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EDITORIAL

Six Questions to Ask Before We Shorten Radiation Treatments for Intact Prostate Cancer

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Three multicenter, randomized, noninferiority trials comparing moderate hypofractionation (2.5 Gy to 3.0 Gy per fraction) with conventional fractionation (1.8 Gy to 2.0 Gy per fraction) have reported similar effectiveness and toxicity for intact prostate cancer. The Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHiP) and NRG Oncology 0415 trials have been published (1, 2). The Ontario Clinical Oncology Group/Trans-Tasman Radiation Oncology Group PROstate Fractionated Irradiation Trial (PROFIT) was initially presented at the 2016 American Society for Clinical Oncology meeting in Chicago (3). Most recently, all 3 studies were discussed at a standing-room-only panel session of the American Society for Radiation Oncology annual meeting in September 2016.

Moderate hypofractionation for intact prostate cancer has substantial benefits for patient-centric care, including shorter treatment time, greater convenience, and reduced travel time. Moderate hypofractionation also costs less than conventional fractionation. We pose 6 questions to ask before we shorten radiation treatment for intact prostate cancer.

What Did the Trials Show?

Briefly, as summarized in Table 1, CHHiP included 3216 patients in a 3-arm, noninferiority trial that compared 2 moderate hypofractionation arms (60 Gy in 20 fractions of 3 Gy and 57 Gy in 19 fractions of 3 Gy) with a conventionally fractionated arm (74 Gy in 37 fractions of 2.0 Gy). After a median follow-up of 5.2 years, the 5-year failure-free rates were 90.6% (95% confidence interval [CI] 88.5%-92.3%) in the 60-Gy arm versus 85.9% (95% CI 83.4%-88.0%) in the 57-Gy hypofractionation arm versus 88.3% (95% CI 86.0%-90.2%) in the conventional fractionation arm. The 60-Gy arm was noninferior to the conventional fractionation arm. (The 57.0-Gy arm was not found to be noninferior, and therefore we do not support this fractionation.) The CHHiP trial reported that both clinician-reported late genitourinary (GU) and gastrointestinal (GI) toxicity and patient-reported bowel, urinary, and sexual function was similar between arms (4).

NRG Oncology 0415 included 1115 patients in a 2-arm, noninferiority trial that compared one moderate hypofractionation arm (70 Gy in 28 fractions of 2.0 Gy) with a conventionally fractionated arm (73.8 Gy in 41 fractions of 1.8 Gy). After a median follow-up of 5.8 years, the 5-year disease-free survival rates were 86.3% (95% CI 83.1%-89.0%) in the moderate hypofractionation arm versus 85.3% (95% CI 81.9%-88.1%) in the conventional fractionation arm (the prespecified criteria for noninferiority were met). NRG Oncology 0415 reported slightly increased clinician-reported GU and GI toxicity in the moderate hypofractionation arm; however, patient-reported outcomes for bowel, urinary, and sexual function were similar between arms (5).

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Table 1 Summary of 3 trials of moderate hypofractionation for prostate cancer

Study	N	"Longer" arm	"Shorter" arm	Efficacy at 5 y	Late toxicity	Patient-reported outcomes
CHHiP	3216	37 fx/2.0 Gy	20 fx/3.0 Gy	Similar	Similar	Similar
PROFIT	1206	39 fx/2.0 Gy	20 fx/3.0 Gy	Similar	Similar	Similar
NRG 0415	1115	41 fx/1.8 Gy	28 fx/2.5 Gy	Similar	Small↑ GU/GI	Similar

Abbreviations: CHHiP = Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer; fx = fractions; GI = gastrointestinal; GU = genitourinary; PROFIT = PROstate Fractionated Irradiation Trial.

The PROFIT trial included 1206 patients in a 2-arm, noninferiority trial that compared one moderate hypofractionation arm (60 Gy in 20 fractions of 3.0 Gy) with a conventionally fractionated arm (78 Gy in 39 fractions of 2.0 Gy). After a median follow-up of 6.0 years, the 5-year biochemical–clinical failure-free rates were 79% in both arms. The PROFIT trial also showed similar clinician-reported toxicity and patient-reported outcomes between the 2 arms (6).

Do the Findings Apply to My Patients?

After considering the trials' age and race distribution, presence of comorbid disease, spectrum of disease severity as measured by risk groups, and utilization of androgen suppression in appropriate patients, in a word, the answer is "Yes."

As shown in Table 2, the median age in CHHiP and PROFIT was approximately 70 years. The age range in CHHiP was 48 to 85 years. In NRG 0415 the median was 67 years, and approximately 10% of patients were aged <60 years. In the Surveillance, Epidemiology, and End Results database, the median age at prostate cancer diagnosis is 66 years, and 10% of cases are diagnosed in men aged <55 years (7).

Although CHHiP and PROFIT did not have racial diversity, 17% of patients in NRG 0415 were African American. In the CHHiP trial, 10% of patients had diabetes, 38% had hypertension, and 8% had a prior transurethral resection of the prostate. The majority of patients in CHHiP had intermediate- or low-risk prostate cancer; CHHiP also enrolled a small percentage of patients with high-risk prostate cancer. The PROFIT trial enrolled patients with intermediate-risk prostate cancer. NRG 0415 enrolled patients with low-risk prostate cancer. Nearly all patients in CHHiP received androgen suppression. The PROFIT trial allowed, but the vast majority of patients did not receive, androgen suppression; NRG 0415 did not allow any androgen suppression.

How Can We Sum Up the Evidence?

Taken together, the trials show that in 5537 patients, with mostly low- and intermediate-risk prostate cancer, and with or without androgen suppression, 2 shorter radiation courses lasting 4 or 5 weeks (70 Gy in 28 fractions and 60 Gy in 20 fractions) lead to similar cancer control and side effects as longer radiation courses lasting 7 or 8 weeks (8, 9).

What Does Economics Add?

When 2 treatments have similar effectiveness and toxicity, patient-centric treatment decisions should presumably minimize treatment costs. The economic benefits of shortening radiation treatment for prostate cancer would accrue across stakeholders in the health system.

For patients, moderate hypofractionation would reduce transportation costs and out-of-pocket expenses, especially as high-deductible health plans become more prevalent in American health care. Moderate hypofractionation would reduce time away from work (absenteeism) and distracted work (presenteeism), defined as when employees are at work but not present or productive. In short, moderate hypofractionation would reduce the financial toxicity of prostate cancer and its treatment.

For providers, adoption of shorter radiation schedules for patients with prostate cancer is high-quality and patient-centric cancer care. Such care would distinguish efficient, patient-centric practices in local markets. These practices could achieve greater patient volumes in a rapidly changing

Table 2 Patient characteristics in 3 trials of moderate hypofractionation for prostate cancer

Study	Risk groups	Age (y), median (range)	African American (%)	Comorbid disease	Androgen suppression
CHHiP	All	69 (48-85)	1	Diabetes: 10% Hypertension: 38% Transurethral resection of the prostate: 8%	Yes
PROFIT	Intermediate	71	Not reported	Note reported	Yes
NRG 0415	Low	67, 10% <60	17	Zubrod 1: 8%	No

Abbreviations as in Table 1.

health care environment that faces continued rate pressure irrespective of the potential for major changes to the Affordable Care Act. The benefits of moderate hypofractionation for patients and for practice efficiency outweigh the short-term lower revenues per patient associated with reduced fractions delivered.

For payers, moderate hypofractionation would reduce expenditures while maintaining care quality. A challenge of the fee-for-service payment system in the United States is that the financial benefits of providers' clinical innovation to lessen treatment burden accrues to payers (in the form of lower reimbursement) rather than providers themselves (in the form of margin that can be reinvested into additional improvements in clinical care). Therefore, as moderate hypofractionation diffuses into clinical practice, payers ought to share savings with providers to incentivize its use and compensate providers for better clinical care.

Why Not Change?

There are 3 principle arguments against adoption of moderate hypofractionation for prostate cancer. First, some may be concerned that the conventional fractionation arms in the trials were insufficient in an era of dose escalation. However, the PROFIT trial used 78 Gy in 2-Gy fractions, which is a typical dose-escalated treatment regimen. In addition, if we consider prostate cancer to have an α/β of 2 (as suggested by the CHHiP trial), the fractionation scheme of 79.2 Gy in 44 fractions of 1.8 Gy has a radiobiologically equivalent dose of approximately 76 Gy in 38 fractions of 2 Gy (ie, a lower dose than was used in the conventional arm of PROFIT). From this view, the conventional fractionation arms seem reasonable and the moderate fractionation arms can be considered at least radiobiologicially equivalent to most modern fractionation regimens.

Second, some may be concerned that median follow-up of 5 years is not long enough to compare cancer control. However, there is no relevant hypothesis that 2 iso-effective treatments would diverge on a survival curve for cancer control with extended follow-up.

Third, some might argue we need longer follow-up to evaluate late toxicity before adoption. We do need longer-follow up, and we now have it. Investigators recently published long-term outcomes of moderate hypofractionation of 60 Gy in 20 fractions of 3 Gy with 10.7-year median follow-up; cumulative late grade $\geq$2 GI and GU toxicity was 4% and 12%, respectively, and late grade $\geq$3 GI and GU toxicity was less than 2% at 8 years (10).

The need for longer-term data on moderate hypofractionation was also argued in the breast cancer field. In 2002, investigators reported 5-year randomized data on moderate hypofractionation versus conventional fractionation for whole-breast irradiation (11). Local recurrence rates and cosmetic outcomes were similar in both groups. Adoption of the shorter radiation schedule was slow; however, some argued that the reason was that larger doses of radiation per fraction could lead to greater toxicity over time. However, even after investigators reported 12-year data in 2010, uptake of shorter radiation for whole-breast radiation did not accelerate (12, 13).

We should not repeat the missed opportunities of the past. Although we cannot know what the 3 prostate cancer trials will show in the long term, radiobiologic models simply do not predict increased toxic effects when fraction sizes remain modest (up to 3.0 Gy) and total dose is reduced. We are sufficiently reassured by 2 facts: (*1*) toxicity was uncommon after 5 years and no different whether patients were randomly assigned to moderate hypofractionation or conventional treatment arms; and (*2*) long-term toxicity after moderate hypofractionation has now also been reported and remains minimal (10).

What Can We Do Right Now?

Practice changes slowly in response to evidence. Therefore, we offer 3 practical steps to take as moderate hypofractionation diffuses into routine care for patients with intact prostate cancer.

First, we ought to engage with patients in participatory decision making about the duration of radiation therapy for prostate cancer. In other words, we should talk with our patients about the evidence: 3 trials with more than 5500 patients show that moderate hypofractionation is safe and effective through 5 years and allows patients to get on with their lives, returning to home or work sooner.

Second, we ought to introduce moderate hypofractionation techniques (daily fraction sizes of 2.5 Gy to 3.0 Gy)

Table 3 Duke University current organs-at-risk dose-volume histogram constraints for 70 Gy in 28 fractions of 2.5 Gy

Organ at risk	Dose (Gy)	Volume (absolute or %)
Bladder	70	$<$10 cm^3
Bladder	65	15%
Bladder	40	35%
Rectum	70	$<$10 cm^3
Rectum	65	10%
Rectum	40	35%
Left femoral head	40	0%
Right femoral head	40	0%
Penile bulb	Mean dose $<$50	
Small bowel	40	1%

The clinical target volume is the prostate in low-risk and favorable intermediate-risk patients and includes 10 mm of proximal seminal vesicles in patients with unfavorable intermediate-risk disease. A 3-dimensional expansion of the clinical target volume by 4 to 10 mm is used to create the planning target volume (PTV). A simultaneous boost technique is used to deliver 58.8 Gy in 28 fractions to the PTV including the proximal seminal vesicles. The maximum dose to the PTV cannot exceed the prescription dose by more than 7; up to 10% is a minor, acceptable variation, and $>$10% is a major, unacceptable variation.

into our clinics. The techniques of treatment delivery are available in each trial's published supplemental information (1, 2, 14). As a practical example, in Table 3, we also provide Duke University's current organ-at-risk constraints incorporating tighter metrics than those reported in NRG 0415.

Third, each of us ought to identify a group of patients who are appropriate for moderate hypofractionation. Although this group may differ according to our practices and experience, a reasonable recommendation of eligible patients would be those with decent urinary function (American Urological Association score under 15) and with prostate sizes under 100 cm^3.

Conclusion

The field of radiation oncology, through international clinical innovation, should be recognized for technical advances in clinical care that have achieved safe, effective, curative treatment for prostate cancer in fewer weeks. Increased use of moderate hypofractionation achieves real improvements in patient care for less. The evidence is clear, the value to patients is obvious, and the potential cost savings are substantial. It is time to use moderate hypofractation for patients with intact prostate cancer.

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