SOPHISTICATED PROSTATE CANCER EXTERNAL BEAM RADIOTHERAPY

Does it live up to the hype?

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Top-line summary

Radiation oncology has recently undergone a technologic revolution in treatment delivery. The aim is to improve cure rates while reducing toxicity in normal tissue, and this entails significantly more complex treatment. The progression from 2-dimensional to 3-dimensional treatment planning in external beam radiation therapy (EBRT) was the first major shift in technology, allowing for conformal radiation (i.e. treatment that follows the shape of the targeted area). Highly conformal intensity modulated radiation therapy (IMRT) is now used routinely, and leading centres employ image guidance to ensure that this more precise IMRT is on target. In prostate cancer, these technologies can deliver higher doses to tumours and result in improved cancer control, with fewer and milder side effects due to sparing of adjacent normal tissues such as the rectum and bladder. This report aims to provide an overview of current technologic capabilities in external beam radiation oncology with respect to prostate cancer treatment, including a review of benefits reported in published randomized controlled trials. In addition to EBRT, permanent seed implantation and high-dose rate brachytherapy are other options for this malignancy — the interested reader is directed to review articles on these topics.[1,2]

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Advances in modern radiation delivery allow for higher doses of radiotherapy, leading to better prostate-specific antigen (PSA) control and a lower risk of side effects.

TECHNOLOGIC EVOLUTION OF RADIATION ONCOLOGY

Radiation delivery was initially directed by marks placed on the patient's skin. The physician used his/her knowledge of surface anatomy to guide the treatment beams — hardly high-precision therapy. Next came the introduction of plain x-rays during radiation planning to better guide the beams. This was referred to as 2-dimensional (2D) treatment planning. The target was localized with respect to bony landmarks visualized on a plain x-ray, since soft tissues (such as the prostate) cannot be seen with plain x-rays because organs and muscles surrounding the prostate have a similar x-ray density.

CT and 3-dimensional planning

The introduction of computed tomography (CT) had 2 distinct advantages: it allowed physicians to distinguish soft tissues from one another, and it provided a series of cross-sectional slices through the body, yielding a 3-dimensional (3D) picture of the area being imaged. As CT scans entered into mainstream radiation medicine, radiation oncologists could identify the actual tumour target and surrounding normal organs that were at risk of toxicity. The goal has always been to treat the target but minimize the dose and volume of normal tissues radiated while treating that target, as the dose given to the surrounding tissues and/or organs is what leads to the side effects of radiation treatment. A smaller dose to a smaller volume of normal tissues means fewer and less severe side effects.[3]

With 2D planning, a small number (2–4 fields) of simple square or rectangular fields were used. The field could be shaped using custom-designed heavy blocks manually inserted into the treatment beam — a different set of blocks for each field. This was expensive, slow and arduous work. With the introduction of computers and radiation

The TomoTherapy Hi-Art® helical tomotherapy unit in use at the Odette Cancer Centre. Image provided by Derek Hyde, PhD, Medical Physicist, Odette Cancer Centre.

planning software, fast and accurate calculation of the distribution of the radiation dose from each beam of radiation was possible. Treatment was limited to 1 or 2 fields, with minimal modification of the shape of the radiation beam, because a member of the staff had to calculate by hand what the dose would be across each beam and how it would vary as it traveled through the tissues of the body — hours of work. As computers and software replaced these hand calculations, radiation professionals gained confidence in using more sophisticated beam arrangements and shaping.

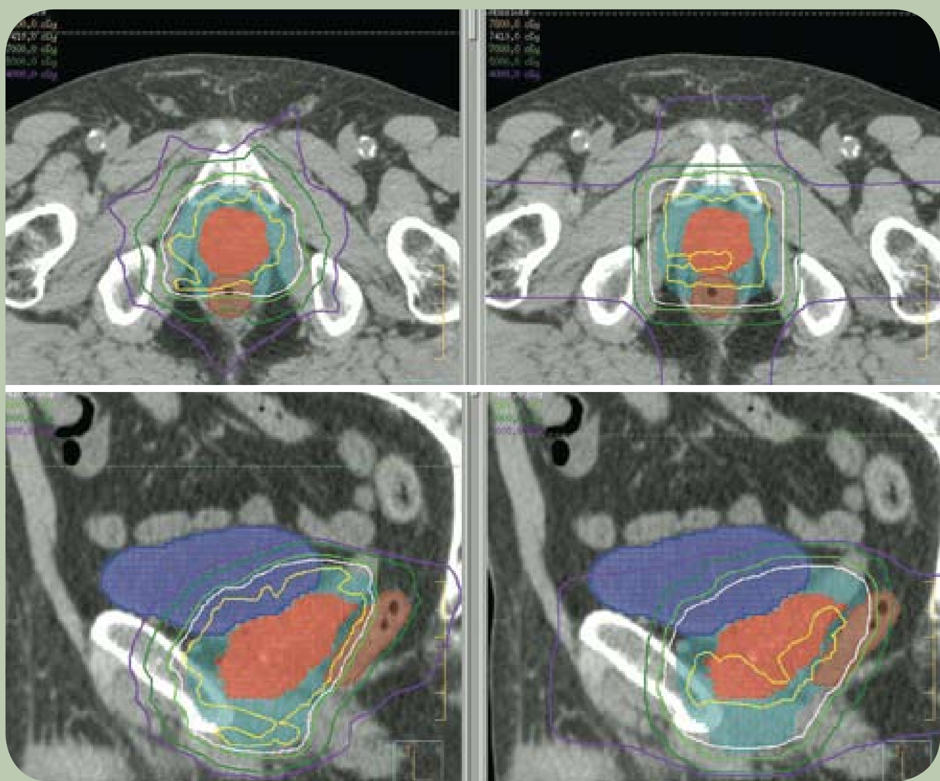
Parallel to the progress being made by calculating doses by computer, the design of radiation delivery machines evolved to incorporate sophisticated, electronically controlled blocking mechanisms called multi-leaf collimators. This innovation allowed for more efficient delivery of multiple-field radiation. Now 3D conformal radiation therapy (3DCRT) uses multiple fields of radiation (typically 4–6), each potentially shaped by multi-leaf collimators.

IMRT and IGRT

Intensity modulated radiation therapy (IMRT) was the next technologic advance in EBRT. Instead of providing the same intensity of radiation across the opening of each field, the machine and planning systems allowed modulation of the radiation intensity across each field. This yielded unprecedented ability to control and sculpt the radiation dose, maintaining good coverage to the target with even lower doses to normal tissues.

The latest advance has been the introduction of image-guided radiation therapy (IGRT), which allows the patient to be positioned on the treatment unit with verification of the precise location of the target just prior to radiation delivery. One example of IGRT technology is cone-beam CT, which allows 3D image guidance of the target area. The cone-beam CT equipment is added to a conventional treatment unit, permitting 3D visualization of the region of interest. In the case of prostate cancer, the prostate gland is imaged by cone-beam CT prior to treatment, confirming that the dose will be delivered to the intended target. If the position of the prostate has changed (possibly due to bladder or rectum filling), the position is corrected by remotely shifting the treatment couch prior to delivery of radiation. TomoTherapy is another example of IGRT. This radiation device is a hybrid of a CT scanner and a linear accelerator, allowing a helical CT scan (a fast, high-definition scan) to be done just prior to radiation delivery.

FIGURE 1. Comparison of 3D conventional to IMRT dose distributions



Top: Sagittal views of the dose distribution using IMRT (left) and conventional 4-field technique (right) to deliver a prescribed dose of 7800 cGy in 39 fractions. The high-dose isodose lines are 7800 cGy (yellow), 7400 cGy (white) and 7000 cGy (light green); the lower-dose isodose lines are 5000 cGy (forest green) and 4000 cGy (purple). Bottom: Axial views of the dose distribution comparison.

IMRT vs 3D conventional imaging

Figure 1, page 29, illustrates both IMRT (left) and 3D conventional sagittal and axial (right) dose distributions for a patient with intermediate-risk prostate cancer given a prescribed dose of 7800 centigray (cGy) in 39 treatment fractions. The aim is to cover the prostate and margin by an approximately 7800 cGy isodose line, the current standard total dose at the University of Toronto. The IMRT plan is generated based on 7 intensity-modulated fields, and the 3D conventional approach is based on 4 non-intensity modulated fields. The high-dose isodose lines (7800, 7410 and 7000 cGy) conform more tightly around the prostate gland (red colour wash) with a safety margin (green colour wash), while sparing more of the rectum (brown contour). The lower-dose isodose lines (5000 cGy and 4000 cGy) also indicate that less normal tissue is being exposed to the specified doses by IMRT compared to 4-field conventional distribution.

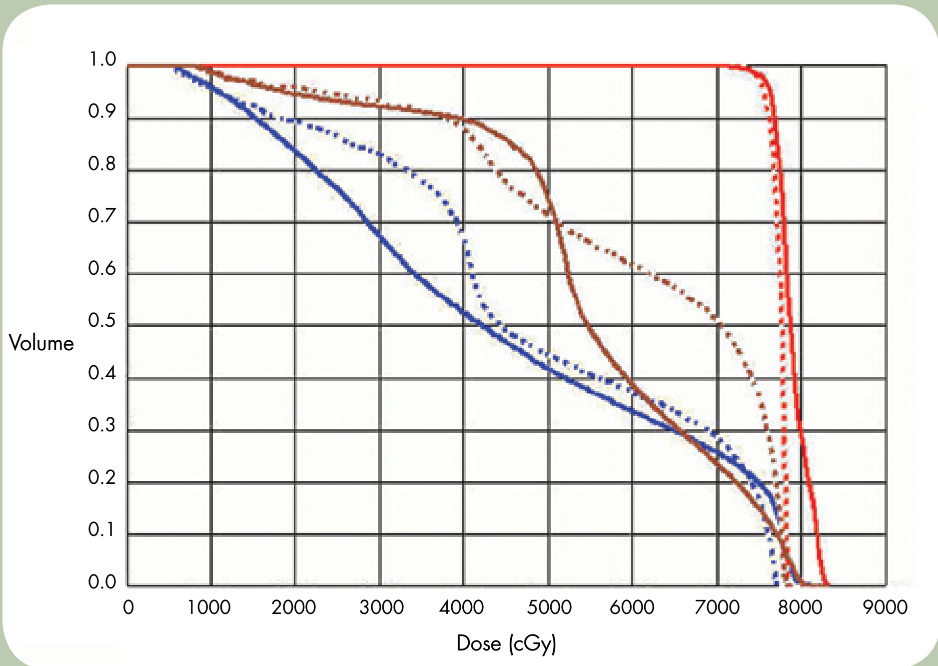
Figure 2 shows a dose-volume histogram (DVH) analysis of the entire dose delivered according to the complete planning target volume (PTV) of the prostate with margin, rectum and bladder. The dose distribution to the target (red lines) is essentially the same with the 2 techniques: the difference is clearly in the rectum and bladder. The rectal distribution (brown lines) for IMRT shows a lower dose between approximately 5000 cGy and 7800 cGy, and allows for less than 25% of the rectum to receive 7000 cGy — the dose shown to correlate with rectal toxicity.[3] The 4-field treatment plan does not satisfy this dose-volume relationship and is therefore unacceptable. The DVH also illustrates more sparing of the bladder in the lower-dose region (below approximately 4200 cGy), but as the bladder is intimately associated with the PTV, sparing at the high-dose region is usually not possible. Further, specific dose-volume constraints to predict for bladder toxicity have not yet been determined — unlike for the rectum.

The benefit of 3DCRT has been established based on a randomized controlled trial (RCT). Dearnaley et al reported on 225 men randomized to either conventional or conformal radiation. The incidence of radiation-induced proctitis and bleeding was reported to be 15% with conventional vs 5% with conformal radiation ($p = 0.01$).[4]

Dose-escalated radiation

The evolution of technology in radiation oncology has resulted in the investigation of doses beyond the traditional 6400-cGy to 7000-cGy range. Further, as we spare normal tissues more effectively using IMRT, hypofractionated high-dose radiotherapy — where the aim is to deliver an equivalent or greater biologic dose in shorter overall treatment time — is now safe to investigate in prostate cancer patients.

FIGURE 2. Dose-volume histogram of the planning target volume



The dashed lines represent the distribution of dose for a given percent volume using the conventional 4-field approach, and the solid lines represent the distribution of dose for a given percent volume using IMRT. Red signifies the planning target volume (prostate and margin), brown represents rectum, and blue represents bladder.

LONG-TERM BIOCHEMICAL CONTROL WITH HIGH-DOSE EBRT

Table 1 presents outcomes reported in several RCTs of dose escalation using EBRT to treat prostate cancer. As the total dose and fractionation vary, the biologic effective dose (BED) for each of the treatment arms is also presented. The BED equates the differences in fractionation, providing a comparison of the dose delivered.

Efficacy

Four of the 7 studies significantly favoured dose escalation. Peeters et al reported a 10% advantage in biochemical control with the addition of 1000 cGy, delivering an additional 2000 cGy_2 BED,[5] with all treatment planned using 3DCRT. Zietman et al reported a significant 19% improvement in biochemical outcome when the dose was increased by 900 cGy, delivering an additional 1700 cGy_2 BED;[6]

these patients all had 3CDRT up to 5040 cGy, then an additional boost dose delivered by proton therapy. Kuban et al recently reported updated results of the landmark M.D. Anderson Cancer Center dose escalation study:[7] the addition of 800 cGy, delivering an additional 1600 cGy_2 BED, yielded a 19% benefit in biochemical control. Dearnaley et al recently reported outcomes of delivering a 1000 cGy increase in the total dose — an additional 2000 cGy_2 BED — resulting in a significant improvement in biochemical-progression-free survival of 11% (hazard ratio 0.67, p = 0.0007).[8]

In one negative study, Shipley et al reported the first prostate dose escalation RCT.[9] All patients had high-risk, clinically advanced disease. They received 5040 cGy by 2D fields followed by a conformal proton therapy boost. An additional 800 cGy, delivering an extra 1800 cGy_2 BED, provided an 8% improvement in non-biochemical local control that was not statistically significant. Because this study was undertaken prior to widespread PSA testing, this result is not comparable to the other studies.

Hypofractionation

Yeoh et al[10] and Lukka et al[11] reported RCTs of similar-dose treatment comparing hypofractionated radiation (shorter treatment time with a roughly equivalent BED) to the then-current standard. Neither trial demonstrated a significant difference in biochemical control, indicating that it is safe to increase the dose per fraction in order to reduce the treatment time. The Ontario Clinical Oncology Group (OCOG) 2005 Prostate Fractional Irradiation Trial (PROFIT) (NCT00304759, ongoing in Alberta, Ontario and Quebec) compares 7800 cGy delivered in 8 weeks vs 6000 cGy in 4 weeks. Results will determine whether shorter and more intense treatment provides equivalent or improved biochemical control compared to standard treatment. This study is important, as it is difficult for prostate cancer patients to commit to daily therapy for 8 weeks. If treatment can be reduced to 4 weeks with the same efficacy and toxicity, both patients and the healthcare system overall will benefit.

TABLE 1. Dose escalation randomized controlled studies of external beam radiotherapy for prostate cancer

author (period of study accrual)	median followup (number of patients)	randomization arms: (dose/fractions/BED/technique)	biochemical relapse-free survival	late toxicity
Yeoh et al[10] (1996–2003)	48 months (217)	5500 cGy/20 fractions/13100 cGy_2/3D vs 6400 cGy/30 fractions/13200 cGy_2/3D	5-year: 57.4% vs 55.5 % (NS)	GI: 51% at 5 years, with some effect on activities of daily living GU: 46% at 5 years, with some effect of activities of daily living
Peeters et al[4] (1997–2003)	50.7 months (669)	7800 cGy/39 fractions/15600 cGy_2/3DCRT vs 6800 cGy/29 fractions/14700 cGy_2/3DCRT	5-year: 64% vs 54% (SIG)	GI: Grade ≥3 : 5% vs 4% GU: Grade ≥ 3 : 13% vs 11%
Dearnaley et al[8] (1998–2002)	63 months (843)	7400 cGy/37 fractions/14800 cGy_2/3DCRT vs 6400 cGy/32 fractions/12800 cGy_2/3DCRT	5-year: 71% vs 60% (SIG)	5 year proctitis Grade ≥ 2: 4% vs 2% 5 year GU: Grade ≥ 2: 11% vs 8%
Zeitman et al[5] (1996–1999)	66 months (393)	7020 cGyE/39 fractions/13300 cGy_2/3CDRT + proton vs 7920 cGyE/44 fractions/15000 cGy_2/3DCRT + proton	5-year: 80.4% vs 61.5% (SIG)	GI: Grade ≥ 3: 2% vs 1% GU: Grade ≥3: 1% vs 1%
Lukka et al[9] (1995–1998)	68.4 months (936)	5250 cGy/20 fractions/12100 cGy_2/2D vs 6600 cGy/33 fractions/13200 cGy_2/2D	5-year: 53% vs 60% (NS)	GI: 1.9% vs 1.9% GU: 3.2% vs 3.2%
Kuban et al[6] (1993–1998)	104.4 months (301)	7800 cGy/39 fractions/15600 cGy_2/2D + 3DCRT boost vs 7000 cGy/35 fractions/14000 cGy_2/2D	8-year: 78% vs 59% (SIG)	10-year GI Grade ≥ 3: 7% vs 1% 10-year GU Grade ≥ 3: 5% vs 4%
Shipley et al[7] (1982–1992)	61 months (202)	7560 cGyE/49 fractions/14800 cGy_2/2D + proton vs 6720 cGyE/32 fractions/13000 cGy_2/2D	5-year clinical local control: 92% vs 80% (NS)	rectal bleeding: 8% vs 2% hematuria: 2% vs 2%

GI: gastrointestinal; GU: genitourinary; cGy: centigray; cGyE: cobalt-centigray equivalent radiation unit associated with proton therapy; NS: non-significant difference with p ≥ 0.05: SIG: significant difference with p < 0.05.

Toxicity

Although toxicity outcomes are reported using various scales, the results presented in **Table 1**, page 31, indicate that the risk of late toxicity requiring medical intervention to both the rectum and bladder is low, at about 5% to 10%. The data suggest that increasing the dose with modern radiation planning does not increase the risk of toxicity, as no significant differences in the rates of Grade 3 or higher complications have been reported.

Although not sufficiently significant to warrant medical intervention, some form of gastrointestinal and genitourinary toxicity does occur, affecting patients' functioning, as reported by Yeoh et al.[10] We aim to further reduce these side effects by learning more about what doses the rectum, bladder and small bowel can safely tolerate, and more precisely conforming the dose away from the organs surrounding the prostate.

LIVING UP TO THE HYPE?

These randomized studies imply that dose escalation does indeed lead to greater PSA control rates with benefit in the range of 10% to 20%, and little or no increase in toxicity. Hypofractionation appears to be equally effective and safe, while saving trips to the cancer centre. OE

Disclosure

The authors report having no potential conflicts of interest related to this article.

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