to 70 Gy with concurrent carboplatin and pemetrexed with or without cetuximab. Interestingly, on subset analysis for those patients in RTOG 0617 with overexpression of EGFR, cetuximab was shown to be associated with a survival benefit. This is consistent with the mechanism of action for cetuximab as a chimerized murine monoclonal antibody to EGFR. Furthermore, the lack of benefit in unselected NSCLC cases is not surprising as only 52% of evaluable tumors on 0617 demonstrated EGFR overexpression, compared to the ubiquitous over expression in head and neck cancers. Given this, it is reasonable that cetuximab did not show a benefit in unselected patients. The secondary analysis should serve to guide future studies on the application of cetuximab.

Future directions in treatment of locoregionally advanced NSCLC

Given the hypothesis that the dose escalation in RTOG 0617 was impacted by normal tissue toxicities, ongoing studies are focused on delivering high dose RT while limiting normal tissue doses. The ongoing RTOG 1106 is randomizing patients between the standard 60 Gy versus the use of adaptive RT using PET/CT performed between 40 and 46 Gy to escalate doses up to 80.4 Gy to a smaller fludeoxyglucose (FDG)-avid volume, sparing normal tissues (39). Additionally, the study investigators took care to take into consideration the findings of 0617 with multiple strategies detailed in the protocol, including limiting radiation duration to 6 weeks, mandated motion management, individualization of radiation dose, and credentialing for radiation planning. Notably, dose escalation will be limited based on achievable MLD, which is constrained to 20 Gy.

RTOG 1308 utilizes proton therapy to achieve a similar goal of sparing normal tissues (40). In particular, proton therapy, particularly with intensity modulated proton therapy (IMPT), has been shown to reduce radiation dose to normal tissues (41,42). Given the futility of 74 Gy, the investigators selected a control arm of the study as 70 Gy [relative biological effectiveness (RBE)] delivered by photons with concurrent platinum-based doublet therapy in comparison with a 70 Gy (RBE) proton therapy arm with concurrent chemotherapy. The trial allows for adjustment of the prescription dose based on organs-at-risk (OAR) constraints, as there is currently no justification of radiation dose escalation beyond 60 Gy when given with concurrent chemotherapy.

Hypofractionation is viewed as another method to increase the BED delivered to treat lung cancer, building off of the more recent effectiveness of hypofractionated image-guided RT, also known as stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) in early stage lung cancer. Several phase I studies have also had promising results using this method (43-45). A recently published phase II study investigated dose escalation in a hypofractionated style reaching 60 Gy in 15 fractions without exceeding the maximum tolerated dose (46). This study was preceded by other studies including a phase II Italian study of 60 Gy over 20 fractions with long-term follow-up showing promising disease control with acceptable toxicity (47,48). Zhu *et al*. also published data using a hypofractionated method with 50 Gy in 20 fractions with sequential chemotherapy (49).

In addition to altering RT approaches for dose escalation, additional systemic agents are being incorporated to improve outcomes in the management of locally advanced NSCLC. RTOG 1306 is an ongoing study incorporating the use of targeted agents for specific mutations (50). Patients with the EGFR TK mutation and EML4-ALK fusion rearrangement are being randomized to concurrent chemoradiation to 60 Gy with or without preceding induction therapy with a targeted agent (erlotinib or crizotinib, respectively). This study leverages findings from prior studies testing the addition of EGFR TK inhibitors to concurrent CRT platforms. In general these studies have found no improved, and possibly worse, survival with concurrent EGFR tyrosine kinase inhibitor (TKI) and CRT, but promising outcomes when they are given alone or sequentially with CRT (51-53).

Poly (ADP-ribose) polymerase (PARP) inhibitors have also emerged as potential agents to be given in the concurrent setting. The ongoing SWOG 1206 (NCI 8811) (54) and Alliance Foundation Trial (AFT)-07 are randomizing patients with unresectable NSCLC

to concurrent chemoradiation with consolidation chemotherapy with or without the addition of ABT-888 (veliparib).

Summary

RTOG 0617 produced unexpected results to most, particularly in its dose escalation comparison, based on the preceding phase II data. Subsequent analyses have been presented to explain the results, potentially describing necessary constraints in escalating radiation dose to treat locoregional disease. Though the addition of cetuximab did not show survival benefit, analysis of EGFR overexpression in a subgroup of patients suggests that implementation in a targeted fashion may offer benefit. Given the findings of RTOG 0617, a number of modifications in dose escalation strategy and incorporation of biological agents have emerged to form ongoing trials in locally advanced NSCLC.

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Footnote

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