Radiation Oncology

Australasian Radiology (2004) **48**, 493–501

Australian and New Zealand three-dimensional conformal radiation therapy consensus guidelines for prostate cancer

M Skala,[1] M Berry,[1] G Duchesne,[2] K Gogna,[3] K-H Tai,[2] S Turner,[4] A Kneebone,[1] A Rolfo[5] and A Haworth[6]

[1]Cancer Therapy Centre, Liverpool Health Service and [4]Radiation Oncology Network, Westmead and Nepean Hospitals, Sydney, New South Wales, [2]Peter MacCallum Cancer Centre and [5]Radiation Oncology Centre, Austin Health, Melbourne, Victoria, [3]Queensland Radium Institute, Brisbane, Queensland, and [6]Department of Radiation Oncology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

SUMMARY

Three-dimensional conformal radiation therapy (3DCRT) has been shown to reduce normal tissue toxicity and allow dose escalation in the curative treatment of prostate cancer. The Faculty of Radiation Oncology Genito-Urinary Group initiated a consensus process to generate evidence-based guidelines for the safe and effective implementation of 3DCRT. All radiation oncology departments in Australia and New Zealand were invited to complete a survey of their prostate practice and to send representatives to a consensus workshop. After a review of the evidence, key issues were identified and debated. If agreement was not reached, working parties were formed to make recommendations. Draft guidelines were circulated to workshop participants for approval prior to publication. Where possible, evidence-based recommendations have been made with regard to patient selection, risk stratification, simulation, planning, treatment delivery and toxicity reporting. This is the first time a group of radiation therapists, physicists and oncologists representing professional radiotherapy practice across Australia and New Zealand have worked together to develop best-practice guidelines. These guidelines should serve as a baseline for prospective clinical trials, outcome research and quality assurance.

Key words: *consensus development conference; dose escalation; practice guidelines; prostatic neoplasms; 3-D conformal therapy.*

INTRODUCTION

Three-dimensional conformal radiation therapy (3DCRT) is a technique designed to deliver high doses of radiation to localized tumours while sparing the surrounding normal tissues. In the treatment of prostate cancer, 3DCRT has been shown to reduce normal tissue toxicity,[1,2] and to improve tumour control through dose escalation.[3–6] These encouraging, but mainly retrospective results, has led to an avid uptake of this technique.

The survey of current definitive external beam radiotherapy (EBRT) practice in Australia and New Zealand by Tai *et al.*, published in this issue, revealed considerable heterogeneity, which reflected the variety of practices reported in the international literature.[7]

The Faculty of Radiation Oncology Genito-Urinary Group (FROGG) identified the need for a workshop that would generate evidence-based guidelines for the safe and effective implementation of 3DCRT. To increase the scope and use of the guidelines, the consensus process involved radiation oncologists, radiation therapists and medical physicists from around Australia and New Zealand.

The tabulated guidelines are intended as a quick reference, and are accompanied by a discussion of the relevant literature.

M Skala MB BS (Hons), FRANZCR; **M Berry** MB BS, FRANZCR, FRCPC; **G Duchesne** MD, FRCR, FRANZCR; **K Gogna** MB BS, FRANZCR; **K-H Tai** MB BS, FRANZCR; **S Turner** MB BS, FRANZCR; **A Kneebone** MB BS, FRANZCR; **A Rolfo** MBA, DipAppSci, GradDipBus; **A Haworth** BSc (Hons), MSc.

Correspondence: Dr Keen-Hun Tai, Division of Radiation Oncology, Peter MacCallum Cancer Centre, St Andrew's Place, East Melbourne, Victoria 3002, Australia. Email: KeenHun.Tai@petermac.org

Submitted 18 July 2003; resubmitted 22 March 2004; accepted 3 June 2004.

Present address: Dr Marketa Skala, Radiation Oncology Department, Princess Margaret Hospital, Toronto, Ontario, Canada

METHODS

All directors of radiation oncology departments in Australia and New Zealand were invited to complete a survey of their current definitive EBRT practice for prostate cancer, and to send representatives from radiation therapy, medical physics and radiation oncology to the consensus workshop.

During the workshop, selected expert speakers from the three disciplines presented information and data from published studies. Key issues with regard to patient selection, simulation, planning, and treatment delivery of 3DCRT were identified and discussed in small interdisciplinary groups. Each group presented a set of guidelines in a consensus forum based on their discussion. Forum participants voted on the guidelines.

If consensus could not be reached, working parties were formed to review the evidence and make recommendations.

Draft guidelines were circulated to all workshop participants and other interested individuals for comment. Suggestions for change were discussed by the FROGG executive and, where relevant, were incorporated into the final draft (Fig. 1).

RESULTS

The consensus workshop took place at the Peter MacCallum Cancer Centre in Melbourne, Victoria, on the 31 May and 1 June 2002, and was attended by 24 radiation oncologists, 16 radiation therapists and 12 medical physicists.

Consensus was reached on most key issues; however, it was agreed that patient immobilization and rectal toxicity guidelines need clarification, and working parties were formed to address these (Table 1).[1–4, 8–20]

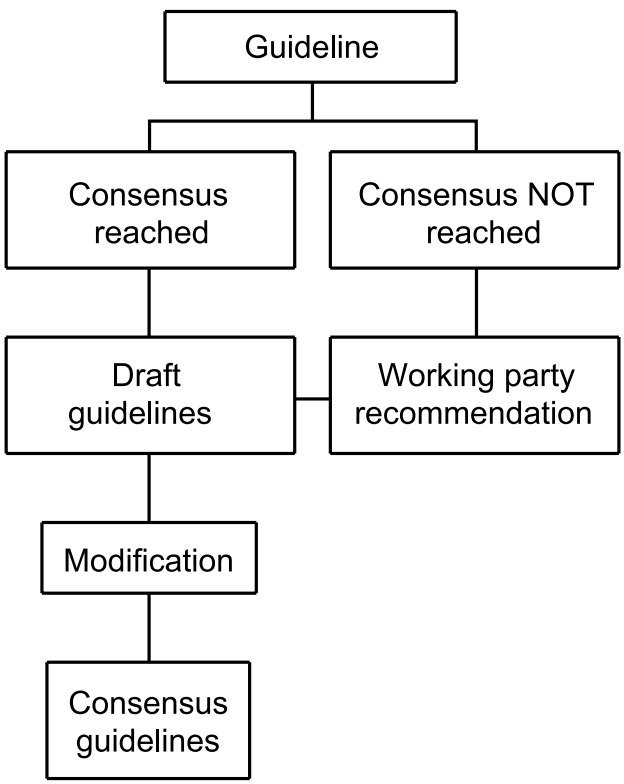

Fig. 1. Guidelines' development process.

DISCUSSION

Patient selection and risk stratification

Low risk: (T1–T2a, and prostate specific antigen <10 ng/mL, and Gleason score < 7)

There is little evidence to suggest that dose escalation beyond 70 Gy improves outcome in the low-risk group of patients. Although retrospective analysis of the Cleveland Clinic data showed that doses ≥72 Gy improved biochemical no evidence of disease (bNED) rates in all patients, the median follow up was short, and there were few events in the low-risk group.[21]

A randomized study by Pollack *et al.* comparing the effect of 70 Gy versus 78 Gy[3] and a dose escalation study by Hanks *et al.*[4] found no improvement in bNED rates with doses >70 Gy in patients with pretreatment prostate specific antigen (PSA) levels ≤10 ng/mL.

The rationale for the use of 3DCRT in the low-risk group is the reduction in rectal toxicity. Dearnaley *et al.* randomized 225 prostate cancer patients to receive 60–64 Gy using conformal or conventional technique. The conformal technique significantly lowered the risk of late radiation-induced proctitis and rectal bleeding.[1]

Koper *et al.* compared the acute toxicity of 66 Gy delivered using a conventional or 3DCRT technique; the incidence of grade 2 gastrointestinal toxicity was 32 and 19%, respectively. This difference was attributed to a reduction in anal toxicity with 3DCRT.[2]

Intermediate risk: (T2b–T2c, prostate specific antigen 10–20 ng/mL, Gleason score 7)

Men with intermediate-risk prostate cancer are most likely to benefit from dose escalation.

Pollack *et al.* showed a significant improvement in freedom from failure (FFF) for patients with pretreatment PSA >10 ng/mL treated to 78 Gy. The 6-year FFF was 62% for patients in the 78 Gy arm and 43% in the 70 Gy arm.[3]

Hanks *et al.* showed 5-year bNED rates of 35% at 70 Gy and 75% at 76 Gy for patients with pretreatment PSA 10–19.9 ng/mL.[4] These findings are supported by a dose escalation study from Memorial Sloan-Kettering Cancer Centre (MSKCC).[6]

High risk: (T3–T4, or prostate specific antigen >20 ng/mL, or Gleason score 8-10)

Dose escalation may be superior to surgery in high-grade (Gleason score 8-10) carcinoma of the prostate.[5] There is

Table 1. Three-dimensional conformal radiation therapy (3DCRT) consensus guidelines for prostate cancer

Guideline	Level of evidence (Appendix IV, Table 7)	Reference
1. Patient selection and risk stratification		
Low risk: T1–T2a (AJCC 2002, Appendix I), and PSA <10 ng/mL, and GS <7.	II and III	1–4,8
Currently insufficient clinical evidence to recommend dose escalation above 70 Gy; however, 3DCRT reduces acute and late radiation proctitis.		
Intermediate risk: T2b–T2c, PSA 10–20 ng/mL, GS 7. 3DCRT to >70 Gy improves biochemical bNED rates.	II and III	3,6,8
High risk: T3–T4, or PSA >20 ng/mL, or GS 8–10. 3DCRT to >70 Gy improves bNED rates.These patients are at high risk of pelvic lymph node involvement and occult metastases at diagnosis.	II and III	3,5,6,8
2. Simulation		
CT Scan: Scan from bottom of SI joints to 1.5 cm below the level of ischial tuberosities. Maximal slice thickness of 5 mm		
Patient set-up: It is recommended that patients be treated in the supine position. Fixed table height technique should be used, together with at least 3 skin reference points.	III	9,10
Immobilization: Departments should employ immobilization system that keeps random and systematic errors to acceptable limits (see QA). Recommended devices include Hipfix, alpha cradle, knee supports and ankle stocks.	IV	11
Bladder size should not vary between simulation and treatments. Consider specific bladder filling protocol (e.g. bladder to be emptied 1 h prior to treatment, patient to drink two glasses of water soon thereafter).	III	12
Constant *rectal volume* is desirable. Consider starting patients on a fibre-bulking agent or laxative 1 week before planning and only cease this if bowel frequency develops. Instruct patients to evacuate their bowels prior to planning and treatment.	III	12
Urethrogram is not indicated as it may result in contraction of urogenital diaphragm and superior shift of prostate. Use CT or MRI to determine position of prostate apex (sagittal and coronal reconstructions may assist).	III	13
3. Planning		
Treatment planning system: † A CT 3-D planning system should be employed, allowing definition of relevant structures in 3-D. Provides DVHs and DRRs.		
Contouring: Prostate apex is not well visualized on CT. It is situated above the urogenital diaphragm (transversus perineus muscle) on sagittal reconstruction. Five millimetres above the bulbospongiosus on axial slice is a useful guide.		
Contour *base of SV* only, if no clinical SV involvement.	III	14
Contour *rectal wall* from 1 cm above to 1 cm below the PTV. Consider contouring the whole length of the rectum.		
Contour external *bladder* wall from its apex to the dome.		
Contour the *femoral heads* from the inferior margin of PTV to the superior lip of acetabulum.		
Treatment volume:		
Low risk: GTV = prostate		
Intermediate risk: GTV1 = prostate and base of SV; GTV2 = prostate		
High risk: GTV = prostate and any extra-capsular spread and base of SV as well as any SV extension	III	14
CTV = GTV		
PTV1 = CTV and 1–1.5 cm margin except posteriorly where 0.5–1.0 cm is used	III	12
PTV2 = CTV and 0–1.0 cm margin except posteriorly where ≤0.5 cm is used.		
Dose prescription: Prescribe to ICRU 50 reference point and record the covering isodose. Record maximum and minimum dose to PTV.		
Deliver 2 Gy per fraction, 9–10 fractions per fortnight.	III	15
Total dose		
Low risk: 70 Gy		
Intermediate risk: 74 Gy		
High risk: 74 Gy		
Assuming dose constraints for rectum and femoral heads are met.		
Change from PTV1 volume to PTV2 volume between 46 and 60 Gy.		
Dose constraints†		
The maximum dose to be delivered to a percentages of the *rectal volume*:	III	16
65 Gy 40%		
70 Gy 30%		
75 Gy 5%		
There are no evidence based dose constraints for the *bladder*.		
The maximum dose to percentage *femoral heads* should not exceed these constraints:		
35 Gy 100%		
45 Gy 60%		
60 Gy 30%		

Table 1. *continued*

Guideline	Level of evidence (Appendix IV, Table 7)	Reference
4. Treatment delivery		
Verification		
As a minimum it is recommended that an isocentre check using AP and lateral films be acquired at least weekly during treatment. If available, daily localization with fiducial markers or ultrasound/CT imaging is preferred.	III	17
QA†		
The following criteria should be met before escalating the dose		
For a dose prescription of 70–74 Gy, 90% of treatment isocentres should coincide with the planned isocentre within 5 mm along each of the orthogonal axes.		
For a dose prescription of 78 Gy, 90% of treatment isocentres should coincide with the planned isocentre within 3 mm along each of the orthogonal axes.	III	18
5. Toxicity reporting		
It is recommended that the following toxicity data be collected:		
Acute effects		
MD Anderson modified RTOG criteria (Appendix II)		19
Late effects		
MD Anderson modified RTOG-LENT scales for rectal and urinary morbidity scoring (Appendix III)		19
Short version of the International Index of Erectile Function for scoring sexual dysfunction (Appendix IV)		20

†Recommendations as per RADAR (A randomized trial investigating the effect on biochemical (PSA) control and survival of different durations of adjuvant androgen deprivation in association with definitive radiation treatment for localized carcinoma of the prostate) protocol. This Trans-Tasman Radiation Oncology Group (TROG) study is currently open for accrual.

AP, anteroposterior; bNED, biochemical no evidence of disease; CTV, clinical target volume; DRR, digital reconstruction radiograph; DVH, dose–volume histogram; GTV, gross tumour volume; GS, Gleason score; ICRU, International Commission on Radiation Units and Measurements; PSA, prostate specific antigen; PTV, planning target volume; QA, quality assurance; RTOG, Radiation Therapy Oncology Group; SV, seminal vesicles.

evidence to support higher doses of radiotherapy for PSA ≥ 20 ng/mL.[4–6]

Simulation

Computed tomography scan

Discrepancy between the CT and treatment couch is a source of systematic error and should be avoided.

Although the consensus was to obtain 5 mm slices, 3 mm slices are required to produce sufficient resolution digital reconstruction radiographs for electronic portal imaging device matching. With newer contouring tools, outlining the relevant structures on a 3 mm slice data set should not prove too onerous.

Patient set-up

The consensus was to treat patients in the supine position as this has been shown to reduce set-up error, through greater patient stability.[9] A study from the MSKCC showed better rectal dose distribution in the prone position, largely because of the anterior displacement of the seminal vesicles.[22] This effect may be lost if only the base of the vesicles is included within the gross tumour volume (GTV), as recommended by these guidelines.

The fixed table height technique consists of setting the couch height so that the isocentre is at a fixed height above the couch top. It gives more accurate localization than aligning the lasers with lateral skin tattoos.[10]

Immobilization

During the workshop, Mr Aldo Rolfo presented Peter MacCallum Cancer Centre data that showed greatest patient stability with the use of a Hipfix board (MED-TEC, Orange City, IA, USA), and good stability with the alpha cradle. Similar results have been reported internationally.[11] The cost versus benefit of introducing these immobilization devices was discussed. It was agreed that departments should assess the set-up reproducibility of their current immobilization technique, and decide whether it satisfies the quality assurance criteria for dose escalation.

Bladder and rectal filling protocols

Interfraction prostate movement is a potential source of treatment error and is usually accounted for by expanding the planning target volume (PTV). In a study from Princess Margaret Hospital, controlling the bladder and rectal volumes throughout the course of radiotherapy by instructing patients in specific bladder and rectal protocols reduced interfraction prostate movement. Displacements resulting from prostatic motion, with standard deviations of 5.8 mm in the anteroposterior (AP) and 3.3 mm in the superoinferior directions, were found to be more significant than set-up errors.[12]

Rectal balloons can standardize rectal volume during treatment and significantly reduce AP displacement.[23] The objections to routine use of rectal balloons were increased set-up time, and reluctance of radiation therapists to insert balloons.

Urethrogram

This method is widely used in conventional radiotherapy planning to determine the position of the prostate apex. The introduction of a urethral catheter frequently causes contraction of the urogenital diaphragm, which displaces the prostate in a superior direction.[13] The axial, coronal and sagittal reconstructions generated in 3-D planning allow non-invasive definition of the prostate apex.

Planning

Treatment planning system

A 3-D margin-growing algorithm is preferable to a 2-D algorithm as the latter can underestimate the PTV.[24]

Contouring

Time and expertise are required to outline the tumour volume and dose-limiting structures. It is recommended that the GTV, rectum, bladder, and femoral heads be contoured as a minimum. Clinicians should decide whether to contour the anal canal and penile bulb, which have been associated with symptoms related to radiation-induced proctitis[2] and erectile dysfunction,[25] respectively.

Significant intra and interobserver variability is reported in the literature when contouring organs and structures of interest.[26] Review of all available diagnostic information including MR scans and high-resolution sagittal reconstructions is recommended, as well as enlisting the help of an expert radiologist.

Treatment volume

The rarity of seminal vesicle involvement in the low-risk group of patients does not justify the increased rectal toxicity associated with their inclusion in the clinical target volume (CTV). Kestin *et al.* reviewed 344 prostatectomy specimens and found that only 1% of low-risk patients had pathological seminal vesicle involvement. In the intermediate-risk group, 27% of patients had seminal vesicle involvement. The authors recommend that only the proximal 2–2.5 cm of the vesicle be included in the CTV, as only 7% of specimens had seminal vesicle involvement beyond 1 cm, and 1% beyond 2 cm.[14]

The consensus was to use a two-phase technique to treat patients with intermediate-risk prostate cancer. Clinical target volume 1 should encompass the prostate and base of seminal vesicles, and CTV 2 the prostate only.

Patients in the high-risk group are at significant risk of seminal vesicle and pelvic lymph node involvement, as well as occult metastatic disease. RTOG 9413 showed increased progression-free survival for whole pelvic radiotherapy (WPRT) with combined androgen suppression, but no overall survival benefit.[27]

This trial was published in abstract form only at the time of the workshop and it was decided to await full publication before making any recommendations with regard to WPRT.

The question of optimal duration of androgen deprivation will be addressed by the RADAR study.

Dose prescription

Accurate dose reporting is essential for any dose escalation study. The minimum International Commission on Radiation Units and Measurements 50 and 62 reporting requirements include the reference dose, maximum and minimum dose to the PTV, dose–volume histogram (DVH) data and dose to organs at risk.[15]

The conformity index (CI) has been used to quantitatively compare 3DCRT plans. It is calculated by dividing the volume encompassed by the 95% isodose by the PTV. The RADAR protocol specifies CI $\leq$ 1.5 for phase I and II.

Dose constraints

A dose–volume effect in the development of radiation-induced toxicity has been established by a number of investigators. However, comparison of dose–volume constraints is limited by the structures contoured in individual studies. The dose constraints reported by Boersma *et al.* were derived by contouring the anatomical rectal wall. The caudal border of the rectum was defined as 15 mm inferior to the prostate apex, with the cranial rectal border at the level of the recto-sigmoid junction.[16]

Consensus was not reached with regard to rectal dose constraints. Dr Kumar Gogna headed a working party that addressed the controversies. The recommendations were to contour two rectal volumes: the critical area of interest, 1 cm above and below the PTV, and the anatomical rectum as per Boersma *et al*. It was recommended that the rectal wall volume be contoured, as it is less prone to interfraction variation than the rectal volume. Outlining the inner rectal wall is a challenge, particularly at the level of the ano-rectal junction. Most planning systems can apply a uniform rectal wall thickness to the whole length of the rectum; however, this technique has not been validated. It was suggested that the Boersma *et al.* dose constraints be adopted.

From discussion at the workshop it appeared that, at the majority of centres, the outer rectal wall only is contoured from 1 cm above to 1 cm below the PTV. It is important to realize that in this case, a significantly greater proportion of rectum will fall within the high-dose region, and the recommended dose constraints are therefore conservative, though may be difficult to achieve for a prescribed dose >74 Gy.

Storey *et al.* analysed the toxicity data from the M. D. Anderson phase III trial.[19] Their recommendation was to limit the volume of rectum receiving 70 Gy to less than 25%. It

is important to note that most of the rectum received 46 Gy during the conventional phase I. Jackson *et al.* suggest that the volume of rectal wall exposed to doses between 40 and 50 Gy and the absence of a reserve of unexposed tissue may interfere with repair in the high-dose region.[28] An interim report from the RTOG 9403 dose escalation study showed excellent tolerance of 3DCRT at 79.2 Gy.[29]

No dose constraints were recommended for the bladder. Koper *et al.* found that 3DCRT improved bladder DVH, but this was not associated with an improvement in urological toxicity.[2] In the study of Pollack *et al.,* late bladder toxicity did not correlate with the absolute volume of bladder that received doses above 60 Gy or 70 Gy.[3] It is possible that radiotherapy effects on the bladder base and urethra (structures closely related to the PTV), rather than the bladder per se, are the main cause of urological toxicity.

Tolerance dose for the femoral heads is not well defined. The consensus was to adopt the dose constraints recommended in the RADAR study protocol.

Treatment delivery

Verification

Systematic errors may be detected by performing a minimum of three consecutive port films at the start of treatment, and weekly thereafter. Decision-rule protocols will help distinguish between real systematic error requiring patient position movement and random daily set-up errors.[17,30]

Radiation therapists should be allowed to make field adjustments of up to 1 cm, after adequate training and accreditation.

If available, daily localization with fiducial markers or ultrasound/CT imaging is preferred.

Quality assurance

In vivo dosimetry using diodes or thermoluminescent devices to verify individual patient treatment planning errors is encouraged. Entrance doses should be within 5% of predicted value.

The following set-up accuracy criteria were considered reasonable benchmark levels based on data published in the literature:[18]

- For a dose prescription of 70–74 Gy, 90% of treatment isocentres should coincide with the planned isocentre within 5 mm along each of the orthogonal axes.
- For a dose prescription of 78 Gy, 90% of treatment isocentres should coincide with the planned isocentre within 3 mm along each of the orthogonal axes.

Toxicity reporting

The consensus was to collect as much toxicity data as practicable (Appendices II, III, and IV), especially if treating to 74 Gy and higher. The proposed scoring systems have not been validated; however, they are widely used and frequently quoted in the literature.

Acute effects

Weekly reviews by the radiation oncologist are recommended during treatment and at 6 weeks after completion of radiotherapy. The worst toxicity experienced should be recorded, along with any treatments instituted.

Late effects

A major shortcoming of the gastrointestinal toxicity scoring system is that it takes account of the number of coagulation procedures performed. This may reflect the treatment modality used (laser or formalin), and physician expertise rather than symptom severity. Prolonged use of steroid enemas has not been shown to be effective in the treatment of chronic proctitis, and toxicity should not be scored as grade 3 based on this criterion alone (Dr Peter O'Brien pers. comm. 2003).

Future directions

Although there is no single strategy for the implementation of 3DCRT, these guidelines should serve as a starting point without being overly prescriptive.

The multidisciplinary consensus workshop has opened up a valuable dialogue and highlighted areas of controversy, which require further study. The FROGG plans to monitor implementation and review the guidelines as new clinical evidence emerges, at future workshops.

ACKNOWLEDGEMENTS

We would like to thank all workshop participants, and others who contributed to these guidelines.

REFERENCES

1. Dearnaley DP, Khoo VS, Norman AR *et al.* Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomized trial. *Lancet* 1999; **353**: 267–72.
2. Koper PC, Stroom JC, van Putten WP *et al.* Acute morbidity reduction using 3DCRT for prostate carcinoma: A randomized study. *Int J Radiat Oncol Biol Phys* 1999; **43**: 727–34.
3. Pollack A, Zagars GK, Starkschall G *et al.* Prostate cancer radiation dose–response: results of the M.D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002; **53**: 1097–105.
4. Hanks GE, Hanlon AL, Schultheiss TE *et al.* Dose escalation with 3D conformal treatment: Five year outcomes, treatment optimization, and future directions. *Int J Radiat Oncol Biol Phys* 1998; **41**: 501–10.
5. Fiveash JB, Hanks G, Roach M *et al.* 3D conformal radiation therapy (3DCRT) for high-grade prostate cancer: a multi-institutional review. *Int J Radiat Oncol Biol Phys* 2000; **47**: 335–42.
6. Zelefsky MJ, Leibel SA, Gaudin PB *et al.* Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998; **41**: 491–500.
7. Tai K-H, Duchesne G, Turner S *et al.* Three-dimensional conformal radiotherapy in the treatment of prostate cancer in Australia and New Zealand: Report on a survey of radiotherapy centres and the proceedings of a consensus workshop. *Australas Radiol* 2004; **48**: 502–508.
8. Brundage M, Lukka H, Crook J *et al.* The use of conformal radiotherapy and the selection of radiation dose in T1 or T2 low or

intermediate risk prostate cancer – a systemic review. *Radiother Oncol* 2002; **64**: 239–50.
9. Weber DC, Nouet P, Rouzaud M, Miralbell R. Patient positioning in prostate radiotherapy: is prone better than supine? *Int J Radiat Oncol Biol Phys* 2000; **47**: 365–71.
10. Greer PB, Mortensen TM, Jose CC. Comparison of two methods for anterior-posterior isocentre localization in pelvic radiotherapy using electronic portal imaging. *Int J Radiat Oncol Biol Phys* 1997; **41**: 1193–9.
11. Malone S, Szanto J, Perry G *et al.* A prospective comparison of three systems of patient immobilization for prostate radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; **48**: 657–65.
12. Wu J, Haycocks T, Alasti H *et al.* Positioning errors and prostate motion during conformal prostate radiotherapy using on-line isocentre set-up verification and implanted prostate markers. *Radiother Oncol* 2001; **61**: 127–33.
13. Malone S, Donker R, Broader M *et al.* Effects of urethrography on prostate position: considerations for radiotherapy treatment planning of prostate. *Int J Radiat Oncol Biol Phys* 1999; **46**: 89–93.
14. Kestin L, Goldstein N, Vicini F, Yan D, Korman H, Martinez A. Treatment of prostate cancer with radiotherapy: should the entire seminal vesicles be included in the clinical target volume? *Int J Radiat Oncol Biol Phys* 2002; **54**: 686–97.
15. International Commission on Radiation Units and Measurements (ICRU). *Prescribing, Recording, and Reporting Photon Beam Therapy, Report 50.* ICRU, Washington DC, 1992.
16. Boersma LJ, van den Brink M, Bruce AM *et al.* Estimation of the incidence of late bladder and rectum complications after high-dose (70–78 Gy) conformal radiotherapy for prostate cancer, using dose-Volume histograms. *Int J Radiat Oncol Biol Phys* 1998; **41**: 83–92.
17. van Herk M, Remeijer P, Rasch C, Lebesque JV. The probability of correct target dosage: dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys* 2000; **47**: 1121–35.
18. Bel A, Vos PH, Rodrigus PT *et al.* High-precision prostate cancer irradiation by clinical application of an offline patient setup verification procedure, using portal imaging. *Int J Radiat Oncol Biol Phys* 1996; **35**: 321–32.
19. Storey MR, Pollack A, Zagars G, Smith L, Antolak J, Rosen I. Complications from radiotherapy dose escalation in prostate cancer: preliminary results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2000; **48**: 635–42.
20. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; **49**: 822–30.
21. Kupelian PA, Buschbaum JC, Reddy CA, Klein EA. Radiation dose-response in patients with favorable localized prostate cancer (Stage T1–T2, biopsy Gleason ≤ 6, and pre-treatment prostate-specific antigen 10). *Int J Radiat Oncol Biol Phys* 2001; **50**: 621–5.
22. Zelefsky MJ, Happersett L, Liebel SA *et al.* The effect of treatment positioning on normal tissue dose in patients with prostate cancer treated with three-dimentional conformal radiotherapy. *Int J Radiat Oncol Biol Phys* 1997; **37**: 13–19.
23. Wachter S, Gerstner N, Dorner D *et al.* The influence of a rectal balloon tube as internal immobilization device on variations of Volumes and dose-volume histograms during treatment course of conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2002; **52**: 91–100.
24. Khoo SV, Bedford JL, Webb S, Dearnaley DP. Comparison of 2D and 3D algorithms for adding a margin to the gross tumour volume in the conformal radiotherapy planning of prostate cancer. *Int J Radiat Oncol Biol Phys* 1997; **42**: 673–9.
25. Merrick GS, Butler WM, Wallner KE *et al.* The importance of radiation doses to the penile bulb vs crura in the development of postbrachytherapy erectile dysfunction. *Int J Radiat Oncol Biol Phys* 2002; **54**: 1055–62.
26. Fiorino C, Reni M, Bolognese A, Cattaneo GM, Calandrino R. Intra- and inter-observer variability in contouring prostate and seminal vesicles: implications for conformal treatment planning. *Radiother Oncol* 1998; **47**: 285–92.
27. Roach M, DeSilvio M, Lawton C *et al.* Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol* 2003; **21**: 1904–11.
28. Jackson A, Skwarchuk MW, Zelefsky MJ *et al.* Late rectal bleeding after conformal radiotherapy of prostate cancer. II. Volume effects and dose-volume histograms. *Int J Radiat Oncol Biol Phys* 2001; **49**: 685–98.
29. Ryu JK, Winter K, Michalski JM *et al.* Interim report of toxicity from 3D conformal radiation therapy (3D-CRT) for prostate cancer on 3DOG/RTOG 9406, level III (79.2 Gy). *Int J Radiat Oncol Biol Phys* 2002; **54**: 1036–46.
30. See A, Kron T, Johansen J *et al.* Decision-making models in the analysis of portal films: a clinical pilot study. *Australas Radiol* 2000; **44**: 72–83.

APPENDIX I

Prostate cancer T stage

T1: Clinically inapparent tumour not palpable nor visible by imaging
- T1a: Tumour incidental histologic finding in 5% or less of tissue resected
- T1b: Tumour incidental histologic finding in more than 5% of tissue resected
- T1c: Tumour identified by needle biopsy (e.g. because of elevated PSA)

T2: Tumour confined within prostate
- T2a: Tumour involves one-half of one lobe or less
- T2b: Tumour involves more than one-half of one lobe but not both lobes
- T2c: Tumour involves both lobes

T3: Tumour extends through the prostate capsule
- T3a: Extracapsular extension (unilateral or bilateral)
- T3b: Tumour invades seminal vesicle(s)

T4: Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall.

(Reproduced from Greene F, Page DL, Fleming ID *et al. AJCC Cancer Staging Manual*, 6th edn. Springer–Verlag, New York, 2002.)

APPENDIX II

Table 2. Acute lower gastrointestinal (GI) radiation toxicity grading using modified RTOG criteria

Grade 1	Grade 2	Grade 3	Grade 4
Increased frequency or change in quality of bowel habits not needing medications. Rectal discomfort not requiring analgesics.	Diarrhoea needing para-sympatholytic drugs (e.g. Lomotil). Mucous discharge infrequently requiring sanitary pads. Rectal pain needing analgesics or occasional narcotics. Mild rectal bleeding.	Diarrhoea needing parenteral support. Severe mucous discharge requiring extended use of sanitary pads. Abdominal distension. Rectal pain requiring frequent narcotics. GI bleeding requiring one transfusion.	Acute or subacute obstruction. Fistula or perforation. GI bleeding requiring more than one transfusion. Abdominal pain or tenesmus requiring bowel diversion.

RTOG, Radiation Therapy Oncology Group.

Table 3. Acute urinary radiation toxicity grading using modified RTOG criteria

Grade 1	Grade 2	Grade 3	Grade 4
Frequency or nocturia twice pretreatment habit. Dysuria not needing medication.	Frequency or nocturia less frequent than hourly. Dysuria, bladder spasm needing local anaesthetic (e.g. Pyridium or occasional narcotics). Infrequent gross haematuria. Temporary catheterization.	Frequency or nocturia hourly or more. Dysuria, pain or spasm needing frequent narcotics. Gross haematuria requiring one transfusion. Prolonged urinary obstruction due to prostate inflammation or clots requiring catheterization (including suprapubic).	Haematuria needing more than one transfusion. Hospitalization for sepsis because of obstruction and/or ulceration, or necrosis of the bladder.

RTOG, Radiation Therapy Oncology Group.

APPENDIX III

Table 4. Late lower GI toxicity RTOG-LENT criteria

Grade 1	Grade 2	Grade 3	Grade 4
Excess bowel movements twice baseline. Slight rectal discharge or blood.	≥ two antidiarrhoeals per week. Two or fewer coagulations for bleeding. Occasional steroids for ulceration. Occasional dilatation. Intermittent use of incontinence pads. Regular non-narcotics or occasional narcotics for pain.	≥ two antidiarrhoeals per day. At least one blood transfusion or more than two coagulations for bleeding. Prolonged steroids per enema. Hyperbaric oxygen for bleeding/ulceration. Regular dilatation. Persistent use of incontinence pads. Regular narcotics for pain.	Dysfunction requiring surgery. Perforation. Life-threatening bleeding.

RTOG-LENT, Radiation Therapy Oncology Group and Late Effects Normal Tissue Task Force.

Table 5. Late urinary toxicity RTOG-LENT criteria

Grade 1	Grade 2	Grade 3	Grade 4
Nocturia twice baseline. Microscopic haematuria. Light mucosal atrophy and minor telanglectasia.	Moderate frequency. Nocturia more than twice baseline. Generalized telanglectasia. Intermittent macroscopic haematuria. Two or fewer coagulations. Intermittent use of incontinence pads. Regular non-narcotics or occasional narcotics for pain.	Severe frequency and dysuria. Nocturia more frequent than once every hour. Reduction in bladder capacity (150 cc). Frequent haematuria requiring at least one transfusion. More than two coagulations for haematuria. Hyperbaric oxygen for bleeding/ulceration. Persistent use of incontinence pads. Regular narcotics for pain.	Severe haemorrhagic cystitis or ulceration with requirement for urinary diversion and/or cystectomy.

RTOG-LENT, Radiation Therapy Oncology Group and Late Effects Normal Tissue Task Force.

APPENDIX IV

Table 6. International index of erectile function questionnaire and response options – erectile domain

Question†	Response options
Q1: How often were you able to get an erection during sexual activity?	0 = No sexual activity 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q2: When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	
Q3: When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?	0 = Did not attempt intercourse 1 = Almost never/never 2 = A few times (much less than half the time) 3 = Sometimes (about half the time) 4 = Most times (much more than half the time) 5 = Almost always/always
Q4: During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	
Q5: During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	0 = Did not attempt intercourse 1 = Extremely difficult 2 = Very difficult 3 = Difficult 4 = Slightly Difficult 5 = Not difficult
Q6: How do you rate your confidence that you could get and keep an erection?	1 = Very low 2 = Low 3 = Moderate 4 = High 5 = Very high

†All questions are preceded by the phrase 'Over the past 4 weeks'.

Table 7. Levels of evidence

Level I	Evidence is obtained from a systematic review of all relevant randomized controlled trials.
Level II	Evidence is obtained from at least one well-designed randomized controlled trial.
Level III	Evidence is obtained from well-designed controlled trials without randomization; OR from well-designed cohort or case-control analytic studies, preferably from more than one centre of research group; OR from multiple time series with or without the intervention.
Level IV	Represents the opinions of respected authorities based on clinical experience, descriptive studies or reports of expert communities.

Modified from the National Health and Medical Research Council (NHMRC) publication: *Guidelines for the development and implementation of clinical practice guidelines*. NHMRC, Canberra, 1995.