INTERVIEW

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Tracks 1-12

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: Would you discuss the use of stereotactic ablative radiotherapy (SABR) for patients with Stage I NSCLC?

DR LOO: The advent of SABR has changed standard treatment for patients with inoperable tumors. This technology makes it possible to sharply focus the radiation field precisely on the tumor by using several beams at different angles. An intensive course of radiation therapy can be administered safely with minimum exposure to the surrounding organs. A course of radiation therapy (RT) can be compressed into a small number of treatments or even a single treatment with a higher biologically effective dose.

Higher rates of primary tumor control can be achieved than with conventional radiation therapy. Phase II studies have demonstrated primary tumor control rates of 85% to 90%. The landmark Phase II RTOG-0236 study, which evaluated SABR for patients with inoperable early-stage lung cancer, reported the highest primary tumor control rate at 3 years — approximately 98% (Timmerman 2010).

DR LOVE: What are the main complications associated with SABR?

DR LOO: The most common problems that we observe in patients with peripheral tumors are mild chest wall pain or rib fractures, which may or may not be symptomatic. Inflammatory changes surrounding the area of the target may be observed on follow-up CT or PET scans. This generally manifests a few months after treatment and is not of clinical consequence but may persist for a while before resolving. It is often interpreted as tumor recurrence, even though it is not. This is something to be aware of to avoid invasive biopsies.

DR LOVE: How do you determine the dose of SABR?

DR LOO: One of the factors predictive of tumor control is the dose intensity expressed in terms of a biologically effective dose, which could be achieved in a single fraction or multiple fractions. Many nuances exist in terms of how you calculate a biologically effective dose, but it is possible to compare different dosing regimens in the conversion to a biologically effective dose.

At Stanford we're performing a Phase II study of what we refer to as individualized stereotactic ablative radiation therapy, where we adapt the dose and the number of fractions to both the volume of the tumor and the location (NCT00551369). The idea is to optimize the balance between tumor ablation and normal tissue complications.

Tracks 7-8

DR LOVE: Would you discuss the Phase III RTOG study reported at ASCO 2013 comparing high-dose to standard-dose RT with chemotherapy for patients with Stage IIIA/B NSCLC (Bradley 2013a)?

DR LOO: RTOG-0617 was a randomized trial evaluating conformal RT with the standard dose of 60 Gy versus 74 Gy in combination with concurrent and consolidation chemotherapy. The results demonstrated that survival was worse for the 74-Gy arm than for the 60-Gy arm (Bradley 2013a; [2.1]). Patients on the 60-Gy arm had outcomes that were comparable to or better than those observed in any other cooperative group trial. This suggests that modern RT with excellent quality assurance may account for the good results with the standard dose of 60 Gy. It's difficult to understand why higher doses of RT do not result in better outcomes, including local control. Follow-up studies are ongoing based on the suggestion that a higher dose to the heart may correlate with worse outcome in the high-dose arm.

A secondary randomization to the addition of cetuximab or not occurred, but those results were not reported. It will be interesting to know if the combination of cetuximab with chemoradiation therapy results in higher toxicity. Anecdotally, from my own experience, there seems to be a higher rate of esophagitis, mucositis and dermatitis with cetuximab. (Editors note: Subsequent to this interview results from this secondary randomization were presented at the 15th World Conference on Lung Cancer. The authors reported no survival benefit and increased toxicity with the addition of cetuximab to chemoradiation therapy for patients with Stage III NSCLC [Bradley 2013b].)

Track 11

DR LOVE: Would you discuss the use of 4-dimensional computed tomography (4D CT) for radiation treatment planning?

2.1

RTOG-0617: A Phase III Trial Evaluating Standard-Dose (60 Gy) versus High-Dose (74 Gy) Conformal Chemoradiation Therapy for Stage III Non-Small Cell Lung Cancer

Efficacy	**Standard dose**	**High dose**	Hazard ratio	*p*-value
Median overall survival (n = 213, 206)	28.7 mo	19.5 mo	1.56	0.0007
18-mo PFS rate (n = 213, 205)	36.6%	26.3%	1.3	0.0116
18-mo local failure rate (n = 213, 206)	25.1%	34.3%	1.37	0.0319
Select adverse events				
60 Gy (n = 213)	Grade 2	Grade 3	Grade 4	Grade 5
Worst nonhematologic	NR	46%	9.9%	0.9%
Worst overall	NR	46.5%	26.8%	0.9%
Esophagitis/dysphagia	93%	7%	NR	NR
74 Gy (n = 206)	Grade 2	Grade 3	Grade 4	Grade 5
Worst nonhematologic	NR	46.1%	11.2%	4.9%
Worst overall	NR	41.7%	31.6%	4.9%
Esophagitis/dysphagia	79.1%	20.9%	NR	NR

PFS = progression-free survival; NR = not recorded

Bradley JD et al. *Proc ASCO* 2013a;**Abstract 7501**.

DR LOO: 4D CT scanning represents the next step after 3D scanning, which was the last revolution in RT, going from having full spatial information to now having full spatial information and time. Body motion, particularly respiratory motion, makes it difficult to accurately target the tumor.

The 4D scan is essentially a CT movie that we can acquire during treatment planning. We can characterize the motion of tumors as the patient breathes and then develop motion compensation or motion management strategies. The radiation field can be individually adjusted to cover the range of motion of the tumor, if it's limited. If the motion is large, we can employ a technique called respiratory gating, by which we turn on the beam only for a certain portion of the breathing cycle to avoid radiation to normal lung tissue. The key is to make sure that's being done accurately at the time of radiation delivery.

Biofeedback techniques can be used with 4D CT scanning. We can show patients their breathing pattern so that they can hit certain breathing targets, either as a breath hold or a kind of voluntary free breathing, and turn on the beam only at the appropriate time. ■

SELECT PUBLICATIONS

Bradley J et al. **An Intergroup randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) chemoradiotherapy (CRT) +/- cetuximab (CETUX) for stage III non-small cell lung cancer (NSCLC): Results on CETUX from RTOG 0617.** *Proc WCLC* 2013b;**Abstract PL03.05**.

Shirvani SM et al. **Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly.** *Int J Radiat Oncol Biol Phys* 2012;84(5):1060-70.

Timmerman R et al. **Stereotactic body radiation therapy for inoperable early stage lung cancer.** *JAMA* 2010;303(11):1070-6.