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Dear NRG Oncology Lung Cancer Community:

Proton beam and photon therapy are both effective treatments for patients with locally-advanced non-small cell lung cancer. Although proton beam radiation has been shown to offer superior radiation treatment plans ‘on paper,’ it is unclear if proton beam radiation therapy is clinically superior. It is important to understand how to choose patients who would benefit from proton therapy, and a large randomized trial comparing protons to photons is needed to address this.

NRG Oncology investigators hypothesize that proton beam therapy may spare organs (especially the heart) and normal tissue from the effects of radiation thereby reducing side effects and risks to patients, and may also allow increased radiation dose to the targeted tumor possibly resulting in better overall survival for the patient. Randomized trials studying the therapeutic effectiveness of these treatments are still limited, however, so the data critical to informing treating physicians is minimal and, we believe, understated.

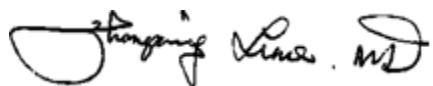
RTOG 1308, a phase III randomized trial from NRG Oncology comparing protons to photons, differs fundamentally from the Adaptive randomized phase II trial from MD Anderson Cancer Center and Massachusetts General Hospital. The MDACC/MGH trial was recently reported at ASCO 2016 as showing no advantage of proton beam radiation therapy in terms of the protocol endpoint (radiation pneumonitis) for patients with locally-advanced non-small cell lung cancer, although it did show significant heart sparing from proton therapy. The NRG Oncology Lung Cancer Committee determined the following points are worth distributing to the broad oncology community:

1. The MDACC/MGH trial was a phase II trial and used a single toxicity, non-survival primary endpoint (radiation pneumonitis or local failure). Other toxicities were not included as endpoints (for example heart). The gold standard for level 1 evidence is a phase III trial using overall survival (OS) as endpoint. RTOG 1308 is a phase III trial designed to generate level I evidence, and this may be the only opportunity to conduct such a trial. The primary endpoint is OS.
2. The MDACC/MGH trial used Bayesian adaptive randomization, which is very good in theory but difficult to perform in reality for the endpoints chosen. The Bayesian adaptive randomization trial design relies on the real-time update of the event information so that the ratio of allocation to treatment arms can be adjusted before the randomization of the next patient. However, the real-time update of the event proved to be challenging. Another issue with Bayesian randomization was that the randomization process did not give greater importance to more recent events. Furthermore, improvements in techniques with experience and technological evolution over the course of the trial were not considered in the allocation of the patients. RTOG 1308 uses the classical 1:1 randomization.

3. The MDACC/MGH trial only randomized patients who had a pair of acceptable IMRT and PSPT plans at same tumor dose. This method may have excluded patients who would benefit from protons thus favoring the IMRT arm. RTOG 1308 will randomize patients first before radiation dosimetric planning.
4. The MDACC/MGH trial forced same tumor dose in both arms in order to test one variable while keeping all other variables as constant as possible. This approach may have prevented the protons from realizing full potential in delivering a higher tumor dose and reducing the normal tissue dose simultaneously. RTOG 1308 will allow IMRT and protons to do its best in terms of the normal tissue sparing and tumor dose escalation up to 70 Gy.
5. High heart V5 and V50 doses were significant adverse factors for OS in RTOG 0617. The MDACC/MGH phase II trial demonstrated consistent heart sparing from protons. The potential impact on OS from heart sparing was an important factor when designing RTOG 1308.
6. Insurance denial of proton therapy caused a few problems. It created the need for two randomized and two non-randomized arms, with 26 patients receiving IMRT instead of being randomized. Insurance refusal also caused an additional reduction in the number of patients in the proton arm, which affected the statistical power. RTOG 1308 should not have this issue.
7. Patient eligibility in MDACC/MGH trial was different than the eligibility for RTOG 1308. It allowed neoadjuvant chemotherapy, which can increase the risk of radiation pneumonitis. It also allowed patients with Stage IV disease and patients who developed recurrent disease after previous surgical resection, which likely reduces the projected overall survival compared to what we will expect with RTOG 1308. The MDACC/MGH trial also enrolled more patients with Stage IIIB disease compared to Stage IIIA, the opposite of what we normally expect with RTOG trial enrollments.

These are the main reasons that continued accrual to RTOG 1308 is of paramount importance. Currently the study is accruing at 2.7 patients per month and has accrued 80 of the required 560 patients. It is critical that participation in this trial is supported, to provide the much needed data on which patients and insurers can make scientifically informed decisions regarding the use and advancement of proton and photon therapy to treat cancer. Please continue to support accrual to RTOG 1308. Thank you for your attention to this important matter.

Respectfully,



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