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REVIEW ARTICLE

Australian & New Zealand Faculty of Radiation Oncology Genito-Urinary Group: 2010 consensus guidelines for definitive external beam radiotherapy for prostate carcinoma

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Summary

External beam radiotherapy for prostate cancer has undergone substantial technological and clinical advances in the recent years. The Australian & New Zealand Faculty of Radiation Oncology Genito-Urinary Group undertook a process to develop consensus clinical practice guidelines for external beam radiotherapy for prostate carcinoma delivered with curative intent, aiming to provide guidance for clinicians on the appropriate integration of clinical evidence and newer technologies. Draft guidelines were presented and discussed at a consensus workshop in May 2009 attended by radiation oncologists, radiation therapists and medical physicists. Amended guidelines were distributed to radiation oncologists in Australia, New Zealand and Singapore for comment, and modifications were incorporated where appropriate. Evidence based recommendations for risk stratification, the role of image-guided and intensity-modulated radiation therapy, prescribed dose, simulation and treatment planning, the role and duration of neo-adjuvant/adjuvant androgen deprivation therapy and outcome reporting are presented. Central to the guidelines is the recommendation that image-guided radiation therapy should be used when definitive external beam radiotherapy for prostate cancer is prescribed. The consensus guidelines provide a co-operatively developed, evidence-based framework for contemporary treatment of prostate cancer with external beam radiotherapy.

Key words: consensus development conference; intensity-modulated radiotherapy; practice guidelines; prostatic neoplasms; radiotherapy dosage.

Introduction

Prostate cancer is the most frequent non-cutaneous malignancy occurring in Australian and New Zealand males, with >16 000 and >2400 new cases diagnosed annually, respectively.[1,2] External beam radiotherapy is a well established treatment modality for prostate cancer and in the high-risk setting confers a survival advantage when compared to androgen suppression alone.[3] Recent years have seen substantial technological advances in the radiotherapeutic treatment of prostate cancer with the introduction of image-guided[4] and intensity-modulated radiation therapy,[5] which have the potential to enhance the therapeutic ratio by improving cancer outcomes and/or reducing treatment-related toxicity. The Faculty of Radiation Oncology Genito-Urinary Group (FROGG), a special interest group of the Royal Australian and New Zealand College of Radiologists Faculty of Radiation Oncology, has previously published the '*Australian and New Zealand three-dimensional conformal radiation therapy consensus guidelines for prostate cancer*'[6] in 2004. The FROGG executive committee

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identified a need to develop updated guidelines for the delivery of external beam radiotherapy for prostate cancer delivered with curative intent.

Methods

Radiation oncology specialists and trainees, radiation therapists, and medical physicists from Australia, New Zealand and Singapore were invited to attend a consensus workshop convened by the FROGG executive. Selected international and local experts presented on key issues with an emphasis on the clinical integration of new technologies for prostate cancer. A literature search was conducted and draft guidelines developed by the FROGG guideline development group, which were presented and discussed at the consensus workshop. The consensus workshop convened on 14–16 May 2009 in Byron Bay, Australia and was attended by 129 delegates. Following the workshop, revised guidelines were circulated by email to a total of 463 radiation oncologists in Australia, New Zealand and Singapore and selected radiation therapists and medical physicists for review and comment. Twelve additional comments were received and considered by the FROGG executive, with further modifications incorporated into the guidelines where appropriate.

Guidelines

Summary guidelines statements are presented in Table 1 and are accompanied by the National Health and Medical Research Council level of evidence that support each recommendation (Appendix 1). The level of consensus for each recommendation achieved at the workshop and in subsequent communication is documented by a 'level of consensus' grade (Appendix 2), which is adapted from the National Comprehensive Cancer Network Categories of Evidence and Consensus.[69]

The limitations of the literature, when applied to contemporary clinical practice are acknowledged. Patients diagnosed and treated prior to the prostate-specific antigen (PSA) era frequently presented with more advanced disease,[70] in contrast to the modern cohort of patients, which consists of a majority of asymptomatic and screened individuals.[7,71] This may confound interpretation of retrospective analyses performed prior to frequent utilisation of PSA screening. Additionally there has been a shift in the grading of prostate cancer, with a trend towards upgrading of Gleason grades,[72] which may result in an apparent improvement in outcomes for all grades of prostate cancer.

Within these limitations, the guidelines are intended to present a safe approach to practice and are not intended to be prohibitive or restrictive. It is recognised that individual patient management decisions are dependent on multiple and frequently complex patient, disease and institutional factors and treatment recommendations should be individualised accordingly.

Risk stratification

The prognostic significance of stratification into low-, intermediate- and high-risk groups based on pre-treatment PSA, Gleason grade and clinical stage was demonstrated by D'amico in 1998,[73] however, significant heterogeneity exists within risk groups. Additional risk factors that have demonstrated prognostic impact for biochemical relapse and/or prostate cancer-specific mortality include; PSA kinetics,[74] degree of core involvement,[75–78] primary Gleason grade (i.e. Gleason $3 + 4 = 7$ versus $4 + 3 = 7$),[79,80] and perineural invasion.[81] However, the predictive utility of these prognostic factors in models that incorporate PSA, Gleason grade and clinical stage has either not been evaluated or, in several studies, found to be of limited additional predictive value.[82,83] (see Table 1 – Guideline 1)

Role of image-guided radiation therapy

Image-guided radiation therapy (IGRT), utilising daily on-line verification of prostate position or surrogate has been shown to reduce systematic and random treatment errors, decrease the risk of geographic miss (for a given margin), and may allow for some reduction in planning target volume (PTV) margins.[8–10] Planar kilovoltage (kV) or megavoltage (MV) imaging of implanted prostate fiducial markers[84] are the most frequently utilised IGRT technique in Australia (unpubl. data, M Lehman, 15 May 2009) and are recommended for institutions implementing prostate IGRT. Alternative IGRT modalities include daily *trans*-abdominal prostate ultrasound,[85] and volumetric verification techniques such as kV cone-beam CT, MV CT and CT-on-rails[4] which allow visualisation of soft tissue structures, although investigation is ongoing as to the optimal utilisation and integration of soft tissue volumetric imaging for verification (see Table 1 – Guideline 2).

Management of verification dose

Optimisation of the verification imaging protocol and reduction in unnecessary verification dose in accordance with the American Association of Physicists in Medicine Task Group 75 is recommended.[86] When daily megavoltage verification is used, the verification image should be captured during treatment or the expected dose should be accounted for in the treatment planning system dose calculation. The dose from daily planar kV imaging is typically less than 0.2% of the prescribed dose and therefore accounting for verification dose in the treatment plan may not be necessary. Cumulative dose from daily three-dimensional (3D) imaging may be significant within the imaged volume but can not be summed with

Table 1. Summary consensus guidelines

	Level of evidence – consensus	Reference
Guideline 1 – Risk stratification		
The following risk stratification groupings are recommended for the purposes of patient and treatment selection.	III-A	7
(a) Low-risk: PSA < 10 ng/mL AND Gleason ≤ 6 AND cT1-cT2a		
(b) Intermediate risk: PSA 10–20 ng/mL OR Gleason = 7 OR cT2b-c (and absence of high-risk features)		
(c) High-risk: PSA > 20 ng/mL OR Gleason 8–10 OR cT3		
Guideline 2 – Role of image-guided and intensity-modulated radiation therapy		
Image guided radiation therapy (IGRT) using daily pretreatment verification of prostate position is recommended when delivering definitive external beam radiotherapy for prostate cancer.	IV-A	8–11
3D conformal radiotherapy (3DCRT) is regarded as the minimum standard of care when delivering external beam radiotherapy. Intensity modulated radiotherapy (IMRT) is preferred where organ at risk dose constraints are not achievable with 3DCRT.	III-B	12–21
Guideline 3 – Prescribed dose		
Minimum acceptable doses are 70 Gy for low-risk patients and 74 Gy for intermediate and high-risk patients. Dose escalation to 78–80 Gy results in improved biochemical failure free survival when compared with conventional radiotherapy doses (68–70.2 Gy). The benefit of dose escalation to 78–80 Gy is seen across all risk groups.	I-C	22–27
Guideline 4 – Dose prescription		
(a) 3DCRT – Dose should be prescribed as per ICRU 50/62 to the ICRU reference point; the PTV should be encompassed within the 95–107% isodose.	IV-A	28,29
(b) IMRT – A volumetric prescription to the PTV/CTV is recommended. For example; 95–98% of the PTV and 100% of the CTV should be encompassed by the prescription dose.	IV-A	30
Guideline 5 – Clinical target volume delineation		
(a) Low-risk prostate cancer The CTV is the prostate only.	IV-A	31–43
(b) Intermediate risk prostate cancer. The CTV is the prostate +/– proximal 1–2 cm of seminal vesicles depending on the risk of seminal vesicle invasion.		
(c) High-risk prostate cancer The CTV is the prostate and proximal 2 cm of seminal vesicles, visible extra-capsular extension of disease should be included in the CTV. The CTV for T3b disease (seminal vesicle involvement) is the prostate and whole seminal vesicles. For patients with T3a disease or a high-risk of extra-capsular extension, a 2- to 5-mm margin around the prostate and known disease (excluding the rectum), can be considered.		
Pelvic nodal irradiation may be considered at the treating clinician's discretion in selected high-risk patients.	II-B	44,45
Guideline 6 – Margins for planning target volume		
The required CTV to PTV margin is determined by the institutional set-up and verification protocol, and measurement of institutional random and systematic errors of prostate position.	IV-A	46
Guideline 7 – Critical structure delineation and dose constraints		
Application of the ALARA principle (as low as is reasonably achievable) regarding dose for organs at risk is recommended.		
(a) RECTUM – Consider contouring the rectum as a solid organ (rectum with filling) or rectal wall from just above the anal verge to recto-sigmoid flexure with a maximum length of 12 cm. Suggested DVH constraints: V75 Gy < 15%, V70 Gy < 25%, V60 Gy < 40% and V50 Gy < 55%	III-B	47–49
(b) BLADDER – There is insufficient evidence correlating late genito-urinary toxicity with bladder DVH parameters to recommend specific constraints. Consider contouring the bladder as a solid organ from base to dome and utilising similar dose constraints that are used for the rectum.	IV-B	50, Consensus
(c) FEMORAL HEADS – There is insufficient evidence correlating late toxicity with femoral head DVH parameters to recommend specific constraints. Consider contouring the bilateral femoral head & neck from 1 cm below the PTV to roof of acetabulum. Suggested DVH constraints: V35 < 100%, V45 < 60%, V60 < 30%	IV-B	Consensus

Table 1. Continued

	Level of evidence – consensus	Reference
Guideline 8 – Role and duration of androgen deprivation therapy		
The role of androgen deprivation therapy (ADT) in the setting of dose-escalated radiotherapy (≥70 Gy) is undetermined.	IV-A	Consensus
Recommendations for neo-adjuvant/adjuvant ADT:		
(a) Low-risk prostate cancer – ADT is not routinely indicated.	IV-A	Consensus
(b) Intermediate risk prostate cancer – short-term (6 months) neo-adjuvant/concurrent ADT may be considered. Review of individual prognostic factors is suggested to determine patient selection for ADT.	II-B	51–53
(c) High-risk prostate cancer – long-term ADT for 2 to 3 years is recommended. Shorter durations of therapy may be considered according to patient tolerance of ADT and the expected benefit/harms of continued therapy	I-B	54–60
Radiation oncologists should take an active role in the investigation and management of the potential adverse skeletal and metabolic complications of androgen suppression in consultation with the general practitioner and relevant specialists.	IV-A	Consensus
Guideline 9 – Quality assurance		
A comprehensive quality assurance program in accordance with international guidelines should be maintained by a multidisciplinary team consisting of appropriately qualified radiation oncology, medical physics and radiation therapy staff.	IV-A	61–64
Guideline 10 – Outcome & toxicity reporting		
Documentation and audit of institutional clinical, biochemical and toxicity outcomes is recommended. The suggested minimum data-set for consistency in toxicity reporting is modified acute & late RTOG rectal and genitourinary toxicity scores, International Index of Erectile Function, and International Prostate Symptom Score.	IV-B	65–68

dose from megavoltage treatment due to differential absorption and relative biological effect. The potential increased risk of secondary malignancy should be considered.[87,88]

Role of 3D conformal and intensity-modulated radiation therapy

The radiation treatment technique should be selected to achieve the goal of delivering the prescribed dose to the target volume and minimising dose to organs at risk, while taking into consideration the prescription dose, departmental resources and the complexity of individual patient anatomy. 3D conformal radiation therapy (3DCRT) has been shown to reduce the risk of rectal toxicity when compared with conventional field based radiation therapy.[12,13] Intensity-modulated radiation therapy (IMRT) can deliver a more sculpted dose distribution resulting in reduced dose to the rectum & bladder, optimised coverage of the PTV by the prescribed dose, and improved conformality of the high dose region when compared with 3DCRT.[14,15] Recently published work indicates that the reduction in dose to critical organs with IMRT is more significant when the seminal vesicles are included in the clinical target volume.[16] Retrospective evidence demonstrates that when compared with 3DCRT, IMRT can reduce the incidence of late gastrointestinal toxicity[17–20] and may allow dose escalation to be ultilized without corresponding increases in toxicity.[21] While there is a lack of high level clinical evidence to recommend IMRT over 3DCRT, the use of IMRT may facilitate the delivery of higher doses of radiotherapy to the prostate while respecting organ at risk dose constraints. Both 3DCRT and IMRT are acknowledged as standard treatment options for prostate radiotherapy, with IMRT preferred where organ at risk dose constraints are unachievable with 3DCRT (see Table 1 – Guideline 2).

Prescribed dose

Five randomised controlled trials[22–26] (Table 2) and a recent meta-analysis[27] have demonstrated improved biochemical failure free survival with higher radiotherapy doses (74–80 Gy) when compared with doses ≤70.2 Gy. There is heterogeneity in the significance of the results when stratified by risk group in individual trials; however, improved biochemical outcomes have been demonstrated in all risk groups. Several non-randomised studies have reported a decrease in the incidence of distant metastases with increasing radiation dose[89–91] and a pooled analysis of four Radiation Therapy Oncology Group (RTOG) trials demonstrated that higher radiation dose was associated with improved disease-specific and overall survival in patients with high grade prostate cancer.[92] However, some uncertainties remain regarding the generalised and routine application of dose escalation. Firstly, an unacceptable increase in late rectal toxicity is apparent with dose escalation when conven-

Table 2. Randomised trials of dose escalation in prostate cancer

	N	FU (yrs)	Dose	Failure definition	Overall bFFF	Low-risk bFFF	Intermediate risk bFFF	High-risk bFFF
Kuban 2008[17]	305	8	70 Gy vs 78 Gy	Phoenix	59% vs 78% $P = 0.004$	63% vs 88% $P = 0.042$	76% vs 86% $P = 0.36$	26% vs 63% $P = 0.004$
Zeitman 2010[18]	393	10	70.2 GyE vs 79.2 GyE	ASTRO	67.7% vs 83.3% $P = 0.001$	71.8% vs 92.3% $P < 0.001$	57.9% vs 69.6% $P = 0.06$	
				Phoenix	68.0% vs 82.6% $P < 0.001$			
Dearnaley 2007[19]	843	5	64 Gy vs 74 Gy	Phoenix	60% vs 71% HR 0.67 $P = 0.0007$	79% vs 85% HR 0.78	70% vs 79% HR 0.74	43% vs 57% HR 0.6
Al-Mamgani 2008[21]	669	7	68 Gy vs 78 Gy	Phoenix	45% vs 56% $P = 0.03$	Not reported separately		
Beckendorf 2008[20] [Abstract]	306	5	70 Gy vs 80 Gy	ASTRO	61% vs 72% $P = 0.036$			
				Phoenix	69% vs 77% $P =$ NS			

bFFF, biochemical freedom from failure; FU, follow-up; GyE, gray equivalent; HR, hazard ratio; NS, not significant.

tional field-based techniques are used.[27,65,93] This underscores the importance of utilising rectal sparing 3D conformal or IMRT techniques to minimise rectal dose when higher doses are prescribed. Additionally, the trials were conducted prior to the routine use of IGRT; when the risk of geographical miss is minimised, it is unknown if the same magnitude of dose escalation is required to achieve equivalent outcomes. Finally, the relationship between biochemical relapse and clinical progression is complex; many patients who experience biochemical relapse never develop clinical recurrence or suffer prostate cancer mortality. Thus, given the long natural history of prostate cancer, longer follow-up of the randomised trials are awaited with interest to determine if improvements in clinical endpoints will become apparent. Consensus on the minimum recommended dose, particularly for low-risk patients, was not achieved in the guideline development process (see Table 1 – Guideline 3).

Dose prescription and reporting

An inhomogeneous dose distribution within the clinical target volume (CTV) is frequently observed for IMRT, and prescribing to a dose specification point in accordance with the International Commission on Radiation Units and Measurement (ICRU) reports 50 & 62[28,29] for IMRT is less relevant.[94] A volumetric prescription for the CTV/PTV is recommended for IMRT in accordance with ICRU report 83.[30] Dose reporting for IMRT and 3DCRT should be performed in accordance with published recommendations[28–30,95] (see Table 1 – Guideline 4).

Treatment planning

Radiotherapy simulation

Utilisation of multi-slice CT image acquisition and a 3D planning system is highly recommended. Departments should use an immobilisation system that ensures random and systematic set-up errors are minimised.[96] Patients should be simulated and treated with an empty rectum and comfortably full bladder to minimise inter-fraction variation in bladder size and rectal distension.[97,98] A standardised bladder filling protocol should be used and patients should be advised to evacuate bowels prior to treatment. The value of additional/alternative bowel preparation protocols[99,100] remains uncertain. When IGRT is utilised prostate displacement caused by rectal distension is largely corrected for. However, attempts to minimise residual errors related to prostate deformation, rotation and intra-fraction motion via a standardised bowel protocol are justified. Where implanted prostate fiducial markers are utilised, a minimum of three markers should be implanted under ultrasound guidance in the ipsi-lateral apex, base and contra-lateral mid-gland.[101] An interval of 1 week between implantation and simulation is suggested to minimise potential prostate oedema.

Role of magnetic resonance imaging (MRI) in treatment planning

Fusion of MRI to pelvic CT has been shown to reduce inter-observer variability in prostate contouring, reduce overestimation of prostate volume, and may improve accuracy of target delineation, particularly at the prostate apex and base.[102–104] Clinician experience and competency in prostate MR and CT imaging and anatomy is recommended as a minimum. In particular, appropriate education in prostate MRI anatomy should be obtained when incorporating MRI fusion into treatment planning.[105,106] MRI fusion is recommended where significant CT image artefact is present such as from hip prostheses.[107] Co-registration of images based on fiducial marker position is recommended to minimise registra-

tion errors due to prostate motion, as is ensuring the appropriate MRI sequences for fiducial marker identification (T1 weighted) and soft tissue contouring (T2 weighted) are utilised.[108]

Clinical target volume delineation

In addition to PSA, Gleason score and clinical stage; risk factors for seminal vesicle invasion (SVI) include positive cores at the prostate base and percent positive core biopsies.[31–33] The reported risk of SVI in low-risk prostate cancer ranges from 2 to 6%[31–35] hence the recommended CTV is the prostate only. For intermediate risk disease, an estimated risk of SVI that exceeds 15–20% (according to Partin tables[34] or published nomograms[36,37]) is considered a reasonable threshold for inclusion of the proximal SV in the CTV. The length of histopathological SVI has been assessed by Kestin *et al*. who report a median length of involvement of 1 cm, with 6% of involved SV demonstrating >2 cm SVI.[38] This is in contrast to Davis, who report SVI in the distal tip of seminal vesicles in 40% of specimens.[39] Current European guidelines recommend including the proximal 1 cm of SV in all intermediate risk patients, and proximal 2 cm in high-risk patients.[40] Where clinical or radiological evidence of seminal vesicle involvement is present (cT3b disease), the whole SV should be included in the CTV.

The risk of extra-capsular extension (ECE) has been characterised in several clinico-pathological studies. Chao *et al*. report a 35–71, 42 and 19% risk of ECE in high, intermediate and low-risk patients, respectively.[41] The mean radial distance of ECE has been reported as ranging from 1.7 to 2.9 mm with up to 18% of patients demonstrating ECE $\geq$ 2 mm.[41–43] Any visible extra-capsular should be included in the CTV. A prostate-to-CTV margin of 2–5 mm (excluding the rectum) can be considered in patients at high-risk of sub-clinical extra-capsular disease either because of stage T3 a disease, or a high probability of such via predictive models.

Whole pelvic radiotherapy (WPRT) has been utilised in a majority of the trials demonstrating a survival advantage from the addition of androgen deprivation therapy, however, two randomised trials have failed to demonstrate improved survival endpoints with WPRT.[44,45] Acknowledging the limitations of these two trials, current evidence does not support routine use of pelvic nodal irradiation; however, WPRT may be considered in patients with high-risk of nodal involvement. For clinicians who prescribe WPRT, a risk of pelvic lymph node involvement $\geq$15–20% (according to Partin tables[34] or nomograms[109]) is considered a reasonable threshold for inclusion of the pelvic lymph nodes in the target volume. However, clinicians should also remain aware that as the risk of pelvic lymph node involvement increases, so too does the risk of distant metastases, which may negate potential benefits. Reference to RTOG guidelines defining pelvic lymph node volumes for prostate cancer is recommended for target volume delineation[110] (see Table 1 – Guideline 5).

Margins for planning target volume

The appropriate dimension of the CTV-PTV margins should be determined at an institutional level based on estimated set-up error and the verification protocol. Measurement of institutional random and systematic errors of prostate position is strongly recommended, with required margins calculated according to published probability models.[46] Institutional factors to consider include the frequency of verification, use of on-line or off-line corrections and the action threshold for isocentre shifts. As an example, a recent institutional set-up study suggested that the margin required (for set-up errors) to encompass 98% of prostate displacements using fiducial markers was 4, 6 and 7 mm in the mediolateral, superior-inferior and anterior-posterior direction (or 11, 11 and 14 mm using off-line correction to bony anatomy) for the specified institutional protocol.[111] Additional uncertainties that are not accounted for by such margin calculations and should be considered when determining the total margin size include intra-fraction prostate motion; prostate deformation and rotation;[4] limitations in the geometric accuracy of image verification and couch shifts; and inter-observer variations in the image registration process for both planning and on-line treatment verification.[112] Substantial inter- and intra-observer variability in prostate contouring exists, thus target delineation uncertainty should also be considered when deriving margins for the PTV. For many institutions using daily online verification of prostate position or surrogate, CTV to PTV margins in the range of 5–10 mm are likely to be acceptable. Institutions should be cognisant of the risk of under-dosage of the CTV in the presence of inappropriately narrow PTV margins and the adequacy of margins should be evaluated by routine quality assurance protocols (see Table 1 – Guideline 6).

Critical structure delineation and dose constraints

There is a substantial body of literature correlating late rectal toxicity with various rectal dose–volume–histogram (DVH) parameters.[47–49] Despite significant variability in the rectal contouring methodology, there is reasonable concordance in the reported DVH thresholds for increased rectal toxicity.[47–49] The suggested rectal DVH constraints (see Table 1 – Guideline 7) are considered a safe approach to minimising rectal morbidity, however, the constraints represent recommended maximums and lower DVH constraints may be appropriate for IMRT dose optimisation and are recommended if achievable. Alternative rectal contouring strategies (rectal wall contours and/or alternate rectal length definitions) are

also appropriate and should be used in conjunction with corresponding evidence-based DVH constraints. Where loops of small bowel are within the treatment field the absolute volume of small bowel irradiated should be minimised.[47]

The majority of studies have failed to demonstrate a relationship between late genito-urinary toxicity and bladder DVH parameters.[50,113] The reliability of a single pretreatment bladder DVH constraint may be limited by fluctuations in bladder filling during a course of fractionated radiotherapy. Additionally, radiation to the prostatic urethra may contribute significantly to genito-urinary toxicity which is independent of the dose and volume bladder irradiated.[50] Several retrospective series suggest a relationship between high dose bladder volumes and late genito-urinary toxicity,[114,115] however, prospective validation is lacking. Given the inconclusive evidence regarding dose constraints, no specific DVH recommendations are provided; however, it remains prudent to attempt to limit the volume of bladder irradiated, and utilising similar DVH constraints that are applied to the rectum is a pragmatic approach (see Table 1 – Guideline 7).

Role and duration of androgen deprivation therapy

The role of ADT in conjunction with definitive external beam radiotherapy for prostate cancer has been extensively investigated; however, current literature is based on trials using previously conventional lower doses of radiotherapy (≤70 Gy). The therapeutic advantage of ADT has been questioned when higher radiotherapy doses are prescribed,[116,117] and the role of ADT in the context of dose escalation remains under investigation in intermediate-risk patients. Studies of short-term neo-adjuvant/concurrent ADT for 4–6 months have shown improved prostate cancer-specific[51,52] and overall survival.[53] The improved outcomes with neo-adjuvant/concurrent ADT is consistently demonstrated in high-risk patients, however, the role and indication for ADT in intermediate risk disease remains controversial, particularly in the setting of dose escalation. An overall survival advantage with long-term ADT for 2 years, 3 years or indefinitely has been demonstrated in patients with locally advanced or high grade disease,[54–57] which is confirmed in two meta-analyses.[58,59] Longer durations of androgen suppression appear to be superior to shorter durations[51,55,60] however, the optimal duration of androgen suppression remains uncertain, and is the subject of ongoing clinical investigations. The results of the TROG RADAR trial[118] which randomised patients to 6 or 18 months of ADT are eagerly anticipated. Treatment recommendations should be individualised after consideration of the potential benefits, harms and patient tolerability of androgen deprivation therapy (see Table 1 – Guideline 8).

Morbidity of androgen deprivation therapy

For all patients, improved treatment efficacy should be balanced against potential toxicity and adverse effects on quality of life from ADT. Potential adverse effects include decreased bone density and increased risk of fracture,[119,120] decrease in lean muscle mass and increase in body fat, alteration in lipids, impaired insulin sensitivity and increased incidence of diabetes mellitus.[121] An association between ADT and an increased risk of cardiovascular events has been demonstrated in several studies.[122–125] However, no increase in cardiovascular mortality has been identified in individual randomised trials, although they are inadequately powered to detect small increases in cardiac morbidity.

Optimal evidence based prevention, investigation and management of the skeletal consequences of ADT is not well defined in the literature. A suggested approach is to perform a baseline assessment bone mineral density, serum calcium, 25-hydroxy vitamin D and parathyroid hormone, with repeat assessments performed at 1- to 2-year intervals for duration of therapy. Patients prescribed ADT should be encouraged to adopt a 'healthy bone lifestyle' including adequate daily calcium intake, maintenance of normal vitamin D status, regular weight bearing/resistance exercise, moderation of alcohol consumption and cessation of smoking. Routine calcium/vitamin D supplementation for all patients may be considered.[126] Specialist referral is encouraged for patients with established osteoporosis or biochemical abnormalities. Collaboration with the patient's general practitioner to optimise management of potential cardiovascular risk factors is also advised.

Quality assurance

Quality assurance is a necessary and integral component of both the clinical and physical aspects of patient care and treatment delivery. Departments should recognise the organisational and professional standards required for the provision of IMRT and/or IGRT.[61,62] It is recommended that centres utilising IMRT and/or IGRT establish a multidisciplinary team consisting of radiation oncology, radiation therapy and medical physics staff with appropriate levels of experience, qualifications, training and capacity to maintain a quality assurance program in accordance with international guidelines.[64,127] (see Table 1 – Guideline 9)

Outcome & toxicity reporting

Documentation and audit of institutional clinical, biochemical and toxicity outcomes is recommended as a critical component of quality assurance. It also allows inter-institutional and inter-modality comparison of prostate cancer treatment outcomes (see Table 1 – Guideline 10).

Conclusion

The Australian & New Zealand consensus guidelines provide an evidenced based framework for the delivery of definitive external beam radiotherapy for prostate cancer. The guidelines are based on the current available evidence; however, recommendations may be superseded as further evidence become available in the future. Many controversies remain, and ongoing clinical investigations are required to continue to optimise the outcomes of prostate cancer radiotherapy.

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Appendix I

Levels of evidence

Level I	Evidence is obtained from a systematic review of all relevant randomised controlled trials
Level II	Evidence is obtained from at least one well designed randomised controlled trial
Level III	Evidence is obtained from well-designed controlled trials without randomisation; 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.

Appendix II

Levels of consensus

A	Uniform consensus
B	Non-uniform consensus
C	Major disagreement

Adapted from the National Comprehensive Cancer Network Categories of Evidence and Consensus.[69]