Evidence-based Series 3-11 EDUCATION AND INFORMATION 2011

The Use of Conformal Radiotherapy and the Selection of Radiation Dose in T1 or T2 Prostate Cancer

Members of the Genitourinary Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Evidence-based Series 3-11 was reviewed on June 17, 2011 and put in the Education and Information section by the Genitourinary Disease Site Group (DSG) on November 9, 2011. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

Evidence-based Series (EBS) 3-11 EDUCATION AND INFORMATION 2011, the resulting review report, consists of the following 4 parts:

1. Guideline Report Overview
2. Summary
3. Full Report
4. Document Assessment and Review Tool

and is available on the CCO website (http://www.cancercare.on.ca) PEBC Genitourinary Cancer Disease Site Group page at: http://www.cancercare.on.ca/toolbox/qualityguidelines/disease/site/genito-eb/

Release Date: January 10, 2012

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For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Evidence-based Series 3-11 EDUCATION AND INFORMATION 2011

The Use of Conformal Radiotherapy and the Selection of Radiation Dose in T1 or T2 Prostate Cancer

Guideline Report History

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The Use of Conformal Radiotherapy and the Selection of Radiation Dose in T1 or T2 Prostate Cancer

Guideline Review Summary

Review Date: November 9, 2011

The 2002 guideline recommendations are ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other informational purposes.

OVERVIEW
Evidence-based Series History
This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario, in 2002. In November 2011, the PEBC guideline update strategy was applied and the new updated document archived. The Summary and the Full Report in this review remain the same as in the February 2002 version.

Update Strategy
The PEBC update strategy includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new evidence. See the Document Assessment and Review Tool at the end of this document.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Questions Considered
1. When single-modality treatment external-beam radiotherapy is selected as the modality of choice, what is the role of three-dimensional conformal radiotherapy in treating clinically localized (T1 or T2 / N0 or NX / MO) prostate cancer? The outcomes of interest
are biochemical freedom from failure (bNED) rates, clinical recurrence-free survival, disease-specific survival, and acute or late toxicity.

2. What is the appropriate dose and fractionation prescription in this clinical setting?

**Literature Search and New Evidence**

A search for new literature with respect to these questions was not conducted because the guideline and its recommendations are **ARCHIVED**.

**Impact on Guidelines and Its Recommendations**

The Genitourinary Cancer DSG **ARCHIVED** the 2002 recommendations. Therefore this guideline will no longer be updated.

It was determined that the topic should be expanded beyond low- and intermediate-risk patients to include high-risk patients. In addition, the comparison should pertain to IMRT versus conformal radiotherapy rather than conformal versus nonconformal. Because the questions will be substantially changed, a new guideline addressing the new question should be planned or the content be absorbed into another guideline (EBS 3-13) that is currently being updated. The IMRT aspect has been addressed in the 2010 guideline *The Role of IMRT in Prostate Cancer* from the Radiation Therapy Clinical Program.
The Use of Conformal Radiotherapy and the Selection of Radiation Dose in T1 or T2 Prostate Cancer
Practice Guideline Report #3-11

M Brundage, H Lukka, J Crook, P Warde, G Bauman, C Catton, BR Markman, M Charette, and members of the Genitourinary Cancer Disease Site Group

Please see the EBS 3-11 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool.

Report Date: October 1, 2002

SUMMARY

Guideline Questions
3. When single-modality treatment external-beam radiotherapy is selected as the modality of choice, what is the role of three-dimensional conformal radiotherapy in treating clinically localized (T1 or T2 / N0 or NX / MO) prostate cancer? The outcomes of interest are biochemical freedom from failure (bNED) rates, clinical recurrence-free survival, disease-specific survival, and acute or late toxicity.

4. What is the appropriate dose and fractionation prescription in this clinical setting?

Target Population
These recommendations apply to adult men with early-stage prostate cancer (T1 or T2, clinical N0 or NX / MO, with a Gleason score \( \leq 7 \)).

Recommendations
- Patients who have external-beam radiotherapy should be treated using a 3-D conformal technique.
- In light of the preliminary nature of the available evidence for dose escalation from randomized studies, and the corresponding need for confirmatory studies, patients should be offered participation in randomized clinical trials investigating dose escalation if such trials are open to accrual. In the absence of such trials, patients with intermediate-risk disease (prostate-specific antigen [PSA] 10 to 20) who are treated with external-beam radiotherapy alone should be offered doses of 75 to 78 Gy in 180 to 200 cGy fractions. The weight of available evidence suggests that prescribed doses of 75 to 78 Gy reduce biochemical failure rates compared to 70 Gy, particularly in patients with intermediate-risk disease. Randomized controlled studies have shown such treatment to be safe.
Qualifying Statement

- The conclusions are largely based on bNED rates as a surrogate outcome measure for clinical disease recurrence.
- There is insufficient clinical evidence at present to recommend doses above 70 Gy for patients with very favourable prognostic factors (e.g. PSA < 4, or PSA < 10 and Gleason < 7 with no perineural invasion evident).
- Doses of 75 Gy or more can be delivered safely only with conformal radiotherapy techniques.
- Conformal therapy requires that patients are planned using three-dimensional delineation of the target and treatment volumes, with individualized shielding constructed with a beam's-eye-view technique. There is no single prescriptive strategy for the appropriate deployment of conformal radiotherapy. Centres using this technique, however, must address the following elements of safe treatment delivery:
  - reproducibility of treatment set-up in their local setting
  - degree of internal organ movement
  - number of treatment fields
  - appropriate planning target volume margins.

Methods

Entries to MEDLINE (1991 through March 2002) and CANCERLIT (1991 through October 2001) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology were systematically searched for evidence relevant to this practice guideline report.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative Genitourinary Cancer Disease Site Group. A first draft of this practice guideline report was subsequently reviewed in detail by a working group consisting of five members of the Disease Site Group. This practice guideline report has been reviewed and approved by the Genitourinary Cancer Disease Site Group, which comprises urologists, medical oncologists, radiation oncologists, a pathologist, and two patient representatives.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report was obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Key Evidence

- Two randomized trials comparing conventional radiotherapy to conformal therapy, one with and one without dose escalation, reported bNED rates. Three additional randomized controlled trials reported acute or chronic late outcome assessments. Additional studies included phase II studies of dose escalation in sequential patient cohorts and non-randomized comparative assessments of dose-response and bNED rates in controlled analyses.
- There is convincing evidence from randomized trials that the use of conformal therapy reduces acute and late treatment-related morbidity. There is preliminary evidence suggesting that when external-beam therapy alone is used to treat patients, conformal therapy with dose escalation is more efficacious than doses of 70 Gy for patients with intermediate-risk disease (PSA 10 to 20). There is conflicting evidence of the efficacy of
dose escalation in patients with low initial PSA (PSA < 10) and in patients with initial PSA greater than 20.

- When combined with dose escalation, conformal radiotherapy to a dose of 78 Gy appears to be safe with no increase in acute or late effects compared with conventional treatment (up to 70 Gy).

**Treatment Alternatives**

Patients with poor prognostic factors (e.g. PSA > 20) may be candidates for neoadjuvant or adjuvant hormone ablative therapy in addition to radiotherapy. The role of dose escalation of radiotherapy requires further study in the setting of (neo-) adjuvant hormonal therapy and is not addressed by this practice guideline.

**Future Research**

One relevant randomized study still accruing patients was identified. This study will address a limited aspect of dose escalation, because patients in both study arms will have higher-risk disease and will also receive hormone ablative therapy. In addition, the Radiation Therapy Oncology Group (RTOG) is planning a phase III study evaluating dose escalation in the target population. It is not known when this study will be open to patient accrual or how well it will accrue patients in the context of existing clinical evidence.

**Related Documents**

Practice Guideline Initiative Evidence Summary Report #3-10: *The use of brachytherapy in T1 or T2 prostate cancer.*

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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle. The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report is submitted for formal approval to / has been formally approved by the Practice Guidelines Coordinating Committee (PGCC), whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:


For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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The Use of Conformal Radiotherapy and the Selection of Radiation Dose in T1 or T2 Prostate Cancer
Practice Guideline Report #3-11

M Brundage, H Lukka, J Crook, P Warde, G Bauman, C Catton, BR Markman, M Charette, and members of the Genitourinary Cancer Disease Site Group

Please see the EBS 3-11 Archived 2011 Guideline Review Summary and the Document Assessment and Review Tool.

Report Date: October 1, 2002

FULL REPORT

I. QUESTIONS
1. When single-modality treatment external-beam radiotherapy is selected as the modality of choice, what is the role of three-dimensional (3-D) conformal radiotherapy in treating clinically localized (T1 or T2 / N0 or NX / MO) prostate cancer? The outcomes of interest are biochemical freedom from failure (bNED) rates, clinical recurrence-free survival, disease-specific survival, and acute or late toxicity.
2. What is the appropriate dose and fractionation prescription in this clinical setting?

II. CHOICE OF TOPIC AND RATIONALE
Men with clinically localized prostate cancer can be conceptualized as having low-, intermediate-, or high-risk disease according to disease-related prognostic factors including prostate-specific antigen (PSA) level at diagnosis and Gleason Score (1). Patients with clinically localized prostate cancer often have a choice between two curative modalities: radical prostatectomy or radiotherapy in the form of external-beam therapy or brachytherapy. There are no mature, high-quality randomized trials that compare radical prostatectomy to either brachytherapy or external-beam radiotherapy in the setting of clinically localized prostate cancer. Large multi-institutional series of early-stage patients treated with external-beam radiotherapy show results comparable to those with radical prostatectomy (2). The choice of treatment is based, to some extent, on consideration of patients’ preferences and relative toxicities (3). The role of brachytherapy in this patient population has been summarized in a recently published evidence summary (4). The purpose of the present practice guideline is to address the appropriate prescription of external-beam radiotherapy, once selected by the physician and patient as the treatment modality of choice. This guideline does not address the choice of radiotherapy as a modality per se, nor does it address the role of adjuvant/neoadjuvant hormonal therapy in this patient population, or the role of external-beam therapy in clinical or pathologic T3/T4 disease where separate evaluations of evidence-based practices are required.

“Conventional” radiotherapy without dose-escalation, that is, external-beam radiotherapy typically delivered with two-dimensional (2-D) planning and three to four fields to doses of up to
66 Gy in 1.8 to 2.0 Gy fractions, has limited efficacy in eradicating prostate cancer in many men with early-stage disease. The limitations of conventional radiotherapy are highlighted by a retrospective analysis of treatment outcomes at the Princess Margaret Hospital which revealed that a substantial portion of patients treated with conventional radiotherapy for early-stage disease subsequently developed biochemical progression, indicating treatment failure (5). Biochemical relapse was seen in over half (65%) of 794 patients with early-stage prostate cancer treated between 1987 and 1994 (median follow-up > 4 years) (6). Comparable results have been reported in other retrospective analyses from large institutions (7,8). The frequent finding of prostate cancer in post-treatment prostate biopsies underscores the requirement for higher radiotherapy doses to yield higher disease control rates (9).

“Conformal” radiotherapy represents an approach to external-beam treatment that incorporates a number of different technical elements, generally viewed as significant improvements in the delivery of radiotherapy. The term “conformal” is difficult to define precisely because technical advances have been made in many aspects of radiotherapy delivery, including the beam quality generated by linear accelerators, in novel combinations of beams designed to minimize the volume of normal tissues irradiated, in automated methods of shielding unnecessary portions of each beam, in imaging the target volume(s) to be treated, in improving the reproducibility of treatment between and within patients, in verifying the delivered therapy, and in calculating the distribution of radiotherapy dose resulting from complex treatments. The term “conformal” is generally considered as external-beam radiotherapy that contains the following elements:

a. Three-dimensional delineation of the clinical target and planning volumes.
b. Individualized “beam’s eye view” shielding to match the planning volumes.

In addition, “conformal” therapy may variably imply:

c. Escalation of the prescribed dose over that safely used with conventional techniques.
d. Patient immobilization beyond conventional “free” set-up using beam-entry reference points (tattoos).
e. Calculation of dose-volume histograms, which are intended to allow objective comparisons of candidate treatment plans, to optimize treatment technique, and to identify when normal tissue dose tolerance has been exceeded.

Conformal radiotherapy is now considered a standard of care in many cancer centres internationally (10,11). Many of the technical advances associated with the delivery of external-beam radiotherapy, including conformal therapy, have been accepted without formal evaluation of their impact on patient-related outcomes, largely because the evolution of radiotherapy has been on empirical grounds wherein an improvement in the distribution of radiation dose is seen as necessarily beneficial. It is not as clear, however, that increased prescribed doses of radiation are necessarily beneficial (12). In this guideline, therefore, we make the distinction between conformal therapy and dose escalation, where conformal therapy is taken to be the technical elements of treatment planning and delivery, and dose escalation is taken to be the prescription of radiation doses above those given with conventional therapy. The two concepts are linked (and therefore confounded) because dose escalation is only possible when conformal radiotherapeutic techniques are used to protect normal tissues outside the target volume. We address the evidence for each concept separately, however, wherever possible.

The benefits of conformal therapy rest in its potential to increase the therapeutic ratio by allowing, in theory, the delivery of higher doses of radiation to the prostate with little or no increase in normal tissue complications. These goals are achieved by more accurately
delineating the treatment volume, by conforming the irradiated volume more closely to the target, and by reducing the irradiated volume of bladder and bowel. The potential risks of conformal therapy lie in these reduced margins (given the uncertainties associated with tumour delineation, organ movement, patient set-up variation) and in the tolerance of small volumes of normal tissue to high-dose treatment. Briefly stated, should the treatment volumes be conformed too tightly to the prostate contour, uncertainties in treatment reproducibility may lead to geographic “misses” of the target. In addition, dose escalation beyond the tolerance of normal tissues may increase late complications and reduce the therapeutic ratio, and exposure of more normal tissue to modest doses peripheral to the target volume may increase treatment-induced oncogenesis (12).

Given the potential benefits and potential risks of dose escalation with conformal therapy, the Genitourinary Cancer Disease Site Group (GU DSG) elected to assess the evidence pertaining to the potential benefits and the potential risks of both conformal therapy and radiotherapy dose escalation and to summarize this evidence in a practice guideline.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC), using methods of the Practice Guidelines Development Cycle (13). Evidence was selected and reviewed by one member of the PGI GU DSG. A first draft of this document was subsequently reviewed in detail by a working group consisting of five members of the GU DSG. Later drafts of the practice guideline were reviewed and discussed by all members of the GU DSG. Members of the GU DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of conformal radiotherapy and the selection of radiation dose in T1 or T2 prostate cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The body of evidence in this report is primarily comprised of mature randomized controlled trial data; therefore, recommendations by the DSG are offered. The report is intended to promote evidence-based practice. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each guideline report. This process consists of periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

A systematic search for randomized controlled trials and non-randomized comparative studies was carried out using MEDLINE (Ovid) (1991 through March 2002) and CANCERLIT (Ovid) (1991 through October 2001). Medical subject headings included “radiotherapy”; “prostatic neoplasms”; “radiotherapy, computer assisted”; “radiotherapy, conformal” and “prostate specific antigen”. The following text words were also used: “radiotherapy, conformal”, “PSA” and “prostate cancer”. In addition, the proceedings of the 1999, 2000 and 2001 meetings of the American Society of Clinical Oncology (ASCO) and the 1999, 2000 and 2001 meetings of the American Society for Therapeutic Radiology and Oncology (ASTRO) were searched for reports of newly completed trials. Relevant articles identified by the literature search, found in personal files or cited in papers and reviews were retrieved and reviewed. All identified indexed
abstracts were reviewed by one reviewer (MB). The publications meeting the inclusion criteria were reviewed by a working group (PW, HL, GB, JC, and BM) and subsequently by the entire DSG.

The Physician Data Query (PDQ) clinical trials database on the Internet (http://cnetdb.nci.nih.gov/trialsrch.shtml) was also searched for both active and closed ongoing trials in patients with the diagnosis of prostate cancer evaluating the treatment modality of external-beam radiotherapy.

**Inclusion Criteria**

Randomized controlled trials comparing conformal therapy with conventional external-beam radiotherapy, phase II studies, and non-randomized comparative studies evaluating radiotherapy dose escalation and conformal treatment delivery were selected for inclusion in this systematic review of the evidence if the following criteria were met:

- The majority of study patients were diagnosed with T1 or T2 prostate cancer with clinical nodal staging (N0-NX) and Gleason 7 or less. Patients with high-risk early-stage disease (Gleason 8-10) or T3/T4 disease were not included, as combined-modality treatment approaches are already generally recommended in this setting (14). No upper limit of PSA was declared a priori, owing to the variation in cut-off points used in the literature to define high-risk disease.
- The radiotherapy techniques were sufficiently described (dose, fractionation, technique, reproducibility parameters).
- For non-randomized studies, patients were treated on a prospective clinical trial protocol (phase II studies), or comparisons were made employing sequential, prospective patient cohorts and/or appropriate multivariate analyses of institutional data.
- One or more of the outcome measures described in the “Outcome Assessment” section below were recorded.

**Exclusion Criteria**

Papers published in a language other than English were not considered.

**Outcome Assessment**

Although an analysis of overall patient survival duration is the definitive measure of successful treatment of malignancy, the long natural history of prostate cancer promotes the use of surrogate endpoints such as serum PSA control rates and post-treatment prostate biopsy results. Biochemical freedom from failure (bNED) has been variously defined in the studies included in this report, and pitfalls in the interpretation of bNED data have been highlighted by a number of authors (15,16). In this summary, the definition of bNED used in each publication was accepted without modification. Other disease-outcome measures, such as clinical recurrence-free survival or disease-specific survival, were noted where available. In addition to disease-related outcomes, comparative studies were included if they reported toxicity outcomes (acute toxicity or late toxicity) or technical outcomes (improved dose distribution, reproducibility, target delineation).

**Synthesizing the Evidence**

Two randomized trials were located that compared conformal radiotherapy to conventional therapy and reported bNED rates. In one of these trials, patients received the same dose of radiation in both arms; in the other trial, the dose of conformal therapy was escalated. Therefore, it was judged to be inappropriate to pool the bNED data from randomized trials.
Three randomized trials reported on acute toxicity, and three randomized trials reported on late toxicity. Due to the heterogeneity in study design and the differences in outcome instruments to assess toxicity, pooling of toxicity data was not undertaken.

IV. RESULTS

Literature Search Results

Two randomized controlled trials (17,18) and 12 reports of phase II studies or non-randomized comparative studies (19-30) provided data on disease-related outcomes. Three randomized controlled trials (31-33) and four reports of phase II or non-randomized comparative studies (25,36,37,39) provided data on acute toxicity. Three randomized trials (18,34,35) and nine reports of phase II or non-randomized comparative studies (19,20,25,29,37-41) provided data on late toxicity. The randomized trials reporting on acute and late toxicity were not yet mature enough to provide data on disease-related outcomes.

Disease-Related Outcomes

One randomized controlled trial conducted at the M.D. Anderson Cancer Centre compared conformal therapy to lower-dose conventional external-beam radiotherapy and reported bNED rates for 301 randomized patients (Table 1) (17). The observed improvement in bNED rates across all patients treated with conformal therapy did not reach statistical significance (p=0.058) in a univariate model. In a multivariate Cox proportional hazards model of bNED correcting for pre-treatment PSA, stage and, Gleason score, randomization arm (70 Gy v. 78 Gy) was statistically significant, regardless of whether pre-treatment PSA was treated categorically (p=0.028) or continuously (p=0.011). A statistically significant improvement in bNED in favour of conformal radiotherapy was detected in the subgroup of patients with T1/T2 disease and a pre-treatment PSA > 10 (Table 1). Overall survival rates at five years were similar in both groups. Acute (32) and late toxicity (34) of patients treated in this trial have been reported in separate publications.

A second trial randomized 225 patients to receive conventional or conformal treatment at a dose of 64 Gy (18) (Table 1). The two-year bNED rates were 71% for patients treated with conformal techniques, versus 54% for patients treated with conventional radiotherapy. The five-year rates were 39% and 31% respectively. Overall survival rates at two years (91% conformal v. 90% conventional) and five years (66% v. 64%) were similar in both groups (p=0.57).

Table 1 also summarizes a number of non-randomized comparative studies identified by the literature search. Two prospective dose-escalation studies suggested improved bNED survival with higher doses of radiotherapy; the largest magnitude of dose-related effect in these studies was seen in patients with intermediate-risk prognostic factors (20,21). Two reports were published (19,22) involving subsets of patients included in the trial conducted at the Fox Chase Cancer Centre (21). Hanks et al (19) reported improved bNED survival at five years with higher doses of radiotherapy in patients with intermediate-risk prognostic factors. Pinover et al (22) reported that patients with PSA ≤ 10 ng/ml in the poor prognosis group (tumour T2b-T3, Gleason score ≥ 7, or perineural invasion) exhibited improved bNED survival at five years with higher radiotherapy doses. This was not replicated in the good prognosis group (patients failing to demonstrate any poor prognosis features) or the entire cohort.

A number of additional studies showed a statistically significant association between radiotherapy dose and bNED or overall survival in multivariate analyses (23-27). Kupelian et al (30) reported on a subset of patients with favourable characteristics (stage T1-T2, Gleason score ≤ 6, and PSA ≤ 10 ng/ml) treated at the Cleveland Clinic Foundation (24). Higher bNED survival was seen in patients receiving ≥ 72 Gy versus < 72 Gy (five- and eight-year bNED 95% v. 77%; p=0.01). Two retrospective comparative studies showed no statistically significant relationship between radiotherapy dose and bNED survival (28,29).
Toxicity-Related Outcomes

Acute Toxicity
Three randomized trials comparing conventional radiotherapy with conformal radiotherapy reported data on acute toxicity (Table 2) (31-33). The use of conformal treatment, without a corresponding increase in dose, reduced acute toxicity in two of the studies (31,33), consistent with the principles of conformal radiotherapy delivery. The third randomized study, designed with dose escalation in the conformal treatment arm, also showed that the bowel and bladder could be effectively shielded and detected no significant difference in acute toxicity, despite the higher dose delivered to the prostate (32). Additional non-randomized comparative studies reporting on acute toxicity are listed in Table 2.

Late Toxicity
Chronic adverse effects, i.e., symptoms occurring one year or more after treatment, were reported in three randomized trials (18,34,35). Two of the trials reported no significant differences in either late bladder or bowel toxicity despite the higher dose of radiation used in the conformal treatment arms (34,35). The third randomized trial, in which patients received the same dose of radiation in both the conventional and conformal arms, reported significantly more grade 2 or greater bowel toxicity in the conventional arm (15% v. 5%; p=0.01) (18). Additional non-randomized trials reporting late toxic effects are listed in Table 2 (19,20,25,29,37-41).
Table 1. Comparative study results: Disease-related outcomes.

<table>
<thead>
<tr>
<th>First Author, Year (ref), Institution</th>
<th>Treatment (s)</th>
<th>N (eval)</th>
<th>Study Population</th>
<th>bNED Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evidence from Randomized Controlled Trials</strong></td>
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<tr>
<td>Pollack, 2000 (17) MD Anderson</td>
<td>70 Gy conventional</td>
<td>150</td>
<td>Stage: T1/2: 80%; T3: 20%</td>
<td>5-year actuarial: 69%</td>
<td>For T1/2 and PSA&gt;10: 60% v. 90%; p&lt;0.011. Overall independent effect of treatment in Cox model (RR=0.55; p=0.028). Study end-point: “Fraction failing” = PSA rise or clinical progression.</td>
</tr>
<tr>
<td></td>
<td>78 Gy conformal</td>
<td>151</td>
<td>Gleason: 2-6: 49%; 7-10: 51%</td>
<td>79% (p=0.058)</td>
<td></td>
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<tr>
<td>Dearmaley, 1999 (18) Royal Marsden</td>
<td>64 Gy conventional</td>
<td>111 (94)</td>
<td>Stage: T1: 11%; T2: 34%; T3: 53%; T4: 2%</td>
<td>5-year actuarial: 54%</td>
<td></td>
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<tr>
<td></td>
<td>64 Gy conformal</td>
<td>114 (99)</td>
<td>NO,MO (except 1 N1)</td>
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<tr>
<td><strong>Evidence from Phase II Studies or Non-randomized Comparative Studies</strong></td>
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<tr>
<td>Hanks, 2000 (21) Fox Chase</td>
<td>Consecutive patients treated by institutional protocol (range &lt;72.5 to &gt; 76.0 Gy).</td>
<td>618 (618)</td>
<td>Favourable Subgroup: PSA &lt; 10: 36%; PSA 10-19.9: 18%; PSA ≥ 20: 7%</td>
<td>5-year actuarial: Favourable subgroup*: PSA &lt;10: 77% &lt;72.5 Gy; 89% for ≥72.5 Gy PSA 10-19.9: 72% for &lt;76 Gy; 86% for ≥76 Gy PSA ≥20: 63% for &lt;76 Gy; 23% for ≥76 Gy Unfavourable subgroup*: PSA &lt;10: 70% for &lt;76 Gy; 92% for ≥76 Gy PSA 10-19.9: 51% for &lt;76 Gy; 82% for ≥76 Gy PSA ≥20: 29% for &lt;76 Gy; 26% for ≥76 Gy</td>
<td>Favourable: Stage ≤ T2a and Gleason 2-6 and no perineural invasion. Unfavourable: Stage ≥ T2b or Gleason 7+ or perineural invasion. Cox model showed dose independent predictor of bNED, except in PSA &lt; 10, favourable, PSA ≥ 20, unfavourable and PSA 10-19.9 favourable.</td>
</tr>
<tr>
<td></td>
<td>Consecutive patients treated on institutional protocol. Median dose 70.2 Gy (range 57.6-78.0 Gy).</td>
<td>1041 (1041)</td>
<td>Stage: T1: 35%; T2: 54%; T3: 11%; Gleason: 2-6: 56%; 7-10: 44%</td>
<td>5-year actuarial: Overall: 61% 87% for ≥ 72 Gy; 55% for &lt; 72 Gy</td>
<td>Similar results for 8-year actuarial results. Dose independent predictor of bNED survival in Cox model.</td>
</tr>
<tr>
<td></td>
<td>Analysis of patients in 4 prospective (phase III) controlled trials receiving external-beam radiation alone. Median dose 68.4 Gy (range 10.8-77.7 Gy).</td>
<td>1560 (1465)</td>
<td>Stage: T1: 6%; T2: 35%; T3: 59%; Gleason: 2-6: 49%; 7: 17%; 8-10: 27%; unknown: 6%</td>
<td>bNED: Not reported Overall Survival: Overall 27% lower relative risk of death if dose &gt; 66 Gy (dose an independent predictor of overall survival in model). Most significant if Gleason 8-10: 10y Overall Survival 46% for &gt; 66 Gy, 31% for ≤ 66 Gy; p=0.041.</td>
<td>PSA staging and outcome not available in this era of clinical trials. Analysis stratified for length of follow-up and for Gleason score. Analysis repeated for all patients receiving full protocol dose (n=1399) with similar results.</td>
</tr>
<tr>
<td>Magrini, 1998 (25) Italy</td>
<td>Retrospective review of patients receiving radiation therapy (dose range 60-70 Gy).</td>
<td>365 (208)</td>
<td>Stage: T2: 60%; T3: 40%</td>
<td>5-year actuarial: 56% Multivariate analysis showed dose to prostate to be significantly associated with bNED (p&lt;0.001).</td>
<td></td>
</tr>
<tr>
<td>Seung, 1998</td>
<td>Retrospective review of</td>
<td>187</td>
<td>Stage:</td>
<td>4-year actuarial:</td>
<td>All patients with good-prognosis risk factors in</td>
</tr>
<tr>
<td>First Author, Year (ref), Institution</td>
<td>Treatment (s)</td>
<td>N (eval)</td>
<td>Study Population</td>
<td>bNED Results</td>
<td>Comments</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------</td>
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<td>------------------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>(28) UCSF</td>
<td>patients receiving external-beam radiation. Median dose 69.5 Gy (range 60 - 71 Gy). 62 patients treated conformally median dose 76.4 Gy (range 71.6 – 87 Gy).</td>
<td>(187)</td>
<td>T1: 33%; T2: 68%; T3: 0% Gleason: 2-6: 100%</td>
<td>overall 75% Varied by initial PSA group (but not with T category or Gleason score) in multivariate analysis. No association with prescribed dose in univariate analysis.</td>
<td>keeping with the intent of the report.</td>
</tr>
<tr>
<td>Zelefsky, 2001 (20) MSKCC</td>
<td>Sequential patient cohorts receiving escalated doses (phase I/II). 871 patients treated with conformal radiotherapy (range 64.8 Gy to 81.0 Gy). 229 patients treated with intensity modulated radiotherapy (dose 81.0 and 86.4 Gy).</td>
<td>(1100) (1100)</td>
<td>Stage: T1c: 26%; T2a: 32%; T2b: 18%; T3: 24%</td>
<td>5-year actuarial: Favourable†: 85%; (dose-effect p=0.04) Intermediates: 58% overall; 55% for &lt;70.2 Gy; 78% for &gt;75.6 Gy; p=0.008 Unfavourable: 38% overall; 21% for &lt;70.2 Gy; 43% for 75.6 Gy; p=0.03; 67% for 81.0 Gy; p=0.05 Biopsy positive rate (&gt;2 years): Dose-effect demonstrated.</td>
<td>The patient cohorts had different median follow-up times due to the sequential nature of patient accrual. Cox model showed dose independent predictor of bNED. All biopsies were performed after a minimum of two years follow-up.</td>
</tr>
<tr>
<td>Pollack, 1997 (27) MD Anderson</td>
<td>Consecutive patients treated by institutional protocol without hormonal therapy. Mean dose 67.8 Gy (range 60-78 Gy).</td>
<td>938 (938)</td>
<td>Stage: T1: 31%; T2a: 14%; T2b: 18%; T2c: 6%; T3: 31% Gleason: 2-6: 63%; 7: 24%; 8-10: 13%</td>
<td>5-year actuarial: Overall independent effect of prescribed dose in Cox model (χ²=44, p&lt;0.0001); dose-response seen in all patient subgroups except those with initial PSA ≤ 4.</td>
<td>Study end-point was “Fraction failing” = PSA rise or clinical progression.</td>
</tr>
<tr>
<td>Perez, 1993 (26) St. Louis</td>
<td>Retrospective review of patients receiving radiation therapy.</td>
<td>738</td>
<td>Stage: T1b: 7%; T2: 34%; T3: 56%; T4: 4%</td>
<td>5-year: 76% (T1b, T2); 57% (T3); 20% (T4) In T3 tumours, doses greater than 65 Gy better than 60 Gy (local tumour failure 25-30% v. 50%; p=0.01).</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** bNED = biochemical freedom from failure; eval = number of evaluable patients; Gy = gray; MSKCC = Memorial Sloan-Kettering Cancer Centre; N = number of patients; n/s = not specified; PSA = prostate-specific antigen; ref = reference number; RR = relative risk; RTOG = Radiation Therapy Oncology Group; UCSF = University of California, San Francisco; v. = versus.

* Favourable = stage T1, 2A, Gleason 2-6 and no perineural invasion. Unfavourable = stage T2B, T3 and / or Gleason 7-10 and / or perineural invasion.
† Favourable = pre-treatment PSA ≤ 10 ng/ml, stage T1-2, Gleason ≤ 6. An increase in the value of one of the indicators classified the patient as intermediate and two or more in unfavourable.
Table 2. Studies addressing toxicity endpoints.

<table>
<thead>
<tr>
<th>First Author, Year (ref), Institution</th>
<th>Treatment (s)</th>
<th>N (eval)</th>
<th>Study Population</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Toxicity: Evidence from Randomized Controlled Trials</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Koper, 1999 (31) Rotterdam</td>
<td>66 Gy conventional</td>
<td>134 (134)</td>
<td>Stage: T1: 12%; T2: 47%; T3: 38%; T4: 3%</td>
<td>GI*: (conv v. conf) Overall (grade 2): 32% v. 19%; p=0.02. Grade 2 (anal): 16% v. 8%; p &lt; 0.0001. GU* (grade ≥2): 17% v. 18%; p=NS.</td>
<td>No shielding was generally employed in conventional group.</td>
</tr>
<tr>
<td></td>
<td>66 Gy conformal</td>
<td>129 (129)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollack, 1996 (32) MD Anderson</td>
<td>70 Gy conventional</td>
<td>31 (31)</td>
<td>Stage: T2: 65%; T3: 35%</td>
<td>No significant difference in either acute bladder or bowel toxicity despite higher dose in conformal treatment arm*.</td>
<td>Reduced bladder volume treated in a patient subgroup planned with both techniques.</td>
</tr>
<tr>
<td></td>
<td>78 Gy conformal</td>
<td>29 (29)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tait, 1993 (33) Royal Marsden</td>
<td>64 Gy conventional</td>
<td>varied</td>
<td>Varied with outcome of interest.</td>
<td>Volume reduction achieved using conformal treatment; assessment of toxicity complex, requiring analysis of a range of symptoms, dose-levels, and normal-tissue volumes.</td>
<td>Some comparisons made to a hypofractionated treatment schedule. Toxicity data were self-reported.</td>
</tr>
<tr>
<td></td>
<td>64 Gy conformal</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Late Toxicity: Evidence from Randomized Controlled Trials</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Dearnaley, 1999 (18) Royal Marsden</td>
<td>64 Gy conventional</td>
<td>111 (94)</td>
<td>Stage: T1: 11%; T2: 34%; T3: 53%; T4: 2% N0,M0 (except 1 N1)</td>
<td>Grade 2 or greater GI toxicity*: (conv v. conf) 15% v. 5%; p=0.01. Grade 2 or greater GU toxicity*: (conv v. conf) 23% v. 20%; p=NS. 68% received neoadjuvant hormonal therapy. Lack of reduction in GU toxicity attributed to routine inclusion of seminal vesicles in treatment volume.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>64 Gy conformal</td>
<td>114 (99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nguyen, 1998 (34) MD Anderson</td>
<td>70 Gy conventional</td>
<td>NR (50)</td>
<td>Stage: T1/2: 69%; T3/4: 31% Gleason: 2-6: 42%; 7-10: 57%</td>
<td>No clinically significant differences in self-reported serious GU or GI late toxicity between study arms.</td>
<td>Self-reported questionnaire used in all patients who received treatment &gt; 2 years prior. No patient received hormonal therapy.</td>
</tr>
<tr>
<td></td>
<td>78 Gy conformal</td>
<td>NR (51)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storey, 2000 (35) MD Anderson</td>
<td>70 Gy conventional</td>
<td>NR (98)</td>
<td>Stage: T1c: 15%; T2: 59%; T3: 26% Gleason: 2-6: 47%; 7: 33%; 8-10: 20%</td>
<td>No significant difference in either GU or GI toxicity†. 5-year actuarial: GU toxicity ≥ Grade 2†: 20% v. 9%; p=0.8. GI toxicity ≥ Grade 2†: 14% v. 21%; p=0.4. Overall, &lt; 2% Grade 3; no Grade 4. Dose-volume histogram analysis of patients treated with 78 Gy showed that percentage of rectum receiving at least 70 Gy was predictive of late GI toxicity.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>78 Gy conformal</td>
<td>NR (91)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Evidence from Phase II Studies or Non-randomized Comparative Studies</strong></td>
<td></td>
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</tr>
<tr>
<td>Bergstrom, 1998 (36) Sweden</td>
<td>&quot;high-precision&quot; conformal radiotherapy with dose escalation phase II trial (range 70.0-76.0 Gy).</td>
<td>24 (23)</td>
<td>Stage: T1: 14%; T2: 28%; T3: 59%</td>
<td>No increase in acute toxicity with dose escalation. Grade 2 GU*: 25%. Grade 2 GI*: 13%.</td>
<td></td>
</tr>
<tr>
<td>Kupelian, 2000 (37) Cleveland Abstract</td>
<td>191 patients treated with SCIM-RT (70.0 Gy) compared to patients treated conformally with 78 Gy.</td>
<td>101</td>
<td>NR</td>
<td>Acute toxicity*: Grade 3 GU: 1%; Grade 3 GI: 0%. Late toxicity*: Grade 2 GI: 12%; Grade 3 GI: 3%. SCIM-RT and conformal radiotherapy had similar acute and late toxicity profiles.</td>
<td></td>
</tr>
<tr>
<td>Magrini, 1998 (25) Italy</td>
<td>Retrospective review of patients receiving radiation therapy (dose range 60 – 70 Gy).</td>
<td>365 (208)</td>
<td>Stage: T2: 60%; T3: 40%</td>
<td>Acute toxicity: all grades: 20%; grade 3: 8%. Late toxicity: all grades: 3%; ≥ Grade 2: 6%; Grade 4: 1.5%. Late radiation damage (any grade) significantly more frequent among patients treated on larger volumes (p (univariate) = 0.02).</td>
<td></td>
</tr>
<tr>
<td>Leibel, 1994</td>
<td>Consecutive patients in</td>
<td>324</td>
<td>Stage: T1: 15%; T2:</td>
<td>Acute toxicity*: No Grade 3-4 GI toxicity; &lt;1%</td>
<td></td>
</tr>
</tbody>
</table>

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*GI*, *GU*: grade, 
†5-year actuarial"
<table>
<thead>
<tr>
<th>First Author, Year (ref), Institution</th>
<th>Treatment (s)</th>
<th>N (eval)</th>
<th>Study Population</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>(39) MSKCC</td>
<td>dose-escalation study of conformal therapy (range 65-81 Gy)</td>
<td>53%; T3: 32%</td>
<td></td>
<td>Grade 3 GU toxicity. Late toxicity*: Grade 4 GI &lt;1%; Grade 3 GU &lt;1%</td>
<td></td>
</tr>
<tr>
<td>Bey, 2000 (41) France</td>
<td>Consecutive patients in dose-escalation study; all conformally treated (range 66.0-80.0 Gy)</td>
<td>164</td>
<td></td>
<td>No grade 3-4 late GI toxicity. All grades: 26% (66-70 Gy), 36% (74-80 Gy); p=NS. Grade 3 late GU toxicity: 7% (66-70 Gy) vs. 1% (74-80 Gy); p=NS. All grades: 24% (66-70 Gy) vs. 21% (74-80 Gy); p=NS.</td>
<td></td>
</tr>
<tr>
<td>Michalski, 2000 (40) RTOG Abstract</td>
<td>Sequential patient cohorts receiving escalated doses using conformal therapy (level 1: 68.4 Gy; level 2: 73.8 Gy)</td>
<td>424 (396)</td>
<td></td>
<td>Late toxicity: &lt;1% Grade 3 GU toxicity overall* Grade 2 toxicity*: 16% (T1/2 tumours); 25% (T3 tumours)</td>
<td>Event rate significantly lower than that in previous phase III studies (analysis stratified by follow-up time).</td>
</tr>
<tr>
<td>Hanks, 1998 (19) Fox Chase</td>
<td>Consecutive patients in dose-escalation study; all conformally treated (range 63.0-79.0 Gy)</td>
<td>232</td>
<td></td>
<td>Grade 3/4 GI toxicity at 5 years &lt; 1% (RTOG) or 6% (LENT); dose-effect detected for Grade 2 GI toxicity. Grade 3/4 GU toxicity† at 5 years = 4%.</td>
<td></td>
</tr>
<tr>
<td>Zelefsky, 2001 (20) MSKCC</td>
<td>Sequential patient cohorts receiving escalated doses using conformal therapy (range 64.8-81.0 Gy) and intensity-modulated radiotherapy (81.0 and 86.4 Gy)</td>
<td>1100 (1100)</td>
<td></td>
<td>Late toxicity* Grade 0/1 in 90%. 5-year actuarial*: Grade 2 GI 11%, GU 10%; Grade 3 GI 1%, GU 1.5%. Grade 2/3 GI (81.0 Gy): 2.5% (IMRT) v. 14% (conf); p&lt;0.01</td>
<td>Dose was predictive of toxicity in multi-variate model.</td>
</tr>
<tr>
<td>Fukunaga-Johnson, 1997 (29) Michigan</td>
<td>Single cohort descriptive study. All conformally treated (range 49.0-80.0 Gy)</td>
<td>707 (685)</td>
<td></td>
<td>7-year actuarial*: 3% or less Grade 3 or 4 GI toxicity 1% risk of Grade 3 GU toxicity (no Grade 4)</td>
<td></td>
</tr>
<tr>
<td>Lee, 1996 (38) Fox Chase</td>
<td>All patients treated conformally. Median dose 75.78 Gy (range 71.0-79.0 Gy)</td>
<td>257</td>
<td></td>
<td>Late toxicity†: Grade 2-3 GI: 18% (overall), 5% (&lt;74 Gy) v. 17% (74-76 Gy) v. 31% (&gt;76 Gy); p=0.05.</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: conf = conformal radiotherapy; conv = conventional radiotherapy; eval = number of evaluable patients; GI = gastrointestinal; GU = genitourinary; Gy = gray; IMRT = intensity-modulated radiation therapy; LENT = Late Effects Normal Tissue; MSKCC = Memorial Sloan-Kettering Cancer Centre; N = number of patients; NS = not significant; ref = reference number; RTOG = Radiation Therapy Oncology Group; SCIM-RT = short-course intensity-modulated radiotherapy; v., versus.

* Radiation Therapy Oncology Group (RTOG) toxicity criteria.
† Late Effects Normal Tissue (LENT) toxicity criteria.
V. INTERPRETIVE SUMMARY

A summary of the available evidence is shown in Tables 3a and 3b. The interpretation of the evidence relevant to the use of conformal radiotherapy and the use of dose escalation will be addressed in the following sections.

Quality of the Evidence

The published randomized trials reviewed by the working group were all well-conducted and reported. The non-randomized comparative studies reviewed by the DSG and included in this report were all well-conducted studies in that all patients were accounted for in the reports, the treatments were appropriately described, they were conducted in large centres, and they were analyzed with appropriate statistical considerations. While such studies are subject to greater potential bias than randomized studies, the included studies all appropriately accounted for known prognostic factors in examining the efficacy of conformal therapy and dose escalation, respectively (see also the “Consensus of the DSG - Technical Considerations” section below). One study that showed no statistically significant relationship between prescribed dose and bNED survival had a relatively small sample size (N=187) and may not have had sufficient power to detect associations of clinical significance (28). In the second study that did not show a dose-control relationship, the authors provided an analysis that revealed patients with more favourable disease systematically received lower doses of radiotherapy, thus introducing confounding (29). It is not known to what extent publication bias influenced the evidence available to the DSG; the members of the group were not aware of additional relevant unpublished data.

Interpretation of the Evidence - Conformal Therapy

Table 3b illustrates that there is sufficient evidence from randomized controlled trials to support the hypothesis that the use of conformal radiotherapy (without dose escalation) reduces the rates of both early and late bowel and bladder toxicity. These findings are consistent with the improved distribution of radiotherapy dose resulting from conformal techniques. The evidence in Table 3b is shown to relate to all prognostic subgroups because there is no strong a priori reason to expect that the association between conformal techniques and toxicity rates would depend on risk factors predictive of biological control rates (6).

Table 3a. Summary of disease-related evidence from eligible studies.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Patient cohort of interest (All T1/T2, Gleason ≤ 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSA &lt; 10</td>
</tr>
<tr>
<td></td>
<td>PSA 10-20</td>
</tr>
<tr>
<td></td>
<td>PSA &gt;20</td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td>Improvement in biochemical control (1 study) (17)</td>
</tr>
<tr>
<td>Non-randomized trials</td>
<td>Improvement in biochemical control (2 studies)*† (20,21)</td>
</tr>
<tr>
<td></td>
<td>Improvement in biochemical control (7 studies)† (20,21,23-27)</td>
</tr>
<tr>
<td></td>
<td>Improvement in biochemical control (3 studies)‡ (21,23,27)</td>
</tr>
<tr>
<td></td>
<td>no improvement in biochemical control (2 studies) (28,29)</td>
</tr>
<tr>
<td></td>
<td>insufficient follow-up in most studies to show improvement in clinical relapse or overall survival</td>
</tr>
</tbody>
</table>

N/A= not applicable.
* In one study (20), no dose-response seen in group with PSA < 4.
† In one study (21), no dose-response seen in a favourable subgroup (stage < T2b, Gleason < 7, no perineural invasion).
‡ In one study (21), no dose-response seen in an unfavourable subgroup (one or more of: stage ≥ T2b, Gleason ≥ 7 or perineural invasion).
Table 3b. Summary of toxicity-related evidence from eligible studies.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Summary of toxicity-related evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>Randomized controlled trials without dose escalation</td>
<td>reduction in acute toxicity (2 studies) (31,33)</td>
</tr>
<tr>
<td>Randomized controlled trials with dose escalation</td>
<td>no significant difference in acute toxicity despite higher dose in conformal arm (1 study) (32)</td>
</tr>
<tr>
<td>Non-randomized trials</td>
<td>lower than expected acute toxicity* (4 studies) (25,36,37,39)</td>
</tr>
<tr>
<td><strong>Late toxicity</strong></td>
<td></td>
</tr>
<tr>
<td>Randomized controlled trials without dose escalation</td>
<td>reduction in late toxicity (1 study) (18)</td>
</tr>
<tr>
<td>Randomized controlled trials with dose escalation</td>
<td>no significant difference in late toxicity despite higher dose in conformal arm (2 studies) (34,35)</td>
</tr>
<tr>
<td>Non-randomized trials</td>
<td>lower than expected late toxicity* (9 studies) (19,20,25,29,37-41)</td>
</tr>
</tbody>
</table>

* compared to previously reported data.

Interpretation of the Evidence - Dose Escalation

Table 3a summarizes the mounting evidence suggesting that escalation of the radiation dose (i.e. above that delivered using conventional techniques) results in increased biochemical response and control (bNED) rates. Carefully conducted prospective cohort studies, and one randomized trial, appear to indicate that dose escalation combined with conformal therapy increases bNED rates with no increase in either acute or late radiotherapy toxicity (6). For those studies in which some patients received neoadjuvant hormonal ablation, this finding was accounted for in the analyses.

In non-randomized comparative studies, the most consistently observed benefit is seen in patients with intermediate-risk disease (PSA 10 to 20 ng/ml, Table 3a). In this patient group, the evidence suggests that doses of 75 to 78 Gy are safe and are more effective than conventional radiotherapy to a dose of 70 Gy, as determined by bNED rates. This differential effect between patient cohorts is entirely biologically plausible—patients with intermediate-level risk are the most likely to benefit from more effective local treatment. That is, the "effect size" of dose escalation in patients with lower-risk (more indolent) disease is expected to be smaller than that in intermediate-risk patients due to the longer natural history of the cancer, the corresponding effect of competing co-morbidities, and the fact that the disease may respond to lower-dose treatment. Likewise, the effect size in patients with high-risk disease is expected to be smaller due to the comparatively higher incidence of distant metastases and the correspondingly lower impact of local therapy on bNED rates. The differential impact of dose escalation across risk strata implies that there is insufficient follow-up data from randomized trials to address the benefit of dose escalation in lower-risk patients (PSA < 10). The available evidence from non-randomized studies consistently suggests discernible benefit of dose escalation in all but the very best prognostic subgroups (PSA < 4, or PSA < 10 and no other pathological risk factors). The non-randomized evidence also suggests benefit in patients with high-risk disease (20), although one study showed no statistical association in patients in the worst prognostic subgroup (PSA > 20 and either Gleason score > 7 or evident perineural invasion, Table 3a) (21). The interpretation of the evidence is subject to potential bias owing to the differential length of patient follow-up and possible favourable patient selection in non-randomized studies. The extent to which these potential biases contribute to the observed effect of increased dose on bNED outcomes is not known. Members of the DSG acknowledged that publication bias may also be a potential problem with these kinds of studies.

VI. ONGOING TRIALS

**MRC-RT01, EU-98005**: Phase III randomized comparison study of conformal standard radiotherapy versus conformal high dose radiotherapy in addition to neoadjuvant androgen deprivation in patients with localized prostate cancer (Summary last modified April 2002).
RTOG-P-0126: Phase III randomized study of high-versus standard-dose three-dimensional conformal radiotherapy in patients with stage II adenocarcinoma of the prostate (Summary last modified April 2002).

VII. DISEASE SITE GROUP CONSENSUS PROCESS

Consensus of the DSG - Conformal Therapy

The members of the DSG concluded that the evidence for conformal therapy is sufficiently strong to recommend its routine use in the treatment of patients with prostate cancer. The benefits of conformal therapy have been sufficiently demonstrated by evidence from randomized controlled trials and are consistent with the basic principles of radiation oncology as discussed in the “Quality of the Evidence” subsection of the “Interpretive Summary”.

Consensus of the DSG - Dose Escalation

The members of the DSG concluded that the evidence supporting the hypothesis that dose escalation affords improved biochemical control of disease—while not as strong as that for reduced toxicity—is reproducible and is consistent with the natural history of the disease, that is, biologically plausible. Reproducibility is illustrated by the repeated demonstration of dose-related biochemical control in non-randomized comparative studies and by the same association being demonstrated in a randomized study. The results are biologically plausible in that the largest magnitude of effect is observed in intermediate-risk patients, who are those most likely to benefit (see Interpretive Summary above). The role of dose escalation in patients with highest-risk disease was felt to be uncertain, given the lack of use of adjuvant hormonal therapy in extant trials.

The DSG further noted that while the randomized study data may reveal further evidence as patient follow-up increases, the viability of proposed randomized studies is not known, and it will be some years before the results of newly proposed studies are available. As noted in the Ongoing Trials section, the only identified, relevant randomized study still accruing patients will address a limited aspect of dose escalation because patients in both study arms will have higher-risk disease and will all receive hormone ablative therapy. The Radiation Therapy Oncology Group (RTOG) is planning a phase III study evaluating dose escalation in the target population, but it is not known when this study will be open to patient accrual or how well it will accrue patients in the context of existing clinical evidence.

Consensus of the DSG - Technical Considerations

Along with systematically reviewing the literature for evidence of the efficacy of conformal therapy, the working group also considered evidence for technical considerations of conformal treatment delivery. The group, however, did not systematically review this literature, owing to the absence of comparative studies with clinical outcomes and the complexity of the many technical considerations necessary when using conformal therapy. The group did, however, feel strongly that this practice guideline should include a summary of the issues to be considered when implementing conformal radiotherapy for prostate cancer.

The DSG agreed that there is no one, ideal, conformal technique for the treatment of prostate cancer. The appropriate implementation of conformal therapy in any individual centre will be influenced by the equipment available and by an in-centre assessment of the type and magnitude of the errors inherent in their planning and treatment delivery systems. The group addressed the following main clinical issues for specific consideration when developing a conformal therapy technique:

a. Accurate delineation of the prostate into the treatment planning system and in particular, the identification of the prostatic apex on cross-sectional imaging.

b. Choice of supine or prone positioning.

c. Selection of an optimal beam arrangement and treatment delivery system.

d. Minimization of random and systematic field set-up errors.
e. Minimization of treatment delivery errors due to target organ motion.

f. Selection of an optimal planning target volume (PTV) that adequately accounts for residual errors after steps have been taken to minimize them.

**Contouring the Gross Target Volume (GTV)**

Three-dimensional treatment planning systems typically input the GTV from contoured computerized tomography (CT) images acquired from a CT-simulator or a diagnostic unit, and the soft tissue contrast is often inadequate to accurately identify the position of the prostate apex. There is no best accepted method for apical localization, but published methods to improve apical identification include insertion of an ultrasound-guided radio-opaque fiducial marker at the apex (42), use of magnetic resonance imaging (MRI) images or a planning urethrogram (43), or urethroscopy (44). Concern has been expressed that a urethrogram may artificially displace the prostate during planning (45).

**Supine and Prone Positioning**

Supine immobilization is usually accomplished with a pelvic or pelvic and thigh cradle-type immobilization device, or alternatively with leg immobilization alone. Supine patients may be treated with their bladder full or empty. Prone positioning is usually accomplished with a shell-type immobilization device, and prone patients are treated with their bladder empty.

Limited data does not clearly favour one technique over the other. A prospective non-randomized study reported that observed changes in prostate/semenal vesicle position were more related to bladder and rectal filling changes than patient position, and that patients found the supine position more comfortable (46). Stroom et al concluded that increased organ motion observed in the supine position was compensated for by a smaller systematic set-up error and that the required clinical target volume (CTV) was the same in either position (47). Two studies report superior rectal dose-volume histograms (DVH) for the prone position, especially when the seminal vesicles are included in the treated volume (48,49). However, Weber et al reported that the improved DVH for the bladder and rectum in the prone position may be an artefact of the position-dependent air volume in the rectum (50). The available data for conformal prostatic irradiation has not demonstrated a clear advantage to supine or prone positioning for normal tissue protection, although the prone position may improve rectal sparing if the seminal vesicles are included in the treatment volume.

**Selection of an Optimal Beam Arrangement**

A number of published reports have compared the effects of various prostate treatment techniques on the dose-volume histograms for the bladder, rectum, and femoral heads (51-55). A lack of uniformity in the chosen CTV and the methods used to contour the normal tissues has made within-study technique comparisons more suitable than between-study comparisons. These studies do not identify an optimal conformal technique but show that the six-field co-planar and four-field non-co-planar techniques protect the bladder and rectum most effectively outside the high dose volume at the expense of a relatively higher dose to the femoral heads. There appears to be no advantage to using more than six fields. A three-field arc technique has been described that produces DVH for bladder and rectum equivalent or superior to seven-field and four-field non-co-planar techniques, with a substantially lower femoral head dose (56).

Co-planar three-field or four-field box techniques with highly conformed shielding are the most effective of the standard techniques for limiting the amount of tissue outside the PTV that receives close to the full dose of radiation. However, these techniques spare the relatively insensitive lateral periprostatic tissues, achieved at the expense of a larger circumferential rectal volume receiving moderate-dose radiation that, in turn, may increase late rectal toxicity (53,56). One phase I-II dose-escalation study for prostate cancer suggested a higher grade 3 rectal toxicity rate for the four-field technique compared with the six-field technique, which fully
protects the posterior rectal wall (19,39); however the optimum beam arrangements have not been determined and have not been correlated with clinical outcome.

The physical characteristics of intensity modulated radiotherapy (IMRT) make it an attractive consideration for application to prostate radiotherapy, but to date there is no comparative clinical data on its use for this site (57).

**Minimization of Random and Systematic Set-up Errors**

Minimizing set-up errors will improve the therapeutic ratio by increasing the proportion of the prescribed radiation dose delivered to the CTV, and by reducing the dose delivered to the adjacent normal tissues. A single randomized study of pelvic radiotherapy (58) and non-randomized studies have shown that systematic field placement errors can be identified and corrected with portal imaging or portal films, although the frequency with which they should be done is open to question (59-64).

Pelvic immobilization has been proposed as a method to reduce the frequency and magnitude of random set-up errors, although the results of randomized studies for pelvic irradiation have been inconclusive. Nutting et al (65) showed no improvement in set-up accuracy for patients treated with rigid immobilization compared to using leg support alone. However, Rattray et al (66) showed improved accuracy for a non-customized pelvic cradle compared to a free set-up. In their respective non-randomized sequential studies, Fiorino et al (67) demonstrated that ankle immobilization reduced random set-up errors when compared to pelvic or no immobilization, and Catton et al (68) demonstrated that leg immobilization significantly improved set-up error when compared to a free set-up.

It can be concluded from the literature that pelvic radiotherapy portal films or portal images will improve set-up accuracy, though the optimal imaging frequency has not been established. The value of immobilization is less well demonstrated, although leg or ankle support does appear to contribute more to reducing set-up errors than pelvic immobilization does. However, the randomized study that showed no benefit to pelvic immobilization also used routine portal image correction for all cases, and the residual measured errors were small in both treatment arms (65). It is likely that rigid immobilization is of greater value for treatment techniques that do not have a policy of regular portal filming or imaging.

**Minimization of Treatment Delivery Errors Due to Prostatic Motion**

Prostate motion over the course of radiotherapy is another source of error in radiation delivery. The impact of this motion on treatment accuracy can be minimized by either visualizing the target organ before each fraction and setting up treatment on it, or by calculating and using an adequate PTV from population studies of prostatic motion. Presently, there are significant technical limitations to routine visualization of the target organ before each fraction. The use of a PTV based on population-based motion studies will minimize the overall risk of geographic misses but at the expense of including a larger volume of normal tissue in the PTV than is necessary for the majority of patients receiving therapy. Therefore, identifying and taking steps to minimize the sources of prostatic motion is worthwhile, so that the PTV ultimately used will be as small as possible.

Prostate motion over a course of pelvic radiotherapy has been identified both directly and indirectly by means of instilled contrast in the bladder and rectum, sequential pelvic CT scans, or the displacement of implanted radio-opaque prostatic markers (30,69-78). The principal cause of this motion is from day-to-day changes in rectal and bladder volumes. Changes in leg position can produce rotational movement of the pelvis and the prostate gland, and prone positioning increases intra-abdominal pressure and can produce prostatic motion from respiratory incursions (30,75,76). These studies have shown that organ motion is more pronounced in the antero-posterior and supero-inferior planes than in the lateral plane, due to the limiting effect of the pelvic sidewalls, and that the base pivots about the relatively more tethered apex. Displacements of 16 mm have been recorded during therapy, and one study
reported that 30% of all posterior motion was > 10 mm (71). Studies that have considered both prostatic motion and field set-up error confirm that inter-fraction prostatic motion poses the greater risk for errors in delivery of prostate radiotherapy (72,74).

Published PTV margins for conformal prostatic radiotherapy range from 6.0 mm to 18 mm in the antero-posterior plane and from 7.5 mm to 20 mm in the supero-inferior plane (11,19,27,72,74,79-81). These wide variations reflect both the methods used to quantify the radiation set-up and delivery errors and the measures taken to minimize them before measurement. Wu and colleagues reported a relatively narrow standard deviation for prostatic motion compared to others, and this may reflect the effort taken to limit organ motion during therapy by instructing patients to control bladder and rectal filling during planning and treatment (42).

Summary of Group Consensus Regarding Technical Considerations

The DSG concluded that the available evidence does not point to the superiority of any one technique for conformal prostate radiotherapy. However, isocentric six-field conformal techniques have superior dose-volume histogram characteristics to co-planar conformal four-field techniques and are associated with lower rectal toxicity in non-randomized comparisons of phase I-II studies.

With regard to treatment reproducibility, the group concluded that portal filming or imaging reduces systematic set-up errors, although the necessary frequency for this imaging during therapy remains unclear. Ankle/leg support can reduce the magnitude of field set-up errors, and the evidence for the additional value of pelvic immobilization is equivocal. The group recommended that ankle/leg support should be considered routine for conformal prostate radiotherapy and that serious consideration should be given to rigid pelvic immobilization, particularly if regular portal imaging or film is not routine policy. While the ultimate choice of strategy to ensure the reproducibility of treatment delivery was seen by the group to depend on centre-specific considerations, the DSG recommended that each centre using conformal therapy should be aware of the sources and magnitude of set-up and delivery error in their own techniques and should document random and systematic error rates resulting from the locally chosen strategy.

The DSG agreed that prostatic motion is the principal source of error in prostate treatment delivery. The motion must be accounted for either by identifying the target organ position before each fraction and setting up on it or by choosing an adequate PTV that is based on the motion studies from large numbers of patients.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence described above, the Genitourinary Cancer DSG drafted the following recommendations:

Target Population

These recommendations apply to adult men with early-stage prostate cancer (T1 or T2, clinical NO or NX, with a Gleason score ≤ 7).

Draft Recommendations

- Patients who have external-beam radiotherapy should be treated using a 3-D conformal technique.
- In light of the preliminary nature of the available evidence for dose escalation from randomized studies, and the corresponding need for confirmatory studies, patients should be offered participation in randomized clinical trials investigating dose escalation if such trials are open to accrual. In the absence of such trials, patients with intermediate risk disease (PSA 10 to 20) who are treated with external-beam radiotherapy alone should be
offered doses of 75 to 78 Gy in 180 to 200 cGy fractions. The weight of available evidence suggests that prescribed doses of 75 to 78 Gy reduce biochemical failure rates compared to 70 Gy, particularly in patients with intermediate-risk disease. Randomized controlled studies have shown such treatment to be safe.

**Qualifying statements**

- The conclusions are largely based on bNED rates as a surrogate outcome measure for clinical disease recurrence.
- There is insufficient clinical evidence at present to recommend doses above 70 Gy for patients with very favourable prognostic factors (e.g. PSA < 4, or, PSA < 10 and Gleason < 7 with no perineural invasion evident).
- Doses of 75 Gy or more can be delivered safely only with conformal radiotherapy techniques.
- Conformal therapy requires that patients are planned using three-dimensional delineation of the target and treatment volumes, with individualized shielding constructed with a beam’s-eye-view technique. There is no single prescriptive strategy for the appropriate deployment of conformal radiotherapy. Centres using this technique, however, must address the following elements of safe treatment delivery:
  - reproducibility of treatment set-up in their local setting
  - degree of internal organ movement
  - number of treatment fields
  - appropriate planning target volume margins.

**Treatment Alternatives**

Patients with poor prognostic factors (e.g. PSA > 20) may be candidates for neo-adjuvant or adjuvant hormone ablative therapy in addition to radiotherapy. The role of dose escalation requires further study in the setting of (neo-) adjuvant hormonal therapy and is not addressed by this practice guideline.

**Future Research**

One relevant randomized study still accruing patients was identified. This study will address a limited aspect of dose escalation, because patients in both study arms will have higher-risk disease and will all receive hormone ablative therapy. In addition, the Radiation Therapy Oncology Group (RTOG) is planning a phase III study evaluating dose escalation in the target population. It is not known when this study will be open to patient accrual, or how well it will accrue patients in the context of existing clinical evidence.

**Practitioner Feedback**

Based on the evidence and draft recommendations presented above, feedback was sought from Ontario clinicians.

**Methods**

Practitioner feedback was obtained through a mailed survey of 59 practitioners in Ontario (35 radiation oncologists and 24 urologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Genitourinary Cancer DSG reviewed the results of the survey.

**Results**

Key results of the practitioner feedback survey are summarized in Table 4. Thirty-three
surveys (59%) were returned. Twenty-three respondents (70%) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and completed the survey.

Summary of Written Comments

Five respondents (22%) provided written comments. The main points contained in the written comments were:

1. There was a request for a comment on alternative approaches to radiation therapy alone.
2. Another practitioner commented that there is a conflict with the recommendation for patient participation in phase III trials. The practitioner went on to state that it is unclear how this guideline would deal with a planned phase III trial that would randomize patients to radiation therapy at a dose of 70 to 72 Gy versus 78 Gy since the guideline recommends a dose of 75 to 78 Gy off study.
3. Another practitioner questioned a statement in the “Selection of an Optimal Beam Arrangement” subsection of the “Consensus of the DSG - Technical Considerations”, where it was implied that a four-field technique is inferior to a six or non-six planar technique. The practitioner pointed out that this is controversial and that there is very little clinical evidence to indicate that the volume of rectum treated to a low dose is predictive of late morbidity. This practitioner suggested that this statement be modified to state that the optimum beam arrangements have not been determined and have not been correlated with clinical outcome.

Modifications/Actions

1. Alternatives to radiation therapy alone are briefly mentioned under “Choice of Topic and Rationale”, where the focus of this practice guideline is outlined. Therefore, no changes were made to the document to address this comment.
2. The second bullet of the “Key Recommendations” recommends that patients be offered participation in randomized controlled trials evaluating dose escalation of radiotherapy. In the absence of such trials, a recommendation is made for radiation dose. No changes were made to the document to address this comment.
3. The document was revised using the practitioner’s suggested wording.

Table 4. Practitioner responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strongly agree or agree</td>
</tr>
<tr>
<td>The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>23 (100)</td>
</tr>
<tr>
<td>There is a need for a clinical practice guideline on this topic.</td>
<td>22 (96)</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>22 (96)</td>
</tr>
<tr>
<td>The results of the trials described in the report are</td>
<td>23 (100)</td>
</tr>
<tr>
<td>interpreted according to my understanding of the data.</td>
<td></td>
</tr>
<tr>
<td>The draft recommendations in this report are clear.</td>
<td>22 (96)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>23 (100)</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline*.</td>
<td>21 (91)</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice*.</td>
<td>Very likely or likely</td>
</tr>
<tr>
<td></td>
<td>21(91)</td>
</tr>
</tbody>
</table>

*Percentages do not add to 100 because data from one practitioner is missing.
Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Ten of 11 members of the PGCC returned ballots. Five PGCC members approved the practice guideline report as written, two members approved the guideline and provided suggestions for consideration by the GU DSG, and three members approved the guideline conditional on the GU DSG addressing specific concerns. PGCC members requested that three issues be addressed prior to the approval of the guideline report. The first issue concerned the paper by Dearnaley et al (18). One member of the PGCC noted that this paper does report on biochemical control and that this information should be incorporated into Table 1. The second issue related to the p-value reported for the multivariate analysis included in the Pollack paper (17). The third issue related to the section entitled “Synthesizing the Evidence”. It was noted that if the Dearnaley et al (18) trial was added to the section on disease-related outcomes, then the statement about pooling should be modified. Other suggestions made by members of the PGCC included minor editorial changes to sections of the guideline report to improve clarity.

Modifications/Actions

The GU DSG agreed with the three issues raised by the PGCC members and made changes to the practice guideline to address these issues. The Dearnaley et al trial was included in Table 1. The sentence reporting the multivariate analysis of the Pollack trial was reworded to clarify which p-value was reported. The statement regarding pooling included in the “Synthesizing the Evidence” section of the report was modified to reflect the fact that two randomized trials were available which reported bNED rates. The DSG also made the suggested minor editorial changes.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the GU DSG and the PGCC.

Target Population

These recommendations apply to adult men with early-stage prostate cancer (T1 or T2, clinical N0 or NX, with a Gleason score \(\leq 7\)).

Recommendations

- Patients who have external-beam radiotherapy should be treated using a 3-D conformal technique.

- In light of the preliminary nature of the available evidence for dose escalation from randomized studies, and the corresponding need for confirmatory studies, patients should be offered participation in randomized clinical trials investigating dose escalation if such trials are open to accrual. In the absence of such trials, patients with intermediate-risk disease (prostate-specific antigen [PSA] 10 to 20) who are treated with external-beam radiotherapy alone should be offered doses of 75 to 78 Gy in 180 to 200 cGy fractions. The weight of available evidence suggests that prescribed doses of 75 to 78 Gy reduce biochemical failure rates compared to 70 Gy, particularly in patients with intermediate-risk disease. Randomized controlled studies have shown such treatment to be safe.

Qualifying Statements

- The conclusions are largely based on bNED rates as a surrogate outcome measure for clinical disease recurrence.
There is insufficient clinical evidence at present to recommend doses above 70 Gy for patients with very favourable prognostic factors (e.g. PSA < 4, or PSA < 10 and Gleason < 7 with no perineural invasion evident).

Doses of 75 Gy or more can be delivered safely only with conformal radiotherapy techniques.

Conformal therapy requires that patients are planned using three-dimensional delineation of the target and treatment volumes, with individualized shielding constructed with a beam's-eye-view technique. There is no single prescriptive strategy for the appropriate deployment of conformal radiotherapy. Centres using this technique, however, must address the following elements of safe treatment delivery:

- reproducibility of treatment set-up in their local setting
- degree of internal organ movement
- number of treatment fields
- appropriate planning target volume margins.

**Treatment Alternatives**

Patients with poor prognostic factors (e.g. PSA > 20) may be candidates for neo-adjuvant or adjuvant hormone ablative therapy in addition to radiotherapy. The role of dose escalation of radiotherapy requires further study in the setting of (neo-) adjuvant hormonal therapy, and is not addressed by this practice guideline.

**Future Research**

One relevant randomized study still accruing patients was identified. This study will address a limited aspect of dose escalation, because patients in both study arms will have higher-risk disease and will also receive hormone ablative therapy. In addition, the Radiation Therapy Oncology Group (RTOG) is planning a phase III study evaluating dose escalation in the target population. It is not known when this study will be open to patient accrual, or how well it will accrue patients in the context of existing clinical evidence.

**Related Documents**

Practice Guidelines Initiative Evidence Summary Report #3-10: The use of brachytherapy in T1 or T2 prostate cancer.

**X. JOURNAL REFERENCE**


**XI. ACKNOWLEDGEMENTS**

The Genitourinary Cancer Disease Site Group would like to thank Drs. Michael Brundage, Himu Lukka, Juanita Crook, Glenn Bauman, and Padraig Warde for taking the lead in drafting and revising this practice guideline report. The Genitourinary Cancer Disease Site Group would also like to thank Dr. Charles Catton, a radiation oncologist at the Princess Margaret Hospital, Toronto for his help in writing the “Technical Considerations” section of this report.

For a complete list of the Genitourinary Cancer Disease Site Group members, please visit our website at [http://www.ccopebc.ca/](http://www.ccopebc.ca/).
REFERENCES

12. Glatstein E. Dr. strange (high) tech or how I learned to stop worrying and love my MLC/3D treatment planning, stereotactic linac. *Int J Radiat Oncol Biol Phys* 1999;45:1097-1101.


## DOCUMENT ASSESSMENT AND REVIEW TOOL

| Number and title of document under review | 3-11 The use of conformal radiotherapy and the selection of radiation dose in T1 or T2 prostate cancer |
| Date of current version | 1 Oct 2002 |
| Clinical reviewer | Dr. Mike Brundage |
| Research coordinator | Chika Agbassi |
| Date DART initiated | 12 May 2011 |
| Date and final results / outcomes | 17 June 2011 |

### Instructions
Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.

1. **Is there still a need for a guideline covering one or more of the topics in this document as is?**
   - **Answer:** No
   - **Explanation:** This guideline is out of date with respect to the evidence-base and with respect to some modality issues (e.g., the role of HDR Brachytherapy boost in dose-escalation. Thus the topic should be expanded beyond low and intermediate risk patients to include high risk, and the comparison should pertain to IMRT versus conformal rather than conformal versus nonconformal. Because the question is substantially changed, the document should be archived and a new guideline addressing the new question should be planned or absorbed into another guideline being updated (i.e., 3-13). The IMRT aspect is addressed in the 2010 guideline 21-3-1 “The role of IMRT in prostate cancer” from the Radiation Therapy Clinical Program.

   If No, then the document should be ARCHIVED with no further action; **go to 11.** If Yes, then **go to 2.**

2. **Are all the current recommendations based on the current questions definitive or sufficient, and have less than 5 years elapsed since the latest search?**
   - **Answer:** Not applicable
   - **Explanation:** document to be Archived

   If Yes, the document can be ENDORSED with no further action; **go to 11.** If No, **go to 3.**

3. **Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?**
   - **Answer:** Not applicable

   If Yes, the document should be taken off the website as soon as possible. A WARNING should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, **go to 4.**

4. **Do current resources allow for an updated literature search to be conducted at this time?**
   - **Answer:** Not applicable

   If No, a DEFERRAL should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, **go to 5.**

5. **Guideline Research Questions.** Please review the original guideline research questions below and if applicable, list any MINOR changes to the questions that now must be considered. If a question is no
longer relevant, it can be deleted. The DART process evaluates the guideline as is and CANNOT accommodate significant changes to the questions or the addition of new questions introducing new patient populations or new agents/interventions because if this what is required in order to make this guideline relevant, then a brand new document should be produced and this guideline as is should be ARCHIVED (i.e., go back to Q1 of this DART form and answer NO).

Original Question(s):
- No changes to the original question

5b. Inclusion and Exclusion criteria. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence).
- No changes to the original inclusion and exclusion criteria

5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.
- Not applicable, document to be Archived

Go to 6.

6. Is the volume and content of the new evidence so extensive such that a simple update will be difficult?
- Not applicable
  If Yes, then the document should be ARCHIVED with no further action; go to 11. If No, go to 7.

7. On initial review, does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:
- Not applicable
  If Yes, the document can be ENDORSED. If No, go to 8.

8. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references.
- Not applicable
  If Yes, a WARNING note will be placed on the web site. If No, go to 9.

9. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:
- Not applicable
  If Yes, the document update will be DEFERRED, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10.

10. An update should be initiated as soon as possible. List the expected date of completion of the update:
- Not applicable
  An UPDATE will be posted on the website, indicating an update is in progress.

11. Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the website. Notify the original authors of the document about this review.

DSG Approval Date: 09 November 2011

Comments from DSG members: Assessment of new evidence may change recommendations modestly but the current recommendations are not considered harmful or inappropriate.
**DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART**

**STEPS**

**Outcomes**

**Action**

**STEP 1: Initiation of the Document Assessment & Review process**

**STEP 2: First teleconference to determine:**
- the clinical relevance of the guideline,
- if a new literature search is needed, and
- if Yes, the search criteria.

**STEP 3: A new literature search based on input from #5 will be conducted, and the result will be sent to the reviewers with a follow-up date.**

---

**#1. Is there still a NEED for a guideline covering one or more of the topics in this document?**

- Yes → **Endorse**

- No → **Archive**

**#2. Are all the current recommendations based on the current questions definitive or sufficient, and have less than 5 years elapsed since the latest search?**

- Yes → **Endorse**

- No → **Deferral**

**#3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?**

- Yes → **Warning**

- No → **Deferral**

**#4. Do current resources allow for an updated literature search to be conducted at this time?**

- Yes → **New search**

- No → **Deferral**

**#5. List any new and relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Determine the search criteria.**

---

RC emails DSG reviewer(s) the protocol

Discuss questions #1-5

Please note: No teleconference needed, IF the answers lead to one of these outcomes, PLUS the reviewer(s) complete & return the form with the answers & explanations.

Teleconference with the reviewer(s) will focus the discussion on #5: the search strategies, i.e., scope, key word(s), and inclusion and exclusion criteria.
FLOW CHART (cont.)

<table>
<thead>
<tr>
<th>STEPS</th>
<th>Outcomes</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP 4: Second teleconference to determine the ultimate status of the document</strong></td>
<td></td>
<td><strong>Review questions #6-9</strong></td>
</tr>
<tr>
<td><strong>#6.</strong> Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?</td>
<td>Yes</td>
<td>Archive</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td><strong>Please note:</strong> No teleconference needed, IF the reviewer(s) complete and return the form with answers &amp; explanations.</td>
</tr>
<tr>
<td><strong>#7.</strong> Does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?</td>
<td>Yes to all</td>
<td>Endorse</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td><strong>Warning</strong></td>
</tr>
<tr>
<td><strong>#8.</strong> Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?</td>
<td>Yes</td>
<td>Deferral</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td><strong>Teleconference with the reviewer(s) to discuss the type of update, priority, and resources.</strong></td>
</tr>
<tr>
<td><strong>#9.</strong> Is there a good reason (e.g., new, stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline?</td>
<td>Yes</td>
<td></td>
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<tr>
<td>No</td>
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<td><strong>Update</strong></td>
</tr>
<tr>
<td><strong>#10.</strong> An update should be initiated as soon as possible. List the expected date of completion of the update.</td>
<td>Yes</td>
<td></td>
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<td></td>
<td>No</td>
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<tr>
<td><strong>STEP 5: Final outcome approval; Document Assessment &amp; Review questions #11</strong></td>
<td></td>
<td><strong>RC emails draft for DSG approval</strong></td>
</tr>
<tr>
<td><strong>#11.</strong> Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

*DEFINITIVE RECOMMENDATIONS - Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

SUFFICIENT RECOMMENDATIONS - Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

WARNING - A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the website, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DEFERRAL - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.