Dose escalation of an antineoplastic modality such as radiotherapy (RT) may result in an increased therapeutic ratio with the use of effective strategies to mitigate normal tissue toxic effects. Successful execution of dose escalation using external beam RT (EBRT) approaches has yielded unintended outcomes.\(^1,2\) While increased disease control and survival are a focus of such strategies to increase the therapeutic ratio, quality of life (QOL), as measured by appropriate patient-related outcomes tools, are nearly as important. To that end, Movsas et al,\(^3\) in this issue of JAMA Oncology, document that an attempt to deliver nearly a quarter higher total dose (74 Gy vs 60 Gy) of EBRT given concomitantly with a platinum-taxane doublet for locally advanced non-small-cell lung cancer (LA-NSCLC) results in a clinically meaningful decrement in QOL at 3 months.\(^3\)

However, the Radiation Therapy Oncology Group 0617 trial is not the definitive treatise regarding the RT dose-escalation question for locally advanced non-small-cell lung cancer: an analysis of RTOG 9801. Int J Radiat Oncol Biol Phys. 2008;72(5):1378-1384.


8. The Importance of Quality of Life Assessment

Charles R. Thomas Jr, MD, PhD

Dose escalation of an antineoplastic modality such as radiotherapy (RT) may result in an increased therapeutic ratio with the use of effective strategies to mitigate normal tissue toxic effects. Successful execution of dose escalation using external beam RT (EBRT) approaches has yielded unintended outcomes.\(^1,2\) While increased disease control and survival are a focus of such strategies to increase the therapeutic ratio, quality of life (QOL), as measured by appropriate patient-related outcomes tools, are nearly as important. To that end, Movsas et al,\(^3\) in this issue of JAMA Oncology, document that an attempt to deliver nearly a quarter higher total dose (74 Gy vs 60 Gy) of EBRT given concomitantly with a platinum-taxane doublet for locally advanced non-small-cell lung cancer (LA-NSCLC) results in a clinically meaningful decrement in QOL at 3 months.\(^3\)

However, the Radiation Therapy Oncology Group 0617 trial is not the definitive treatise regarding the RT dose-escalation question for LA-NSCLC. The QOL assessments, as well as the survival results, likely were influenced by numerous factors that are difficult to control for in a multi-institutional, cooperative group clinical trial setting. Emerging data on molecular signatures that may predict radiosensitivity and/or radioresistance of tumor, as well as normal tissues, may be helpful in future assessment of baseline patient characteristics for those enrolled in prospective, large-scale cancer clinical trials of RT-based treatment. Moreover, not all modes of potential RT delivery and dose escalation are equal. Currently, radiation oncologists see patients on a weekly basis and basically assess symptoms as a “snapshot in time.” This is fraught with recall bias and other factors that contribute to a diminished appreciation of real-time patient-related outcomes, which should ideally be recorded on a continuous 24/7 basis to assess QOL during treatment. Movsas and colleagues are to be congratulated for executing a trial that will help in the design of next-generation QOL trials for LA-NSCLC.
Dose Escalation in Stage III Non–Small-Cell Lung Cancer
Patients Agree With the Clinical Results

David Cella, PhD

As we conduct clinical research to continue to “move the dial” of progress against lung cancer, it has become increasingly important to consider the patient’s perspective alongside that of more standard efficacy and safety endpoints. Besides the obvious reason of patient centricity, there are several compelling clinical reasons to do so. In this issue of JAMA Oncology, the article by Movsas and colleagues provides us with more evidence to illustrate the importance of the patient’s perspective on efficacy and safety in clinical trials, and especially the importance of studies in advanced disease. The results reaffirm a few principles of quality-of-life measurement in advanced tumor oncology that can now be considered teachable facts, supported by robust results, reproduced in multiple studies, using various questionnaires. Three such facts are (1) quality-of-life reports taken at the start of a new therapy for advanced disease are predictive of survival; (2) clinician-rated toxicity on the Common Terminology Criteria for Adverse Events (CTCAE) grading system underestimates the adverse effects of treatments on patients’ lives, and (3) dose escalation, whether chemotherapeutic or radiotherapeutic, has predictable, deleterious effects on quality of life, as reported on a well-validated lung cancer questionnaire. To frame these “facts,” I will discuss them in the context of the article by Movsas et al.

Despite promising phase 2 trial data in patients with unresectable stage III non–small-cell lung cancer (NSCLC), escalating dose of radiation therapy (RT) and adding cetuximab did not lengthen survival when compared with standard dose RT with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non–small-cell lung cancer (RTOG 0617).


Lessons learned:

1. Quality-of-life reports taken at the start of a new therapy for advanced disease are predictive of survival. As has been shown in several prior studies, across many groups of patients with advanced disease, baseline patient report of quality-of-life (TOI score) was associated (P = .046) with survival time. It has also been shown in several investigations, although not apparently analyzed in this investigation, that change in patient report while on therapy is also predictive of survival, above and beyond the baseline report. Analysis of both baseline scores and early change in scores can shed further light on which patients benefit, and which do not, from therapy in early treatment, perhaps contributing to clinical decision-making after initiation of treatment.

2. Clinician-rated toxic effects on the CTCAE grading system underestimates the adverse effects of treatments on patients’ lives. On the one hand, Movsas and colleagues reported that very few of the clinician-rated adverse events were worse in the treatment arm receiving the escalated dose of RT. On the other hand, patient report of symptoms, adverse effects, and functioning, as manifest in the FACT-LCS TOI and its components, were significantly and meaningfully worse in the arm receiving the escalating dose. Significantly more patients in the arm receiving 74-Gy (45% vs 30%) had clinically meaningful decline in FACT-LCS at 3 months than those receiving 60 Gy (P = .02).

3. Dose escalation, whether chemotherapeutic or radiotherapeutic, has predictable, deleterious effects on quality of life. Here are some of the most novel and interesting findings by Movsas et al. Those clinicians planning future studies that include dose escalation can learn from these results, especially with regard to making hypotheses and then measuring and testing them. To their credit, these investigators studied several patient-reported toxic effects, and they asked the right questions to answer their questions. Several dosimetric factors were associated with clinically meaning-