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

Cons: concurrent chemo-radiotherapy remains the ideal treatment in fit patients with inoperable large volume stage III non-small cell lung cancer

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The treatment of stage III unresectable non-small cell lung cancer (NSCLC) remains a significant challenge despite approximately 40 years of clinical trial activity in this patient population (1,2). Medical imaging, nuclear medicine, image-guided radiation treatment, radiation treatment delivery, and systemic treatments all have significantly improved the medical care of these patients (3). Historically, part of the challenge in the management of stage III NSCLC has been its heterogeneity in terms of tumor location, primary (T4—multifocal or invasive disease versus lower T stage) and nodal (N3 *vs.* lower N stage) extent of spread, cancer histology as well as various patient factors such as patient age, weight loss, performance status, and comorbidities. More recently, the diversity of NSCLC in terms of potential EGFR and ALK genetic alterations have further defined (and complicated) the ideal treatment of this disease entity.

Almost half of patients diagnosed with an unresectable stage III lung cancer in 2016 will die of their disease within 2 years (4). Disappointingly, recent clinical trial evidence from the Radiation Therapy Oncology Group (RTOG) 0617 dose escalation trial have demonstrated that treatment intensification (in this case testing 74 *vs.* 60 Gy of concurrent chemoradiation) can have its limits both in terms of optimizing survival outcome (5) and health-related quality of life (HRQoL) (6). In this trial, dose intensification was associated with hazard ratio of 1.38 [95% confidence interval (CI), 1.09–1.76, P=0.004] for death (4). Additionally, patient reported HRQoL was reported to be worse (at 3 months) in patients receiving the dose intense 74 Gy treatment (6). This trial specifically demonstrated to the lung cancer treatment community that continued intensification of concurrent chemoradiation (in this case with higher dose radiotherapy) may not necessarily lead to improved patient outcomes.

Despite the failure of RTOG 0617 in the demonstration that further treatment intensification can lead to improved patient outcomes, the routine use of concurrent chemoradiation as a treatment option for fit patients with unresectable stage III NSCLC is on a solid clinical trial footing (1,2). Initially, the focus was on the development of sequential chemotherapy followed by radiotherapy. Both the Cancer and Leukemia Group B (CALGB) (7) and intergroup trials (8) demonstrated survival benefit (on the order of 2–4 months median survival improvement) of this combined approach. Two meta-analyses were performed demonstrating improved 1- and 2-year survival with sequential chemoradiation versus radiation alone (9,10). Subsequently, the West Japan Lung Cancer Group (11) and the RTOG 9410 (12) investigated the concurrent chemoradiation approach versus sequential therapy. Both

trials demonstrated survival improvements (3 months median survival and 6–7% 5-year survival) in favour of concurrent chemoradiation. However, this modest benefit in favour of concurrent chemoradiation was at the expense of treatment toxicity which was reported to be almost a twenty percent increase (53% *vs.* 35%) in grade three or higher non-hematological acute side effects (12).

Based on these clinical trials, I offer (and routinely treat) patients concurrent chemoradiotherapy to fit patients with unresectable stage III NSCLC. However, this is not the only approach that can be utilized for this patient population. Patient preferences can often deviate from guideline recommended clinical practice (13) and these preferences have been shown to be, in part, related to patient age (14). Specifically for stage III NSCLC, the modest survival benefits of concurrent chemoradiation over other radical approaches (radiotherapy alone or sequential chemoradiation) combined with additional treatment toxicity (e.g., acute esophagitis and pneumonitis) set up a situation where a competent patient can select either sequential chemoradiation or radiation therapy alone as their primary treatment. The patient rationale for this potential decision is to potentially reduce treatment related toxicity but maintain the opportunity for other clinical gains such as tumor control, progression-free survival, and cure. Additionally, no definition of patient "fitness" has been agreed upon, factors such as performance status, comorbidities, and weight loss are factors that should be considered by oncologists and other health care professionals in the selection of primary lung cancer treatment (1). Both alternative approaches (radical radiation alone or sequential chemoradiation) have been recently codified in the ASTRO practice guideline for stage III NSCLC in both an evidence-based and consensus-based approach (see guideline statements KQ1B and KQ3D, respectively) (1).

Part of the dismal outcomes associated with stage III NSCLC chemoradiotherapy is due to early mortality within 6 months of primary treatment. In a recent multi-institutional analysis of 1,245 patients in 13 centres, 10% of patients died within 180 days of treatment (15). Multivariable analysis identified tumor bulk (GTV ≥100 cc: odds ratio 2.61, 95% CI, 1.10–6.20) and pulmonary function (FEV1 <80% predicted: odds ratio 2.53, 95% CI, 1.09–5.88) as predictive factors for early mortality. The presence of both factors lead to an odds ratio for early death of 4.43 (95% CI, 2.07–9.51). Other factors informed a nomogram for early mortality prediction inclusion N stage and maximum esophageal dose. Collectively, this data demonstrates that patients with larger tumors (by GTV size and/or N stage), impaired pulmonary function, and esophageal dosimetry (and likely related toxicity) can be at risk of early mortality. These are the patients that in general are likely to benefit less from aggressive chemoradiation programs. In a single institution retrospective study of 121 patients, patients with planning target volumes of greater than 700 cc were found to be associated with death within 6 months of concurrent chemoradiotherapy (16). This effect was magnified in patients with Charlson comorbidity index greater than or equal to 1 in which 1 in 4 patients died within 6 months of treatment. These analyses and nomograms are not robust enough to entirely exclude patients from concurrent chemoradiation treatment, but they do provide important information for oncologists to consider in an individualized approach to patient counselling and treatment selection.

Another scenario that requires careful consideration prior to routine administration of concurrent chemoradiation is that of a large volume stage III NSCLC in which radiation planning approaches lead to unacceptable dosimetry in one or more critical structures such as the bilateral lung or spinal cord (as well as potentially other organs such as heart and esophagus). Although modern planning intensity modulated and adaptive radiotherapy approaches have converted previously palliative-intent patients to potential radical cases, there are still dosimetric limits to the safe treatment of very large volume disease with radiotherapy. One approach commonly used is to treat patients with neoadjuvant chemotherapy to debulk the disease prior to radical radiation planning to see if more optimized and safe radiation planning can occur. The alternative of adaptive radiotherapy planning where successive plans are created to take advantage of tumor response can be an option to maintain the concurrent chemoradiation paradigm; however, this is only feasible if there is sufficient tumor regression during the course of radiation therapy. This is often not the case leaving suboptimal radiation doses tolerances (on the range of 45 Gy out of a minimum target radiation dose of 60 Gy) to be delivered based on lung and spinal cord.

Ultimately, the current paradigm of concurrent chemoradiation is not "ideal" given its inferior clinical outcomes in terms of death and its modest improvements compared to less toxic treatment paradigms of sequential chemoradiation and radical radiotherapy alone. Various issues including patient preferences, patient age, tumor bulk, N stage, performance status, pulmonary function, and treatment

dosimetry interact with the ultimate treatment decision between patients and oncologists. Better predictive models and selection criteria are needed to guide oncologists for which patients are best suited for concurrent chemoradiation or alternatively for other less toxic radical treatments. Additionally, further study on the ideal systemic agents (based on patient tolerability and tumor genetics) is required to better individualize treatment choices and outcomes.

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Footnote

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