

### Editor's note:

In the era of personalized medicine, a critical appraisal new developments and controversies are essential in order to derived tailored approaches. In addition to its educative aspect, we expect these discussions to help younger researchers to refine their own research strategies.

## Controversies on Lung Cancer: Pros and Cons

# Rebuttal from Prof. Kong and Dr. Rabatic

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We have the fortune of an eloquent consideration to the alternatives of concurrent chemoradiation offered by our esteemed colleague for patients diagnosed with stage III non-small cell lung cancer (NSCLC). Dr. Rodrigues rightfully clarifies the significant challenges of a concurrent treatment regimen in this very heterogeneous patient population. Understandably from his viewpoint, there exists low success of cure in the face of such advanced cancer. We concur that treating patients with significant morbidity may potentially increase treatment-related toxicities, and possibly, death. While toxicity seen with the use of concurrent chemotherapy for stage III NSCLC cancer can be an argument for avoiding a concurrent treatment paradigm, we must recognize that we do not have data which demonstrates mortality is significantly higher in patients treated with concurrent chemoradiation, compared to those treated with sequential chemoradiation or radical radiation therapy alone. Additionally, the negative result of poorer survival in high dose arm of RTOG 0617 cannot support the “Con” for concurrent chemoradiation, as the standard arm of concurrent chemoradiation had outstanding survival (1).

Physicians utilize age, performance status, pulmonary function, weight loss, and even gross tumor volume in order to determine the appropriate treatment paradigm. We intend use of these objective measures to ensure proper patient selection for a particular treatment modality. Further driving the use of objectivity, are the data from several

large randomized trials investigating concurrent regimens in a patient with unresectable stage III NSCLC. This data serves as the focus of the concurrent chemoradiation *vs.* alternative treatment paradigm debate.

Consistent with the toxicity theme, one would not be incorrect to argue there is increased toxicity with concurrent chemoradiation. As described in the associated “Pro” text, grade 3 toxicities can exceed 30% (2). However, one has to consider that most curative regimens are associated with toxicity and even mortality. For instance, adjuvant chemotherapy with cisplatin has been shown to have absolute risk increase of 2% for treatment-related death (3). Furthermore, we agree that the mortality within the 1<sup>st</sup> 6 months after concurrent chemoradiation is notable (4), however we do not have data to show such mortality is significantly higher than patients treated with sequential chemoradiation or radical radiation alone in the modern era. These gaps of knowledge confine clinicians and patients to question when toxicity outweighs a treatment benefit. This is particularly compelling when we have randomized control trial data proving a benefit in regards to cancer specific survival and OS at 5 years with concurrent chemoradiation.

Constraining dosimetry of radiotherapy to within publicized organ at risk (OAR) limits (e.g., QUANTEC) provides a means to limit toxicities. And, as stated by Dr. Rodrigues, we may incorporate an adapted RT approach to reduce potential toxicities of normal structures. We

have demonstrated that NSCLC tumor burden can reduce remarkably (40% on CT, 70% on PET) after 45 Gy and such reduction made adaptive treatment possible to improve the OAR dosimetry (5-8), and may positively impact functional status (9). Furthermore, we would be remiss if we did not mention that most toxicity reports were associated with less-conformal radiotherapy techniques. In the modern era, highly conformal radiotherapy can effectively improve OAR dosimetry and reduce treatment toxicities. Despite the toxicity argument, we know there is a 3-9% progression free survival advantage of concurrent chemoradiation *vs.* sequential chemotherapy followed by radiation. This carries over to a 5-9% actuarial survival benefit with a concurrent approach (2,10-12). We would like to drive home the point that in this patient category, the disease itself is the major cause of death.

While we agree with Dr. Rodrigues that “better predictive models and selection criteria are needed to guide oncologists for which patients are best suited for concurrent chemoradiation...”. Our opinion is firm, until further randomized trial results become available, a good performance status patient, having lost 5-10% body weight, and limited pulmonary co-morbidity, would better tolerate concurrent chemoradiation, and should receive this therapy. A patient with these characteristics would be best able to extract the published survival benefit of concurrent chemoradiation. This opinion is supported by the West Japan, RTOG, Czech, and French data (2,8-10). Above and beyond the published trial data, we are comforted in knowing that our stance is consistent with recommendations of advisory organizations responsible for cancer treatment guidelines (13-16). We would like to add, when safe dosimetry is impossible, we recommend enrolling the patient in RTOG 1106, a trial designed to elucidate the effectiveness of adaptive radiation therapy.

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## Footnote

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

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