Complete Summary

GUIDELINE TITLE

The use of conformal radiotherapy and the selection of radiation dose in T1 or T2 prostate cancer.

BIBLIOGRAPHIC SOURCE(S)

Cancer Care Ontario Practice Guideline Initiative (CCOPGI), Genitourinary Cancer Disease Site Group. Brundage M, Lukka H, Crook J, Warde P, Bauman G, Catton C, Markman BR, Charette M. The use of conformal radiotherapy and the selection of radiation dose in T1 or T2 prostate cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Oct. 23 p. (Practice guideline; no. 3-11). [81 references]

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SCOPE

DISEASE/CONDITION(S)

Early-stage prostate cancer

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To make recommendations about the role of three-dimensional (3-D) conformal radiotherapy in treating clinically localized (T1 or T2, clinical N0 or NX/MO) prostate cancer when single-modality treatment external beam radiotherapy is selected as the modality of choice
- To make recommendations about the appropriate dose and fractionation prescription in this clinical setting

TARGET POPULATION

Early-stage prostate cancer (T1 or T2, clinical N0 or NX/MO, with a Gleason score $\leq$7)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Conventional 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

   Note: Conventional external-beam radiotherapy is considered for comparative purposes, but not recommended.

2. Conformal external-beam radiotherapy, typically containing three-dimensional (3-D) delineation of the clinical target and planning volumes and individualized "beam´s eye view" shielding to match the planning volumes

MAJOR OUTCOMES CONSIDERED

- Biochemical freedom from failure (bNED) rates
- Clinical recurrence-free survival
- Disease-specific survival
- Acute or late toxicity
- Technical outcomes, such as improved dose distribution, reproducibility, target delineation

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

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. The publications meeting the inclusion criteria were reviewed by a working group and subsequently by the entire Disease Site Group.

The Physician Data Query (PDQ) clinical trials database on the Internet (www.cancer.gov/search/clinical_trials/) 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.

Study Selection (inclusion and exclusion 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. No upper limit of prostate specific antigen (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 following outcome measures were recorded:
    - Biochemical freedom from failure (bNED)
    - Other disease-outcome measures, such as clinical recurrence-free survival or disease-specific survival
    - 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).

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

NUMBER OF SOURCE DOCUMENTS

7 randomized controlled trials and 18 phase II studies or non-randomized controlled trials

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Two randomized trials were located which compared conformal radiotherapy to conventional therapy and reported biochemical freedom from failure (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 biochemical freedom from failure 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.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

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 theis practice guideline should include a summary of the issues to be considered when implementing conformal radiotherapy for prostate cancer. The full details of this summary are provided in the original guideline document.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

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 Disease Site Group reviewed the results of the survey.

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Patients who have external-beam radiotherapy should be treated using a three-dimensional (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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Two randomized controlled trials and 12 reports of phase II studies or non-randomized comparative studies provided data on disease-related outcomes. Three randomized controlled trials and four reports of phase II or non-randomized comparative studies provided data on acute toxicity. Three randomized trials and nine reports of phase II or non-randomized comparative studies 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.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- 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.

- 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 (prostate specific antigen [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).

Subgroups Most Likely to Benefit:

Patients with intermediate-risk disease (prostate specific antigen [PSA] 10 to 20)

POTENTIAL HARMS

- The potential risks of conformal therapy lie in the reduced margins (given the uncertainties associated with tumour delineation, organ movement, patient set-up variations) 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.
- Three randomized trials comparing conventional radiotherapy with conformal radiotherapy reported data on acute toxicity (see Table 2 of the original guideline document). The use of conformal treatment, without a corresponding increase in dose, reduced acute toxicity in two of the studies 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. Additional non-randomized comparative studies reporting on acute toxicity are listed in Table 2 of the original guideline document.
- Chronic adverse effects, i.e., symptoms occurring one year or more after treatment, were reported in three randomized trials. 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. 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). Additional non-randomized trials reporting late toxic effects are listed in Table 2 in the original guideline document.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guideline does not address the choice of radiotherapy as a modality per se, nor does it address the role of adjuvant/neo-adjuvant 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.
- The conclusions are largely based on biochemical freedom from failure (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., prostate specific antigen [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
- 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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Cancer Care Ontario Practice Guideline Initiative (CCOPGI), Genitourinary Cancer Disease Site Group. Brundage M, Lukka H, Crook J, Warde P, Bauman G, Catton C, Markman BR, Charette M. The use of conformal radiotherapy and the selection of radiation dose in T1 or T2 prostate cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Oct. 23 p. (Practice guideline; no. 3-11). [81 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Oct

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Genitourinary Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Genitourinary Cancer Disease Site Group Members: Dr. H. Lukka, (Chair), Radiation Oncologist; Dr. J. Barkin, Urologist; Dr. G. Bauman, Radiation Oncologist; Dr. J. Bowen, Radiation Oncologist; Dr. M. Brundage, Radiation Oncologist; Dr. J. Chin, Urologist; Dr. R. Choo, Radiation Oncologist; Dr. J. Crook, Radiation Oncologist; Dr. L. Eapen, Radiation Oncologist; Dr. N. Fleshner, Urologist; Dr. L. Klotz, Urologist; Dr. W. Orovan, Urologist; Dr. R. Segal, Medical Oncologist; Dr. T. Short, Urologist; Dr. J. Srigley, Medical Oncologist; Dr. J.

Trachtenberg, Urologist; Dr. P. Warde, Radiation Oncologist; Dr. E. Winquist, Medical Oncologist; Two community representatives

Resource group members working with the Genitourinary Cancer Disease Site Group: Faculty: Dr. K. Pritchard; Staff: *B.R. Markman, T. Kirchner. For this practice guideline report, M. Charette provided research support as well.

*Members that have completed term with the Genitourinary Disease Site Group.

For a current list of members, please visit the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Genitourinary Cancer Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- The use of conformal radiotherapy and the selection of radiation dose in T1 or T2 prostate cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2002 Oct. 3 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- The use of brachytherapy in T1 or T2 prostate cancer. Toronto (ON): Cancer Care Ontario (CCO), 2001 May. 13 p. (Evidence Summary Report No. 3-10) Electronic copies: Available in PDF from the Cancer Care Ontario Web site.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on January 27, 2003. The information was verified by the guideline developer on February 24, 2003.

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