Randomized Clinical Trials Using New Technologies in Radiation Oncology

Ethical Dilemma for Medicine and Science

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In this issue of the *Journal of Thoracic Oncology*, Dr. Roelofs et al. present the results of multicenter comparative planning study of 25 consecutive stage I–IIIA non-small cell lung cancer (NSCLC) patients with the use of three-dimensional conformal photon (3DCRT), intensity modulated photon (IMRT), and passive scattered proton radiotherapy (ROCOCO study).[1] The patients were scanned with four-dimensional 18F-fluorodeoxy-glucose-positron emission tomography/computed tomography and targets were delineated at the Department of Radiation Oncology, Maastricht University. Subsequently, participating centers used their own treatment planning systems according to predefined criteria and reported their plans through a centralized database. The results are shown according to two scenarios—with prescribed dose of 70 Gy in 35 fractions to planning target volume and by adapting the fraction dose to fulfill the toxicity criteria for organs at risk (isotoxic dose escalation per fraction).

This and other in silico trials in radiotherapy raise several important issues. Rapid technological progress in diagnostic and therapeutic use of radiation allows for more accurate treatment planning and higher dose delivery to the tumor. This often leads to change in standard of care without documenting the benefit of the innovative intervention by conclusive phase III trial—a widely accepted golden standard in the era of evidence-based medicine. Indeed, radiation oncologists are tempted to rely on better dose distribution within the tumor volumes and on assuming the benefit from known dose-response relationships if exposure to organs at risk may be reduced. The widespread introduction of IMRT to clinical practice in head and neck, prostate, and many other cancers serves as a good example. A review of clinical evidence for IMRT has identified 61 comparative prospective studies, including only six randomized controlled trials, powered mostly for comparison of toxicity and not efficacy.[2] Most of these studies became available when many radiation oncology departments already adopted IMRT. Not surprisingly, acute and late toxicity has consistently been shown to be improved with IMRT, whereas the benefit in local control or health-related quality of life has been less apparent. The limited number of randomized studies addressing the benefit of new technologies in radiotherapy underlines the difficulties in performing such studies. Is randomization ethical in the case of clearly worse dose distribution to organs at risk? Should dose escalation to the tumor be performed with new radiotherapy techniques when dose constraints for organs at risk are fulfilled? Prospective assessment of outcome measures remains extremely important, particularly when fundamentally different innovative radiation technologies, such as proton therapy, are applied. The benefits in efficacy, toxicity, and quality of life endpoints should be quantified to better understand the magnitude of benefit and also for incremental cost-effectiveness analyses.

The ROCOCO study provides several important findings. The authors should be complimented for their multi-institutional collaboration in careful modeling of potential

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benefit from proton therapy and IMRT as compared with 3DCRT. Even if proton therapy plans are associated with better dose distribution to organs at risk in most patients, this treatment may not be applicable for all, and it is difficult to clearly foresee which technology would suit better to particular clinical situations. With the use of proton therapy, esophageal toxicity, already being a dose limiting toxicity in many patients administered photon (chemo)radiation, may become a real concern. Proton therapy, and also IMRT, opens the room for dose escalation without increasing overall treatment time and thus provides a potential for improvement of local control and survival. The enthusiasm of safe dose escalation to the tumor volume with proton therapy to optimize local control should, however, be tempered by the fact that most relapses in stage II and III NSCLC patients will appear at distant sites, which together with comorbidities constitute substantial competing risks for survival. Thus, the ultimate benefit from proton therapies in NSCLC patients remains to be proven in prospective controlled trials using as comparators alternative technologies, such as 3DCRT and IMRT, and also volumetric modulated arc therapy, which gains increased attention in NSCLC.[3] Although most radiation oncologists will agree that "more is better" in terms of safe dose delivery to the tumor, a recent closure of high-dose arms for futility reasons in the RTOG 0617 four-arm trial comparing in stage III NSCLC 60 Gy and 74 Gy conformal radiotherapy combined with carboplatin and paclitaxel with or without cetuximab (http://www.clinicaltrials.gov/ct2/show/NCT00533949?term=rtog+0617) calls for particular attention when assessing the benefit from dose escalation in lung cancer.

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