Stereotactic body radiation therapy

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The U.S. Radiation Therapy Oncology Group has greenlighted the routine use of SBRT, but physicians overseas call for more scientific evidence to support its widespread use.

Stereotactic body radiation therapy borrows the best elements of other forms of radiotherapy. Like intracranial stereotactic radiosurgery, stereotactic body radiation therapy uses multiple beams to spread out entrance dose and achieve dose fall-off to normal tissues. It also uses advanced imaging techniques to target and relocate the tumor for each treatment and employs 4D imaging for motion control technology.

By combining all these factors, SBRT delivers a potent radiation dose in five or fewer fractions and offers unique results that are different from conventionally fractionated radiotherapy, according to Robert D. Timmerman, MD, professor of radiation oncology and neurosurgery at the University of Texas Southwestern Medical Center in Dallas. This puts SBRT in position to be the standard of care for frail patients with stage I non-small-cell lung cancer (NSCLC).

It's true that SBRT has a lot of bells and whistles, but are proponents guilty of worshiping technology for technology's sake? Quite possibly, said David Ball, MD, deputy director of the division of radiation oncology at Peter MacCallum Cancer Centre in Melbourne. While SBRT offers no shortage of razzle-dazzle, it lacks the clinical and scientific evidence to support its routine use in stage I, inoperable NSCLC, he said.

Dr. Timmerman and Dr. Ball debated the pros and cons of SBRT as the standard of care in stage I NSCLC at the 2009 World Conference on Lung Cancer in San Francisco.

**Dramatic improvement in local control**

The first clinical models for SBRT were in patients with early-stage NSCLC who had multiple comorbidities and whose tumors were medically inoperable, said Dr. Timmerman. "The intent originally was to improve the rather poor tumor control these patients experienced after conventionally fractionated radiotherapy," he explained. "And most investigators using [SBRT] early on assumed that this would probably be at some expense at least in terms of increased toxicity compared with conventionally fractionated radiotherapy. "But honestly that experience has not borne out. Tumor control has been dramatically improved [with SBRT] and the treatment is surprisingly well tolerated even with long-term follow up," he added.

The benefits of SBRT in early-stage NSCLC include:

- The tumor is significantly debulked and/or eradicated for a local control rate ranging from 60% to 90%.
- Local immune function is, on the whole, preserved, especially in comparison with conventional radiotherapy.
- Necrosis is avoided.

There are a number of multicenter trials to support the use of SBRT. In the phase II RTOG 0236 trial, SBRT achieved a 98% local control rate. SBRT delivered a dose of 60 Gy to the tumor in three fractions over one week. The three-year overall survival (OS) was 56% in NSCLC patients with documented comorbidities, such as emphysema, heart disease, and stroke (ASTRO 2009 abstract...
Also, **Pia Baumann, MD**, and colleagues at institutions in Sweden, Norway, and Denmark reported a three-year local tumor control rate of more than 90%, with limited toxicity, in fifty-seven patients with NSCLC stages T1N0M0 and T2N0M0. SBRT was delivered three times at a dose of 15 Gy, 67% isodose of the planning target volume (*J Clin Oncol* 27:3290-3296, 2009).

The Japan Clinical Oncology Group is currently analyzing data from a trial of SBRT in patients with operable tumors (trial 0403), but in their previous research, the Japanese trial leaders have described excellent outcomes, including good long-term survival, for patients who have had SBRT, and favorable comparisons with patients treated with standard surgery have been made. However, Dr. Timmerman stressed that these studies were retrospective and not controlled (*J Clin Oncol* online, January 11, 2010).

"So the level of evidence shows SBRT for the frail patients is showing very good results, consistent results in mature phase II trials over many continents," Dr. Timmerman said. "The Scandinavian group is considering a study to randomize [patients] to SBRT or to conventional radiotherapy. The question is: Is that trial feasible? Is it necessary?" Historically, phase III data are required before a treatment method can become the standard of care, he said, but is it a must-have? Not necessarily.

"Admittedly, in the modern era we generally require newer therapies to be proven by such high level evidence, especially if the standard and experimental therapy are similar. My position, however, in this case is that the evidence is so overwhelming that a phase III trial is unnecessary," he said. Like any treatment method, SBRT does have its drawbacks, Dr. Timmerman pointed out. "This is not a perfect therapy; there is tissue damage," he said. "This collateral damage occurs close in proximity
to the targeted tissue. The tissue next to the target simply doesn't function after the treatment, and this can be confirmed on things like functional nuclear medicine scans. The toxicity with SBRT seems more related to tubular structures or wire structures from so-called serial functioning tissues rather than parallel functioning tissues."

The question with SBRT isn't so much whether it should be used in frail NSCLC patients, Dr. Timmerman said, but rather does it qualify as a new standard of care? "Do we have a new standard of care? I've listed here a number of things that I think would be required to say that [SBRT] is a new standard of care," he said.

First, ASTRO, the American College of Radiology, and the American Association of Physicists in Medicine have published guidelines on the use of SBRT. Second, the general radiation oncology community has the right equipment to perform SBRT. "[With SBRT], we need the ability to accurately target the extent of tumor and this is done mostly on CT scans, so we have that," Dr. Timmerman said. "We can assess motion with 4D scans, but in our center we still use fluoroscopy to do the initial assessment. Once you assess this motion you need to account for it, and there are various ways to do that. The simplest way is to use abdominal compression, and I think nearly all centers have access to that technology."

Third, results from the previously mentioned trials speak to the reproducibility of SBRT results (see Figure 1). Fourth, outcomes with SBRT have been steady and stable thus far. A phase II trial out of Indiana University in Indianapolis reported a local control rate of 88% after three years in patients with stage T2 tumors and a three-year OS of 42.7% in treating patients with the largest tumors of any prospective SBRT trial [up to 7 cm in diameter] (J Clin Oncol 24:4833-4839, 2006; Int J Radiat Oncol Biol Phys 75:677-682, 2009).

"The data show that local tumor control is dramatically better and survival appears considerably better than conventionally fractionated radiotherapy with no accounting for the fact that SBRT trials are mostly prospective and conventionally fractionated reports are nearly all retrospective," Dr. Timmerman said. "With prospective vs retrospective comparisons, the opposite is usually true."

Finally, reimbursement for SBRT in the U.S. is a reality, Dr. Timmerman said. The Centers of Medicare and Medicaid Services has assigned billing codes to SBRT in NSCLC and, in 2008, the payer-driven California Technology Assessment Forum approved SBRT as standard treatment for NSCLC despite the lack of phase III evidence.

Failure to meet the criteria for standard of care

Dr. Ball began his argument against SBRT as the standard of care in early-stage NSCLC with the story of a tribe in New Guinea that were so enthralled by an airplane, they fashioned one out of grass mats and then proceeded to worship it.

"This is an example of what I call a cargo cult behavior. I would suggest to you that cargo cult behavior, or worshiping technology, is creeping into medicine. I would also suggest to you that the use of megadoses of radiation, to small volumes using advanced technology, is an example of this cargo cult behavior," he said.

In fact, a survey of ASTRO members, led by Fengming P. Kong, MD, PhD, on how they treated their last case of stage I lung cancer showed that 21.7% reported using a stereotactic approach while 24% said they would have done it stereotactically if they had the equipment available. "So almost half appear to be prepared to treat their patients with a radically new form of treatment without any phase III evidence," Dr. Ball said (ASTRO 2007 abstract 2508).
three other conditions:

- New technology must demonstrate that local control is superior.
- Technology must lead to longer survival.
- Technology must be safe.

Dr. Ball cited an "excellent systematic review" of all hypofractionated small-volume radiotherapy for early-stage NSCLC. This meta-analysis analyzed data from 17 reports. While the results from these studies were impressive—a 65% survival rate at two years and an 89% progression-free survival (PFS) rate for local disease—the reports made "no comment on how many of the cases of disease had been verified pathologically and no comment on how many patients had operable disease, that is, they were medically operable as well as technically operable. Medically and technically operable patients have different survival compared with patients who are medically inoperable," he said. The reviewers concluded that there was not enough "robust data" to justify a consensus on SBRT and that additional research was still needed (Clin Oncol 20:666-676, 2008). Another problem with the stereotactic approach is that there is no agreed-on dose as demonstrated by the ASTRO survey (see Figure 2). "When Dr. Kong conducted her survey, she asked people what treatment they used. Some people preferred three fractions, some preferred four, some five, some preferred 10. The doses ranged from 6 Gy to 20 Gy," Dr. Ball said. "Now when I see a spread of data like this, and all treating the same disease process, my immediate reaction is, 'Do these guys really know what they're doing?''"

Dr. Ball said that a phase III trial is under way in Australia and New Zealand (TROG 09.02 CHISEL) to test the hypothesis that local control is improved with three fractions of 18 Gy vs 60-66 Gy in patients who go without chemotherapy. "I believe that until the results of those trials are available, we still will lack the phase III evidence," he said.

In terms of local control and survival, Dr. Ball turned to data from two studies: the Indiana University data mentioned by Dr. Timmerman and another study done at Peter MacCallum. Marie-Pierre Campeau, MD, Dr. Ball, and colleagues retrospectively reviewed local control and survival following concomitant chemoradiotherapy (CRT) or radical radiotherapy (RT) alone for inoperable stage I NSCLC. "This is state-of-the-art conventional radiotherapy. Patients were all staged with PET and all were histologically or cytologically verified," Dr. Ball said. "And in this study, we published this because a portion of the patients were treated with concomitant chemotherapy, which is a standard of care. Patients were treated with either 20 or 30 fractions."

According to the results, local PFS at two years was 66% with CRT and 55% with RT. The two-year distant PFS was 60% after CRT and 63% after RT. The two-year survival rate for patients treated with CRT was 57%, and for patients receiving RT, 33% (Int J Radiat Oncol Biol Phys 74:1371-1375, 2009). "Let's compare it with the updated Indiana University study, which Dr. Timmerman just referred to,"
Dr. Ball said. "The local control does look better: 88% in the Indiana University data compared with 58% [in the Peter MacCallum study]. But what about survival? It's absolutely identical. So this raises the question: If we're not improving survival for these patients, are we doing harm?"

Finally, there is the issue of toxicities, including rib fracture, chest wall pain, esophageal ulceration, fistula, and pericardial effusion. "Let's look at the dose issue. We can convert three fractions of 18 Gy into a biologically effective dose, which for early-reacting tissues is 151 Gy, a very significant dose," Dr. Ball explained. "But no one talks about the late-reacting tissues. If you use an alpha/beta ratio of 3 Gy, you end up with a dose of 378 Gy, which would irreparably damage most of the structures in the mediastinum" (Int J Radiat Oncol Biol Phys 60:1241-1256, 2004).

"Now these are just numbers derived from mathematical models because I don't know anyone who has treated anyone to a dose of 378 Gy in conventional fractionation to verify the effect. But whatever way you look at it, this is a very, very large dose of radiation and not something we should take lightly," he added.

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