Radiation therapy in prostate cancer: a risk-adapted strategy

A.J. Hayden MD, C. Catton MD,† and T. Pickles MD‡*

ABSTRACT

External-beam radiotherapy and brachytherapy, widely utilized as curative treatment modalities for prostate cancer, have undergone significant clinical and technological advances in recent decades. Contemporary radiotherapy treatment algorithms use pretreatment prognostic factors to stratify patients into low-, intermediate-, and high-risk groups that correlate with both pathologic stage of disease and risk of recurrence after treatment. The use of risk groups and additional prognostic factors guide selection of the optimal treatment modalities for individual patients. Here, the roles of external-beam radiotherapy, brachytherapy, and neoadjuvant or adjuvant androgen deprivation therapy are discussed in that context. Additional prognostic factors for recurrence in the post-prostatectomy setting and the role of adjuvant and salvage radiation therapy are also reviewed. The risk-adaptive approach in radiotherapy for prostate cancer aims to optimize cancer control outcomes while minimizing the morbidity of treatment.

KEY WORDS

Prostatic neoplasms, radiotherapy, brachytherapy, nomogram, adjuvant androgen deprivation therapy

1. INTRODUCTION

Risk-adaptive strategies for curative radiotherapy (RT) in prostate cancer (PCa) take advantage of recognized pre-treatment clinical and pathologic indicators to assess the probability that an untreated PCa is organ-confined, localized but extracapsular, or accompanied by micrometastases. These indicators can include use of tumour–node (TN) category to assess local tumour bulk and extent; biopsy core mapping and percentage core involvement; tumour grading with Gleason score; and biochemical parameters such as absolute level of prostate-specific antigen (PSA) and PSA velocity or doubling time. These indicators are variously used to assign a patient to a defined risk category (Table I) [1] or are entered into a nomogram to provide a probability of the actual pathologic TN (pTN) category [2]. In the postoperative setting, additional information such as margin status, pTN category, and postoperative PSA kinetics can be used to assess the risk of failure without additional treatment and the utility of postoperative RT to the tumour bed to reduce that risk [3]. In this brief article, we review the current role of RT in the context of the foregoing risk groupings.

2. DISCUSSION

2.1 Prostate Brachytherapy: Not Just For Low-Risk Cancer

Low-dose-rate (LDR) permanent prostate brachytherapy involves the permanent implantation of multiple radioactive sources within the prostate and periprostatic tissues under real-time transrectal ultrasonography guidance. The characteristics of the radioactive isotopes create a steep radiation dose gradient that allows a high dose of radiation to be delivered to the prostate gland, with a rapid decrease in dose beyond the periprostatic treatment margin, minimizing the volume of normal tissue irradiated.

A small randomized trial comparing radical retropubic prostatectomy and LDR prostate brachytherapy in low-risk PCa demonstrated equivalent outcomes, with a 5-year biochemical progression-free survival (bPFS) of 91.0% for surgery versus 91.7% for brachytherapy [4]. Patients treated with brachytherapy experienced fewer quality-of-life side effects, leading some to suggest that brachytherapy is the preferred treatment. Further randomized data are absent, but large retrospective comparative analyses in localized disease suggest equivalent outcomes for brachytherapy in comparison with surgery or with high-dose external-beam RT (EBRT) [5].

Current international guidelines [1,6] advise that monotherapy with LDR prostate brachytherapy is suitable for patients with low-risk disease. The role of LDR brachytherapy in intermediate-risk disease

TABLE I National Comprehensive Cancer Network prostate cancer risk groups and suggested radiation therapy (RT) framework

Risk group	*Definition*	*Role of RT*
Very low	T1c, Gleason score ≤ 6, PSA 10 ng/mL, fewer than 3 cores positive with 50% or less of each core involved, AND PSA density < 0.15 ng/mL/g	Low-dose-rate brachytherapy or external-beam RT are alternatives to active surveillance, which is the preferred option.
Low	T1–T2a, Gleason score ≤ 6, AND PSA ≤ 10 ng/mL	Low-dose-rate brachytherapy or external-beam RT without androgen deprivation therapy.
Intermediate	T2b–c, Gleason score 7 OR PSA 10–20 ng/mL, AND absence of high-risk features	Low-dose-rate brachytherapy (lower intermediate risk and selected higher risk) or external-beam RT with or without androgen deprivation therapy (4–6 months) and dose escalation by means of intensity-modulated RT or low- or high-dose-rate brachytherapy boost.
High	T3–T4 OR Gleason score 8–10 OR PSA > 20 ng/mL	External-beam RT with androgen deprivation therapy (1–3 years) and dose escalation by means of intensity-modulated RT or low- or high-dose-rate brachytherapy boost.
Very high	T3b–T4	

PSA = prostate specific antigen.

remains more controversial, but a growing body of literature is demonstrating excellent biochemical outcomes from brachytherapy for patients with both low- and intermediate-risk disease—outcomes that are at least comparable to the best reported outcomes for the alternative treatment modalities [4,7–9]. Concerns about the ability of brachytherapy alone to adequately treat extracapsular extension and seminal vesicle invasion are overcome by contemporary brachytherapy techniques, which typically specify that the brachytherapy target volume include the prostate with a 3–5 mm margin (or more) to encompass potential extracapsular extension, with or without the base of the seminal vesicles [10].

The biochemical outcomes with brachytherapy are also durable with longer term follow-up. Taira *et al.* reported 12-year bPFS rates of 97.4% and 96.4% respectively for low- and intermediate-risk patients ($n = 463$) treated with prostate brachytherapy monotherapy [7]. Results from the BC Cancer Agency for 1006 patients with low- and "favourable" intermediate-risk disease, of whom 65% received neoadjuvant androgen deprivation therapy (ADT), demonstrated 5- and 7-year bPFS rates of 95.6% and 94% [8]. For 1449 patients, 27% of whom received ADT and 20% supplemental EBRT, Potters *et al.* reported 12-year bPFS rates of 89%, 78%, and 63% for low-, intermediate-, and high-risk patients [9].

Results are not as good in all series, and this variation may reflect "implant quality," which can be assessed by dosimetric analysis of post-implant computed tomography imaging. The largest published series of patients treated with prostate brachytherapy monotherapy, which included 2693 patients with T1–T2 PCa from 11 institutions, did not achieve such results: their 8-year American Society for Radiation Oncology bPFS rates for low-, intermediate-, and high-risk groups were 82%, 70%, and 48%. However, patients receiving "high quality" implants (as measured by dosimetric parameters) demonstrated superior results, with an overall bPFS of 92%–93% [11].

Excellent results have also been demonstrated for LDR prostate brachytherapy combined with supplemental EBRT. The Seattle group achieved 15-year bPFS rates of 86%, 80%, and 68% for low-, intermediate-, and high-risk patients respectively [12]. Whether the combination of LDR brachytherapy and EBRT is superior to brachytherapy alone in higher-risk patients remains unanswered, but combined treatment provides improved dose coverage of the seminal vesicles and gives the clinician the option of treating the pelvic lymph nodes in higher-risk patients.

External-beam RT may also be combined with high-dose-rate (HDR) prostate brachytherapy. As with the combination of LDR brachytherapy and EBRT, the combination of HDR brachytherapy and EBRT has produced biochemical outcomes of 96%, 88%, 69% at 5 years for modified low-, intermediate-, and high-risk groups [13].

In patients with large prostate glands (>50–60 mL), ADT can be used for cytoreduction, reducing prostate volume and making the gland suitable for implantation. The benefit of planned neoadjuvant or adjuvant ADT in patients treated with brachytherapy remains controversial, with no clear consensus about the added value in any situation other than cytoreduction.

The optimal selection of patients for brachytherapy monotherapy as opposed to combined treatment with EBRT with or without ADT depends on pretreatment prognostic factors and risk group, and on multiple patient factors such as comorbidities, life expectancy, baseline urinary function, and patient treatment preference. Patients with low-risk disease are adequately treated with LDR brachytherapy alone, having excellent biochemical outcomes. Contemporary evidence supports the use of LDR brachytherapy monotherapy in intermediate-risk PCa [7,8], although the recurrence risk, as expected with any treatment, will also increase with higher-risk disease. A common strategy is to recommend brachytherapy monotherapy for favourable intermediate-risk disease, with combined EBRT and brachytherapy reserved for patients with unfavourable features—although the tipping point for "unfavourable" is highly variable among clinicians. In patients with high-risk disease who are at higher risk of any or all of seminal vesicle invasion, pelvic nodal involvement, or distant metastatic disease, combined-modality treatment with EBRT (with or without supplemental brachytherapy) and ADT is frequently preferred.

2.2 External-Beam RT

External-beam RT has a very long history in the curative treatment of localized PCa. This flexible, noninvasive outpatient therapy can effectively treat a wide range of patients, including those with organ-confined and locally advanced disease. It has the disadvantage of requiring that treatment be given in fractionated courses extending for 8 weeks or more in some circumstances.

Once a decision to treat with RT has been made, the RT plan is defined either to limit treatment to the gland (in the most favourable situations) or to extend treatment to include the periprostatic tissues, seminal vesicles, and even the pelvic lymph nodes (in less favourable situations). The aim is to minimize treatment-related toxicity for those with more favourable disease and to maximize locoregional tumour control for those with less favourable disease. Combined RT and systemic ADT (discussed later in this article) may be used to treat presumed micrometastatic disease beyond the locoregional RT treatment volumes.

The continual technical advancements in RT target delineation and in RT planning and delivery since the mid-1990s have improved tumour control and reduced the side effects of treatment. Prostate RT has been a major beneficiary of those advancements. Early work with three-dimensional conformal prostate RT demonstrated that toxicity could be reduced when RT volumes were more precisely conformed to the intended target. This improvement provided an opportunity for safe dose escalation of radiation to the prostate [14].

Four randomized trials of conformal RT have shown an advantage with dose escalation for localized PCa [15–18], and two of those trials recently reported long-term biochemical outcomes [15,16]. The trials enrolled men in all risk groups with clinically localized PCa and compared conformal RT at conventional doses of 64–70.2 Gy with conformal RT at escalated doses of 74–79.2 Gy. The highest dose escalation was achieved with a proton boost [15]. These four trials varied in sample size, risk stratification of patients entered, duration of follow-up, and use of adjunctive ADT. All showed an advantage in bPFS ranging from 7% to 19% with RT dose escalation—an advantage that appears to be holding with longer follow-up. Only the U.K. Medical Research Council (MRC) trial stratified patients by risk groups, and advantages for dose-escalation were seen for patients at low, intermediate, and high risk of PSA failure. However, that advantage reached statistical significance only for the high-risk group, which represented 44% of the patients entered. Still, the advantages of dose escalation probably apply to all risk groups, as shown in a recent meta-analysis [19].

A radiation dose of at least 74 Gy should be the standard of care for all men with localized PCa who choose treatment with EBRT. The optimal dose of EBRT has not yet been established for these patients, and an argument can be made for additional dose escalation, provided that it can be delivered safely.

The foregoing trials were completed before modern RT targeting and delivery techniques such as intensity-modulated RT (IMRT) and image-guided RT (IGRT) became widely available. More bladder and rectal tissues were included in the treatment volume than is currently considered appropriate, and substantial toxicity was reported for dose escalation (although that toxicity was consistent with conventional RT of the time). In trials of dose escalation, reported rates of late rectal grade 2 toxicity were 25% at the MD Anderson Cancer Center [20], 26% in the Netherlands [21], and 33% by the MRC [18]. Those results compare with reports of IMRT treatment to 81 Gy (3% of patients experienced late rectal toxicity at grade 2 or higher) [22] and treatment with conformal radiotherapy and IGRT to 79.8 Gy (12% of patients experienced late rectal toxicity at grade 2 or higher) [23]. Those reductions in late toxicity with IMRT and IGRT provide an opportunity for further dose escalation with conventional fractionation [22]. An alternative strategy is to use the improved precision of IGRT or IMRT (or both) to safely compress a standard course of dose-escalated RT into a shorter overall course with larger daily fraction sizes. This "hypofractionation" approach is currently under investigation in randomized trials [24].

2.3 Postoperative RT

The likelihood of surgical cure with radical prostatectomy is determined by the experience of the surgeon [25], by patient selection [26,27], and possibly by the surgical technique used [28–30]. Surgical margin positivity rates currently fall between 11% and 38% [31], although those rates may increase, given the trend toward selecting patients with higher-risk and more locally advanced disease for surgery [32–34].

Data from large surgical series have demonstrated that pT3a and pT3b disease, or a positive surgical margin, predicts for an increased risk of biochemical failure [35] and that a detectable postoperative PSA is associated with a high risk of subsequent clinical failure [36]. Postoperative RT is potentially curative for these high-risk men, provided that their presumed microscopic residual disease can be safely encompassed in a pelvic RT volume.

Three randomized trials [37–39] have shown an advantage in biochemical relapse-free survival with postoperative RT for men with a positive surgical margin or pT3 disease, or both. The trial with the longest follow-up has also shown an advantage in overall survival. These trials compared postoperative RT with no RT and were completed before the era of sensitive PSA testing. They undoubtedly demonstrated an advantage for postoperative RT in men with high-risk pathologic features at prostatectomy, but they also demonstrated that not all men with these adverse findings will relapse and not all who are treated with RT will be cured. The combined therapy also carries an increased risk of late toxicity compared with surgery alone. With the intention of selecting candidates that might benefit from postoperative RT, one option is to delay RT until clinical or biochemical evidence of relapse is obtained. However, no prospective data support that approach, and available retrospective data on postoperative salvage RT is confounded by highly variable patient selection, follow-up, and use of hormonal therapy.

In contrast with adjuvant RT, salvage RT has postoperative results that are disappointing. In one large multi-institutional pooled series, 6-year biochemical relapse-free survival was 37% [40]. Outcome is related to postoperative PSA kinetics and PSA level at treatment, and a postoperative selective salvage strategy based on modern ultrasensitive PSA assays could possibly be as effective as immediate postoperative RT. This hypothesis is currently under investigation in a large international randomized trial, RADICALS (Radiotherapy and Androgen Deprivation in Combination After Local Surgery), by the MRC and the National Cancer Institute of Canada Clinical Trials Group (see NCT00541047 at www.ClinicalTrials.gov). Trials such as RADICALS should be strongly supported.

In the absence of these data, it is important that patients with adverse postoperative findings such as pT3 disease and positive surgical margins be given the opportunity to discuss with a radiation oncologist the merits and limitations of immediate postoperative RT or the option of participation in a clinical trial [41].

2.4 Androgen Deprivation Therapy

One of the great advances in the management of higher-risk PCa has been the appreciation of the extra value of ADT when combined with RT. Several foundational trials [42–45] showed survival benefits with such a combined-modality approach.

The European Organisation for Research and Treatment of Cancer (EORTC) trials showed that adjuvant ADT for 3 years is superior to none, with a hazard ratio (HR) for survival of 0.51 [42]. It was hoped that a shorter duration might be as efficacious, but a more recent trial showed that 6 months was inferior to 3 years, albeit with a HR of 0.7 [43]. Older U.S. studies showed that ADT for 4 months was superior to none, as was "lifelong ADT" (median actual duration: 3.6 years) [46]. Completed but not yet reported trials are also exploring other durations such as 18 months versus 36 months (see NCT00223171 at www.ClinicalTrials.gov), and 2 months versus 6 months (see NCT00005044 at www.ClinicalTrials.gov).

The optimal duration of ADT when combined with EBRT is thus not known; it likely varies with tumour and treatment factors. A recent multi-institution analysis [47] showed that most of the benefit is obtained from the first 6 months of ADT (57% of total potential benefit), with further benefit from the next 6 months (88% of total potential benefit), but with little additional benefit beyond 18 months (100% benefit), and no further additional benefit from longer durations. Patients with cancers of higher T stage and those treated to lower radiation doses showed significantly greater benefit with increasing ADT duration ($p = 0.016$ and $p = 0.007$ respectively). Pre-treatment PSA, Gleason score, age, and risk group were not predictive of response to ADT.

The timing of ADT in relation to EBRT has also been studied. Animal models have suggested a greater benefit from neoadjuvant use [48], but clinical support for neoadjuvant use is weak. The Radiation Therapy Oncology Group (RTOG) 9413 trial randomized 1300 patients to either 4 months of neoadjuvant and concurrent ADT or 4 months of pure adjuvant ADT; no differences in the subsequent biochemical control rates were observed. Our own work also shows that duration drives the benefit, rather than precise timing—that is, predominantly neoadjuvant or adjuvant use [49].

More recently, survival benefits have also been shown for ADT in patients with intermediate-risk PCa [50]. At 12 years after 2000 men had been randomized to 4 months of ADT (2 months neoadjuvant, 2 months concurrent) or to no ADT, a small but significant overall survival advantage favouring ADT (51% vs. 46%) was observed. Further details of the trial are pending

and will need to be considered when determining the risk–benefit picture for individual patients. A small randomized trial from the United States, in which about three quarters of the patients had non-high-risk cancer, also showed a survival benefit [51].

It is instructive to consider why ADT leads to such profound improvements when combined with RT, but has not shown a benefit when combined with surgery [52]; and why ADT alone is inferior in comparison with its combined use with EBRT [53]. At least four possible mechanisms have been postulated:

- Additive cell death from cytoreduction as a consequence of ADT use (there appears to be no radiosensitization) [54]
- Decreased tumour hypoxia (an oxic state is required for optimal cell kill from radiation) [55]
- Increased apoptosis (which is a minor mechanism, accounting for only about 6% of cell kill) [54]
- Possible immune modulation (ADT with RT appears to stimulate a treatment-associated autoantibody response, which may affect cancer cell clones outside the radiation volume) [56]

An unanswered question is the extent to which higher radiation doses might obviate the benefit from adjuvant ADT. As suggested earlier [47], some retrospective data suggest that ADT is less efficacious when higher radiation doses are used.

Toxicity with ADT has increasingly been recognized in the last few years. Some potential side effects may be mitigated by appropriate lifestyle changes [57] or by monitoring with selective intervention [58]. The emergence of increased risk for diabetes and excess cardiac mortality is of more concern [59]. It is important to note that excess cardiac mortality has not been shown in the already-discussed randomized trials in which it was studied [60]. Nonetheless, the overenthusiastic use of ADT in men outside the risk groups described is not encouraged because of the quality-of-life detriment that usually accompanies its use and the lack of evidence of benefit with low-risk cancer.

Current guidelines from the National Comprehensive Cancer Network (NCCN) [1] recommend consideration of short-course ADT with RT for those with intermediate-risk cancer and of long-term (2–3 years) ADT for high-risk cancers. It should be noted that the clinical trials demonstrating benefit for ADT in intermediate-risk disease used conventional-dose RT and that the utility of short-course ADT with dose escalation is not currently known. Use of ADT in low-risk cancer is not recommended, except in the setting of cytoreduction before brachytherapy.

3. SUMMARY

A risk-adaptive strategy is recommended to guide RT treatment selection and to inform prognosis for PCa patients. Ongoing research into additional prognostic markers to further identify the patients that may not require treatment and those that may benefit from more-intensive or less-intensive therapy is encouraged.

4. REFERENCES

1. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer V.2.2010.* Fort Washington, PA: NCCN; 2010. [Available online at: www.nccn.org/professionals/physician_gls/PDF/prostate.pdf (free registration required); cited June 16, 2010]
2. Makarov DV, Trock BJ, Humphreys EB, *et al.* Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. *Urology* 2007;69:1095–101.
3. Schroeck FR, Kattan MW, Moul JW, *et al.* Re-calibration and external validation of an existing nomogram to predict aggressive recurrences after radical prostatectomy. *BJU Int* 2009;105:1654–9.
4. Giberti C, Chiono L, Gallo F, Schenone M, Gastaldi E. Radical retropubic prostatectomy versus brachytherapy for low-risk prostatic cancer: a prospective study. *World J Urol* 2009;27:607–12.
5. Kupelian PA, Potters L, Khuntia D, *et al.* Radical prostatectomy, external beam radiotherapy < 72 Gy, external beam radiotherapy ≥ 72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1–T2 prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:25–33.
6. Ash D, Flynn A, Battermann J, de Reijke T, Lavagnini P, Blank L. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. *Radiother Oncol* 2000;57:315–21.
7. Taira AV, Merrick GS, Galbreath RW, Wallner KE, Butler WM. Natural history of clinically staged low-and intermediate-risk prostate cancer treated with monotherapeutic permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2010;76:349–54.
8. Morris W, Keyes M, Palma D, *et al.* Population-based study of biochemical and survival outcomes after permanent ^{125}I brachytherapy for low-and intermediate-risk prostate cancer. *Urology* 2009;73:860–5.
9. Potters L, Morgenstern C, Calugaru E, *et al.* 12-Year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2005;173:1562–6.
10. Sylvester JE, Grimm PD, Eulau SM, Takamiya RK, Naidoo D. Permanent prostate brachytherapy preplanned technique: the modern Seattle method step-by-step and dosimetric outcomes. *Brachytherapy* 2009;8:197–206.
11. Zelefsky MJ, Kuban DA, Levy LB, *et al.* Multi-institutional analysis of long-term outcome for stages T1–T2 prostate cancer treated with permanent seed implantation. *Int J Radiat Oncol Biol Phys* 2007;67:327–33.
12. Sylvester JE, Grimm PD, Blasko JC, *et al.* 15-Year biochemical relapse free survival in clinical stage T1–T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. *Int J Radiat Oncol Biol Phys* 2007;67:57–64.

13. Galalae RM, Martinez A, Mate T, *et al.* Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:1048–55.
14. Dearnaley DP, Khoo VS, Norman AR, *et al.* Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. *Lancet* 1999;353:267–72.
15. Zietman AL, Bae K, Slater JD, *et al.* Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol* 2010;28:1106–11.
16. Kuban DA, Tucker SL, Dong L, *et al.* Long-term results of the MD Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67–74.
17. Al-Mamgani A, Van Putten WLJ, Heemsbergen WD, *et al.* Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;72:980–8.
18. Dearnaley DP, Sydes MR, Graham JD, *et al.* Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;8:475–87.
19. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009;74:1405–18.
20. Huang EH, Pollack A, Levy L, *et al.* Late rectal toxicity: dose–volume effects of conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2002;54:1314–21.
21. Peeters STH, Heemsbergen WD, van Putten WLJ, *et al.* Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys* 2005;61:1019–34.
22. Zelefsky MJ, Levin EJ, Hunt M, *et al.* Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:1124–9.
23. Jarad M, Andrew B, Robert B, *et al.* Image guided dose escalated prostate radiotherapy: still room to improve. *Radiat Oncol* 2009;4:50. [Erratum in: *Radiat Oncol* 2009;4:65]
24. Miles EF, Lee R. Hypofractionation for prostate cancer: a critical review. *Semin Radiat Oncol* 2008;18:41–7.
25. Wilt TJ, Shamliyan TA, Taylor BC, MacDonald R, Kane RL. Association between hospital and surgeon radical prostatectomy volume and patient outcomes: a systematic review. *J Urol* 2008;180:820–9.
26. Suekane S, Noguchi M, Nakashima O, Yamada S, Kojiro M, Matsuoka K. Percentages of positive cores, cancer length and Gleason grade 4/5 cancer in systematic sextant biopsy are all predictive of adverse pathology and biochemical failure after radical prostatectomy. *Int J Urol* 2007;14:713–18.
27. Eisenberg ML, Cowan JE, Davies BJ, Carroll PR, Shinohara K. The importance of tumor palpability and transrectal ultrasonographic appearance in the contemporary clinical staging of prostate cancer. *Urol Oncol* 2009;:. [Epub ahead of print]
28. Potdevin L, Ercolani M, Jeong J, Kim IY. Functional and oncologic outcomes comparing interfascial and intrafascial nerve sparing in robot-assisted laparoscopic radical prostatectomies. *J Endourol* 2009;23:1479–84.
29. Zorn KC, Wille MA, Thong AE, *et al.* Continued improvement of perioperative, pathological and continence outcomes during 700 robot-assisted radical prostatectomies. *Can J Urol* 2009;16:4742–9.
30. Choo R, Hruby G, Hong J, *et al.* (In)-efficacy of salvage radiotherapy for rising PSA or clinically isolated local recurrence after radical prostatectomy. *Int J Radiat Oncol Biol Phys* 2002;53:269–76.
31. Stephenson AJ, Kattan MW, Eastham JA, *et al.* Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. *J Clin Oncol* 2009;27:4300–5.
32. Audenet F, Comperat E, Seringe E, *et al.* Oncologic control obtained after radical prostatectomy in men with a pathological Gleason score ≥ 8: a single-center experience. *Urol Oncol* 2009;:. [Epub ahead of print]
33. Boorjian SA, Blute ML. Surgical management of high risk prostate cancer: the Mayo Clinic experience. *Urol Oncol* 2008;26:530–2.
34. Kawamorita N, Saito S, Ishidoya S, *et al.* Radical prostatectomy for high-risk prostate cancer: biochemical outcome. *Int J Urol* 2009;16:733–8.
35. Swindle P, Eastham JA, Ohori M, *et al.* Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urol* 2005;174:903–7.
36. Pound CR, Partin AW, Epstein JI, Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy: patterns of recurrence and cancer control. *Urol Clin North Am* 1997;24:395–406.
37. Bolla M, van Poppel H, Collette L, *et al.* Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). *Lancet* 2005;366:572–8.
38. Wiegel T, Bottke D, Steiner U, *et al.* Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009;27:2924–30.
39. Thompson IM, Tangen CM, Paradelo J, *et al.* Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* 2009;181:956–62.
40. Stephenson AJ, Eastham JA. Role of salvage radical prostatectomy for recurrent prostate cancer after radiation therapy. *J Clin Oncol* 2005;23:8198–203.
41. Sia M, Pickles T, Morton G, Souhami L, Lukka H, Warde P. Salvage radiotherapy following biochemical relapse after radical prostatectomy: proceedings of the Genito-Urinary Radiation Oncologists of Canada consensus meeting. *Can Urol Assoc J* 2008;2:500–7.
42. Bolla M, Collette L, Blank L, *et al.* Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet* 2002;360:103–8.

43. Bolla M, de Reijke TM, Van Tienhoven G, *et al.* Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009;360:2516–27.
44. Pilepich MV, Winter K, Lawton CA, *et al.* Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005;61:1285–90.
45. Pilepich MV, Winter K, John MJ, *et al.* Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001;50:1243–52.
46. Lawton CA, Winter K, Grignon D, Pilepich MV. Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31. *J Clin Oncol* 2005;23:800–7.
47. Williams SG, Pickles T, Buyyounouski MK, Kestin LL, Duchesne GM. The optimum duration of combination androgen deprivation therapy (ADT) with prostate cancer radiotherapy: determining the duration–benefit relationship from multi-institutional analysis. *Int J Radiat Oncol Biol Phys* 2010;:. [In press]
48. Zietman AL, Prince EA, Nakfoor BM, Park JJ. Androgen deprivation and radiation therapy: sequencing studies using the Shionogi *in vivo* tumor system. *Int J Radiat Oncol Biol Phys* 1997;38:1067–70.
49. Pickles T, for the Prostate Cohort Outcomes Initiative. Duration, not timing is important when androgen ablation is combined with external beam RT [abstract]. *Can J Urol* 2004;11:2232.
50. McGowan D, Hunt D, Jones CU, *et al.* Short-term endocrine therapy prior to and during radiation therapy improves overall survival in patients with T1b–T2b adenocarcinoma of the prostate and PSA $\leq$ 20: initial results of RTOG 94-08 [abstract]. *Int J Radiat Oncol Biol Phys* 2010;77:1.
51. D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-Month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. *JAMA* 2004;292:821–7.
52. Klotz L, Gleave M, Goldenberg S. Neoadjuvant hormone therapy: the Canadian trials. *Mol Urol* 2000;4:233–7.
53. Widmark A, Klepp O, Solberg A, *et al.* Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet* 2009;373:301–8.
54. Pollack A, Salem N, Ashoori F, *et al.* Lack of prostate cancer radiosensitization by androgen deprivation. *Int J Radiat Oncol Biol Phys* 2001;51:1002–7.
55. Vergis R, Corbishley CM, Norman AR, *et al.* Intrinsic markers of tumour hypoxia and angiogenesis in localised prostate cancer and outcome of radical treatment: a retrospective analysis of two randomised radiotherapy trials and one surgical cohort study. *Lancet Oncol* 2008;9:342–51.
56. Nesslinger NJ, Sahota RA, Stone B, *et al.* Standard treatments induce antigen-specific immune responses in prostate cancer. *Clin Cancer Res* 2007;13:1493–502.
57. Segal RJ, Reid RD, Courneya KS, *et al.* Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol* 2009;27:344–51.
58. Duncan GG, Corbett T, Lukka H, Warde P, Pickles T. GU radiation oncologists consensus on bone loss from androgen deprivation. *Can J Urol* 2006;13:2962–6.
59. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006;24:4448–56.
60. Efstathiou JA, Bae K, Shipley WU, *et al.* Cardiovascular mortality and duration of androgen deprivation for locally advanced prostate cancer: analysis of RTOG 92-02. *Eur Urol* 2008;54:816–24.

Corresponding author: Tom Pickles, BC Cancer Agency, 600 West 10th Avenue, Vancouver, British Columbia V5Z 4L7 Canada.
E-mail: tpickles@bccancer.bc.ca

* Radiation Oncology Program, BC Cancer Agency, Vancouver, BC.
† Radiation Oncology Program, Princess Margaret Hospital and the University of Toronto, Toronto, ON.
‡ Radiation Oncology Program, BC Cancer Agency, and Division of Radiation Oncology and Developmental Radiotherapeutics, University of British Columbia, Vancouver, BC.