The Role of IMRT in Thyroid Cancers

J. Brierley, R.B. Rumble, P. Warde, and members of the IMRT Indications Expert Panel

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)
and the Radiation Treatment Program, CCO

Report Date: October 29, 2010

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Evidence-Based Series 21-3-8: Section 1

The Role of IMRT in Thyroid Cancers: Guideline Recommendations

J. Brierley, R.B. Rumble, P. Warde, and members of the IMRT Indications Expert Panel

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO) and the Radiation Treatment Program (RTP), CCO

Report Date: October 29, 2010

QUESTIONS

Primary Research Question

- When external-beam radiotherapy (EBRT) is selected as either the primary modality of choice or is given as adjuvant postoperative treatment in locally advanced thyroid cancer, what is the role of intensity-modulated conformal radiation therapy (IMRT) compared to other methods of radiation delivery?

Secondary Research Question

- What are the appropriate doses and fractionation schedules in these settings?

TARGET POPULATION

The target population is comprised of all adult patients with thyroid cancer for whom treatment with external beam radiation is being considered.

INTENDED USERS

This guideline is targeted for radiation oncologists, physicists, dosimetrists, patients, and others involved in the treatment of thyroid or pituitary cancers where treatment with IMRT is being considered. Administrators may find the report of value when considering the benefits of IMRT over other methods of radiation delivery.

BACKGROUND

IMRT is a newer method of delivering radiation to target structures that differs from traditional methods of radiation delivery. The basis of IMRT is the use of intensity-modulated beams that can provide two or more intensity levels for any single beam direction and any single source position (1). Through this mechanism, IMRT treatment plans are able to generate concave dose distributions and dose gradients with narrower margins than those
allowed using traditional methods (1,2). This fact makes IMRT especially suitable for treating complex treatment volumes and avoiding close-proximity organs at risk (OAR) that would otherwise necessitate dose limitations (1). As a consequence of OAR sparing, IMRT theoretically may provide benefits in terms of increased tumour control through escalated dose and reduced normal tissue complications. It must be noted that as total radiation dose delivered via IMRT would be the same as the total radiation dose given via any other method of radiation therapy, no difference in disease-related outcomes would be expected. The main benefit expected with IMRT is a reduction in adverse event rates, especially those associated with radiation damage to nearby OAR.

Given the potential dosimetric advantages of IMRT and the commercial availability of IMRT-enabled treatment planning systems and linear accelerators, IMRT has been introduced clinically for a number of disease sites, including head and neck cancer and prostate cancer. This evidence-based series (EBS) reviews the published experience with IMRT in the treatment of thyroid to quantify the potential benefits of this new technology and make recommendations for radiation treatment programs considering adopting this technique.

RECOMMENDATIONS AND KEY EVIDENCE

Insufficient evidence was obtained in this systematic review; therefore, it is not possible to propose recommendations informed by evidence.

QUALIFYING STATEMENT

Despite the lack of evidence in this disease site, there remain compelling reasons why IMRT should be offered to patients as an alternative to conventional treatment planning. IMRT can improve target coverage in a difficult volume to treat, which may translate into an increase in local control. In head and neck cancer, IMRT has demonstrated efficacy in targeting tumours and thereby increasing disease control, while at the same time sparing adjacent OAR from exposure to unnecessary radiation and thereby reducing long-term morbidity (see EBS 21-3-3: The Role of IMRT in Head & Neck Cancer (in development)). For this reason alone, IMRT may be considered a viable treatment option as it is ethical to recommend a treatment with little known harm over one with greater expected harm prior to scientific proof of the difference in harm being established.

As the volume that must be irradiated in thyroid cancer treatment is technically challenging and involves avoidance of the same nearby structures as in head and neck cancer treatment, it follows that the benefits associated with IMRT in the treatment of head and neck cancer would also apply to thyroid cancer. Although not statically significant, the data from Schwartz et al (3) reports a lower late adverse event rate with IMRT.

FUTURE RESEARCH

Ideally, future research should focus on studies with larger size and longer follow-up that provide data on late toxicity and disease recurrence rates, but this is a challenge given the rarity of thyroid cancers that require external radiation.

RELATED GUIDELINES

Funding
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REFERENCES


QUESTION
Primary Research Question
• When external-beam radiotherapy (EBRT) is selected as either primary modality of choice or is given as adjuvant post-operative treatment in locally advanced thyroid cancer, what is the role of intensity-modulated conformal radiation therapy (IMRT) compared to other methods of radiation delivery?

Secondary Research Question
• What are the appropriate doses and fractionation schedules in these settings?

BACKGROUND
IMRT is a newer method of delivering radiation to target structures that differs from traditional methods of radiation delivery. The basis of IMRT is the use of intensity-modulated beams that can provide two or more intensity levels for any single beam direction and any single source position (1). Through this mechanism, IMRT treatment plans are able to generate concave dose distributions and dose gradients with narrower margins than those allowed using traditional methods (1,2). This fact makes IMRT especially suitable for treating complex treatment volumes and avoiding close proximity organs at risk (OAR) would otherwise necessitate dose limitations (1). As a consequence of OAR sparing, IMRT theoretically may provide benefits in terms of increased tumour control through escalated dose and reduced normal tissue complications. It must be noted that as total radiation dose delivered via IMRT would be the same as the total radiation dose given via any other method of radiation therapy, no difference in disease-related outcomes would be expected. The main benefit expected with IMRT is a reduction in adverse event rates, especially those associated with radiation damage to nearby OAR.
Given the potential dosimetric advantages of IMRT and the commercial availability of IMRT-enabled treatment planning systems and linear accelerators, IMRT has been introduced clinically for a number of disease sites, including head and neck cancer and prostate cancer. This evidence-based series (EBS) reviews the published experience with IMRT in the treatment of thyroid to quantify the potential benefits of this new technology and make recommendations for radiation treatment programs considering adopting this technique.

INTRODUCTION

The thyroid bed volume curves around the vertebral body and includes the air column in the trachea. This U-shaped volume presents a challenge to adequately treating the thyroid bed, while sparing the spinal cord, that is compounded if the regional lymph nodes are included. As these patients are already at high risk of developing xerostomia as a consequence of radioactive iodine (RAI) treatment, the additional impact of external beam radiotherapy (EBRT) can be a major concern. The clinical target volume (CTV) of the thyroid bed is defined as covering the thyroid bed and the jugular and posterior cervical lymph nodes, within the limits defined above, and including level III, IV, VI, and partially level V nodal regions, and that volume is adjusted according to the surgical and pathology findings. The spinal canal is defined as a dose-avoidance structure requiring also an adequate margin when generating an IMRT plan (3).

Prior to the availability of IMRT, many radiation techniques (4,5) were designed to overcome these difficulties, but all required some degree of compromise. In the past, the characteristic rapid fall-off of a direct electron beam and the effect of the neck contour could produce an acceptable high-dose volume with 12- to 20-MeV beams or a mixed beam of two energies. The disadvantage of this was dosimetric uncertainty caused by the change in the shape of the contour and the changing densities of the volume irradiated (the air column of the trachea and the bone of the vertebral bodies). To overcome the dosimetric uncertainties, the dose was often compromised. An alternative technique was to use two anterolateral oblique wedged fields such as those used for laryngeal cancer. The posterior border was placed so as to exclude the spinal cord. The advantage of this technique over a single anterior electron beam was additional skin sparing, but it came at the cost of under dosing the posterolateral part of the volume (4,5).

In order to evaluate the efficacy of IMRT compared with other radiation treatment options in this setting, a systematic review of the literature is warranted.

METHODS

The EBS guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (6). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one member of the IMRT Indications Expert Panel and one methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on the role of IMRT in endocrine cancers. The body of evidence in this review is primarily comprised of published reports of comparative studies between IMRT and other methods of radiation delivery as there is currently no standard in this setting. That evidence forms the basis of the recommendations developed by the IMRT Indications Expert Panel and will be published when completed. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC and the RTP are supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC and any associated Program is editorially independent from its funding source.
Literature Search Strategy
The MEDLINE and EMBASE databases were searched for evidence on thyroid and pituitary cancers and IMRT on June 15, 2009. In both databases, keywords for “endocrine cancer” were combined with keywords for “intensity-modulated radiotherapy” and the following terms were excluded: “brachytherapy”, “proton therapy”, “biological markers”, “gene therapy”, “children”, “childhood cancer”, “pediatric cancer”, “quality assurance”, “treatment plan comparison”, “aperture optimization”, independent dose calculation”, “EPID dosimetry”, and “set up errors.” Results were limited to those published in English from the year 2000 to the current date in 2009.

A search for clinical practice guidelines (CPG), systematic reviews (SR), and health technology assessments (HTA) was also performed. A search of the National Guidelines Clearinghouse (located at: http://www.guideline.gov) was performed on March 9, 2009. Additionally, a search of the MEDLINE and EMBASE databases was performed on March 25, 2009 using keywords for IMRT in combination with terms for all disease sites and limited to review articles published after 2000. Finally, the Scottish Collegiate Guidelines Network (SIGN) (located at: http://www.sign.ac.uk), the National Institute for Health & Clinical Evidence (NICE) (located at: http://www.nice.org.uk), and the Agency for Healthcare Research & Quality (AHRQ) (located at: http://www.ahrq.gov) were searched on March 25, 2009, using keywords for “IMRT”, and “radiation” in combination with disease-site specific terms.

Study Selection Criteria
Inclusion Criteria
- All of the included evidence must contain comparative data on IMRT versus other methods of radiation delivery in the treatment of thyroid or pituitary cancers; must report on at least one of the outcomes of interest, including clinical recurrence-free survival, disease-specific survival, acute toxicity, and late toxicity; and must be one of the following publication types:
  - CPGs, SRs, HTAs
  - Randomized phase II or phase III trials
  - Dose escalation studies, toxicity reports, quality of life (QoL) reports, cohort studies, and retrospective studies

They must also meet the following criteria:
- Report on 50 or more patients
- Be published in English
- Be published in the year 2000 to current date

Exclusion Criteria
- Published in a language other than English
- Do not provide comparative data
- Report on fewer than 50 patients
- Published prior to 2000

Synthesizing the Evidence
No statistical analyses were planned in this systematic review; however, this would be considered if data allow.
RESULTS

Literature Search Results

The MEDLINE and EMBASE searched returned 44 and 53 potential articles, respectively. After removing ineligible articles, based on a title and abstract review, three were considered potentially eligible and were ordered for full-text review (one from the MEDLINE results and one from the EMBASE results). Additionally, two articles were submitted by the lead author for consideration (five papers in total were ordered for full-text review). Of these five papers, only one was retained, and that single paper forms the body of evidence in this systematic review. While the MEDLINE AND EMBASE searches were conducted with the intent of obtaining evidence on all endocrine sites, only a single paper on thyroid cancer was obtained that met the inclusion criteria. Appendix 3 contains a table of the excluded evidence along with the reasons for their exclusion.

Study Design

The single article obtained was a retrospective cohort study. Table 1 details the years on study, the total number of included patients, and the funding source.

Table 1. Study design of included evidence.

<table>
<thead>
<tr>
<th>Author, year published</th>
<th>Years on study</th>
<th>Total included N</th>
<th>Sponsorship</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retrospective cohort study</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwartz et al, 2009 (7)</td>
<td>1996-2005</td>
<td>131</td>
<td>National Cancer Institute grant P01 CA06294</td>
</tr>
</tbody>
</table>

Table 2 describes the study details, including the comparison that was made, the radiation dose administered in each group, the number of patients in each group, the disease stages included in the study population, the overall median follow-up, and what outcomes are reported.

Table 2. Details of included studies.

<table>
<thead>
<tr>
<th>Author, year published</th>
<th>Comparison</th>
<th>Median dose</th>
<th>Total N</th>
<th>Disease stage</th>
<th>Median follow-up (months)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retrospective cohort study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schwartz et al, 2009 (7)</td>
<td>IMRT 3DRT</td>
<td>60Gy (56-66 Gy) 60 Gy (38-72 Gy)/30f (19-40)</td>
<td>57 74</td>
<td>T2-4</td>
<td>38 (0-134)</td>
<td>DRO, AE</td>
</tr>
</tbody>
</table>

Note: IMRT, intensity-modulated radiotherapy; 3DRT, three-dimensional radiotherapy; Gy, gray; f, fraction; T, tumour stage; DRO, Disease-related outcome; AE, adverse events.

Table 3 outlines the technical details of the IMRT regimen, including the planning system used, the type of IMRT administered (step & shoot, sliding window, volumetric arc), the field arrangement (5 field, 7 field), the planned target volume (PTV), the planned target volume expansion (mm), and the image guidance method used (none, implanted fiducial markers, EPID, daily ultrasound, in-room CT).
Table 3. IMRT details of included studies.

<table>
<thead>
<tr>
<th>Author, year published</th>
<th>Planning system</th>
<th>Type of IMRT</th>
<th>Field arrangement</th>
<th>Planned target volume</th>
<th>Planned target volume expansion (mm)</th>
<th>Image guidance</th>
</tr>
</thead>
</table>

Note: IMRT, intensity-modulated radiotherapy.

Study Quality

The single retrospective cohort study by Schwartz et al (7) was assessed for quality according to criteria such as balance between the treatment groups, identification and reporting of prognostic factors, and making adjustments due to any prognostic differences where warranted and possible. Other variances in the study design that could affect the reliability of the study findings were also reported. In this study, the treatment groups were not in balance (57 IMRT:74 three dimensional conformal radiotherapy [3DRT]) as only patients with nondifferentiated histologic types were excluded, leaving an imbalance between the groups. Prognostic factors were reported for the entire study population in aggregate, not according to treatment group, therefore, differences between the groups are unknown. As this was a retrospective cohort design, making adjustments for differences in prognostic factors was not possible.

Outcomes: Disease-Related

In the study reported by Schwartz et al (7), no statistically significant differences were reported between IMRT and 3DRT for local relapse-free survival (p=0.34), disease-specific survival (p=0.19), or overall survival (p=0.15). Disease-related outcomes appear in Table 4.

Table 4. Disease-related outcomes.

<table>
<thead>
<tr>
<th>Author, year published</th>
<th>Comparison</th>
<th>Local relapse-free survival</th>
<th>Disease-specific survival</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwartz et al, 2009 (7)</td>
<td>IMRT 3DRT</td>
<td>HR=0.68 (0.31-1.5), p=0.3386</td>
<td>HR=1.67 (0.76-3.67), p=0.1983</td>
<td>HR=1.72 (0.82-3.60), p=0.1497</td>
</tr>
</tbody>
</table>

Note: IMRT, intensity-modulated radiotherapy; 3DRT, three-dimensional radiotherapy; HR, hazard ratio.

Outcomes: Late Adverse Events

The study by Schwartz et al (7) reported on late adverse events defined as those occurring three to 60 months following the administration of radiation. While fewer events occurred in the IMRT group compared with the 3DRT group (2% versus [vs.] 12%), this difference was not reported to be significantly different. Table 5 describes the late adverse events.
Table 5. Late adverse effects.

<table>
<thead>
<tr>
<th>Author, year published</th>
<th>Comparison</th>
<th>Esophageal stricture requiring dilation</th>
<th>Subglottic laryngeal stenosis requiring tracheotomy</th>
<th>Chronic laryngeal edema requiring tracheotomy</th>
<th>Chronic dysphagia requiring a feeding tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective cohort studies</td>
<td>IMRT</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Schwartz et al, 2009 (7)</td>
<td>IMRT</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3DRT</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Note: IMRT, intensity-modulated radiotherapy; 3DRT, three-dimensional radiotherapy.

ONGOING TRIALS

The U.S. National Institutes of Health online directory of clinical trials (located at http://www.clinicaltrial.gov) was searched on October 14, 2009 for listings of relevant studies. No studies were found comparing IMRT with any other method of radiation delivery in either thyroid or pituitary cancer.

DISCUSSION

In a comparison of conventional (anterior and two anterior oblique fields to the thyroid bed) 3DCRT and IMRT plans to the thyroid bed, and to the thyroid bed and locoregional lymph nodes, Nutting et al (8) found that 3DCRT reduced normal tissue irradiation, compared to conventional techniques, but did not improve PTV or spinal cord doses. IMRT improved the PTV coverage and reduced the spinal cord dose, however, and they concluded that IMRT should reduce the risk of myelopathy or might allow dose escalation in patients with thyroid cancer. In the only clinical comparison of conventional radiation and IMRT, Schwartz et al (7), as described in this review, reported less late morbidity in 56 patients treated with IMRT compared to 76 treated with conventional radiation, but the difference was not statistically different.

Since patients are at a high risk of developing xerostomia as a consequence of previous RAI treatment, the additional impact of EBRT can be a major concern. The risk can be reduced with IMRT designed to avoid the salivary glands as much as possible, as in other tumour sites in the head and neck region. However, as the majority of patients who may derive benefit from EBRT do not require the whole neck to be treated, significant xerostomia may be avoided without IMRT.

There is insufficient data in the literature to review the appropriate dose and fractionation schedules.

CONCLUSIONS

Insufficient evidence was obtained in this systematic review, and it was not possible to propose recommendations informed by evidence. Despite the lack of evidence for this disease site, there remain compelling reasons why IMRT should be offered to patients as an alternative to conventional treatment planning. IMRT can improve target coverage in a difficult volume to treat, which may translate into increased local control with or without the ability to safely increase the maximum tumour dose. In head and neck cancer, IMRT has a demonstrated efficacy in targeting tumours, thereby increasing disease control, while at the same time sparing adjacent OAR from exposure to unnecessary radiation and thereby reducing long-term morbidity (see EBS 21-3-3: The Role of IMRT in Head & Neck Cancer [in development]). For this reason alone, IMRT may be considered a viable treatment option, as
it is ethical to recommend a treatment with little known harm over one with greater expected harm prior to scientific proof of the difference in harm being established.

As the volume that must be irradiated in thyroid cancer treatment is technically challenging and involves avoidance of the same nearby structures as in head and neck cancer treatment, it follows that the benefits associated with IMRT in the treatment of head and neck cancer would also apply to thyroid cancer. Although not statically significant, the data from Schwartz et al (7) supports the reduction of late adverse events with IMRT.

CONFLICT OF INTEREST
None declared.

ACKNOWLEDGEMENTS
The IMRT Indications Expert Panel would like to thank Dr. James Brierley and Mr. R. Bryan Rumble for taking the lead in drafting this systematic review.

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REFERENCES


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<td>Program Manager, Radiation Treatment Program, Cancer Care Ontario</td>
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<tr>
<td>Ms. Kate Bak</td>
<td>Project Coordinator, Radiation Treatment Program, Cancer Care Ontario</td>
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<tr>
<td>Mr. Bryan Rumble</td>
<td>Research Coordinator, Program in Evidence-based Care, Cancer Care Ontario</td>
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<tbody>
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<td>Dr. Anthony Whitton</td>
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<td>Ms. Lisa Favell</td>
<td>Capital Project Representative, Cancer Care Ontario</td>
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<td>Ms. Katrina Fleming</td>
<td>Radiation Therapy Representative, Grand River Regional Cancer Centre</td>
</tr>
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<td>Ms. Esther Green</td>
<td>Chief Nursing Officer and Director of Health Human Resource Planning, Cancer Care Ontario</td>
</tr>
<tr>
<td>Dr. Konrad Leszczynski</td>
<td>Physics Representative, Northeastern Ontario Regional Cancer Centre</td>
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<tr>
<td>Dr. Michael Sharpe</td>
<td>Physics Representative, Princess Margaret Hospital</td>
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Working Group

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. James Brierley</td>
<td>Radiation Oncologist, Princess Margaret Hospital</td>
</tr>
<tr>
<td></td>
<td>Professor, Department of Radiation Oncology, University of Toronto</td>
</tr>
</tbody>
</table>
Appendix 2. Literature search strategies.

Database: Ovid MEDLINE(R) <1996 to June Week 1 2009>

1 endocrine cancer.mp. or exp Endocrine Gland Neoplasms/ (80652)
2 exp Radiotherapy, Intensity-Modulated/ or imrt.mp. (2678)
3 brachytherapy.mp. or exp Brachytherapy/ (8646)
4 Protons/ or proton therapy.mp. (11612)
5 biological marker.mp. or exp Biological Markers/ (316079)
6 gene therapy.mp. or exp Gene Therapy/ (33518)
7 children.mp. or exp Child/ (542180)
8 pediatric cancer.mp. (677)
10 exp Quality Assurance, Health Care/ or quality assurance.mp. (139579)
11 treatment plan comparison.mp. (5)
12 aperture optimization.mp. (30)
13 independent dose calculation.mp. (13)
14 EPID dosimetry.mp. (14)
15 set up errors.mp. (88)
16 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (1019547)
17 1 and 2 (53)
18 1 and 16 (16094)
19 17 not 18 (46)
20 limit 19 to (english language and humans and yr="2000 - 2009") (44)
21 from 20 keep 1-44 (44)

Database: EMBASE <1996 to 2009 Week 24>

1 exp Endocrine Tumor/ or endocrine cancer.mp. (98594)
2 imrt.mp. or exp Intensity Modulated Radiation Therapy/ (3476)
3 brachytherapy.mp. or exp Brachytherapy/ (11022)
4 proton therapy.mp. or exp Proton Therapy/ (718)
5 biological marker.mp. or exp Biological Marker/ (33165)
6 gene therapy.mp. or exp Gene Therapy/ (35195)
7 Child/ or child.mp. or children.mp. (467955)
8 exp Childhood Cancer/ or pediatric cancer.mp. (10099)
9 quality assurance.mp. or exp Quality Control/ (112673)
10 treatment plan comparison.mp. (5)
11 aperture optimization.mp. (31)
12 independent dose calculation.mp. (12)
13 EPID dosimetry.mp. (15)
14 set up errors.mp. (89)
15 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (652162)
16 1 and 2 (97)
17 1 and 15 (12297)
18 16 not 17 (59)
19 limit 18 to (human and english language and yr="2000 - 2009") (53)
20 from 19 keep 1-53 (53)
Appendix 3. Excluded studies (n=4).

<table>
<thead>
<tr>
<th>Title</th>
<th>Reason(s) for exclusion</th>
</tr>
</thead>
</table>
Evidence-Based Series 21-3-8: Section 3

The Role of IMRT in Thyroid Cancers: EBS Development Methods and External Review Process

J. Brierley, R.B. Rumble, P. Warde, and members of the IMRT Indications Expert Panel

A Quality Initiative of the
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Report Date: October 29, 2010

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based guidelines, known as EBS reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

The Evidence-Based Series

Each EBS is comprised of three sections:

- **Section 1: Guideline Recommendations.** Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its
interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- **Section 2: Evidentiary Base.** Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- **Section 3: EBS Development Methods and External Review Process.** Summarizes the EBS development process and the results of the formal external review of the draft version of Section 1: Guideline Recommendations and Section 2: Evidentiary Base.

**DEVELOPMENT OF THIS EVIDENCE-BASED SERIES**

**Development and Internal Review**

This EBS was developed by the IMRT Indications Expert Panel of the CCO PEBC/RTP. The series is a convenient and up-to-date source of the best available evidence on the role of IMRT in central nervous system cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

**IMRT Expert Panel Conference**

On December 3, 2009, the IMRT thyroid cancers guideline was presented to members of the IMRT Expert Panel (n=24), and feedback was obtained on the quality and comprehensiveness of the evidence and the recommendations. Results are as follows:

### Are you responsible for the care of patients for whom this draft report is relevant?

<table>
<thead>
<tr>
<th>Response</th>
<th>Yes</th>
<th>No</th>
<th>Unsure</th>
<th>TOTALS</th>
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<tr>
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<td>29.2</td>
<td>70.8</td>
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### Rate the overall quality of the guideline report.

<table>
<thead>
<tr>
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<th>1.Lowest</th>
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<td>5</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>%</td>
<td>0</td>
<td>4.3</td>
<td>26.1</td>
<td>47.8</td>
<td>21.7</td>
<td>99.9</td>
<td>8</td>
</tr>
</tbody>
</table>

### I would make use of this guideline in my professional decisions.

<table>
<thead>
<tr>
<th>Response</th>
<th>1.Strongly disagree</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.Strongly agree</th>
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<td>4.8</td>
<td>33.3</td>
<td>33.3</td>
<td>28.6</td>
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### I would recommend this guideline for use in practice.

<table>
<thead>
<tr>
<th>Response</th>
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<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.Strongly agree</th>
<th>TOTALS</th>
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<tr>
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<td>8.7</td>
<td>34.8</td>
<td>30.4</td>
<td>26.1</td>
<td>95.8</td>
<td>8</td>
</tr>
</tbody>
</table>

**RECOMMENDATIONS**

1. **Insufficient evidence was obtained in this systematic review; therefore, it is not possible to propose evidence-based recommendations.**

<table>
<thead>
<tr>
<th>Response</th>
<th>1.Strongly disagree</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.Strongly agree</th>
<th>TOTALS</th>
<th>Missing</th>
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<tr>
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<td>27.3</td>
<td>54.5</td>
<td>18.2</td>
<td>100</td>
<td>12</td>
</tr>
</tbody>
</table>
Do you agree with this Recommendation?

<table>
<thead>
<tr>
<th>Response</th>
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<th>No</th>
<th>Unsure</th>
<th>TOTALS</th>
<th>Missing</th>
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<td>3</td>
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<tr>
<td>%</td>
<td>72.7</td>
<td>4.5</td>
<td>22.7</td>
<td>99.9</td>
<td>12</td>
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</table>

Additionally, the following feedback was also obtained (summarized to only include main points that were addressed in subsequent drafts):

**What are the barriers to the implementation of this guideline report?**

- Inclusions regarding qualifying statements:
  1. based on similar anatomical issues where tissue sparing with IMRT is indicated (i.e. H/N disease site), it is reasonable to consider the merits of IMRT in this disease site.
  2. Despite lack of statistical significance in outcomes the clinical significance in terms of a trend toward improved outcomes cannot be underestimated (i.e. potential for decreased toxicity with corresponding impact on improved QoL).

**Comments Recommendation One:**

- Include a statement about the comparative data as part of qualifying statement in the short summary.

**Other Comments:**

- Change title of the document to Thyroid Cancer instead of Endocrine.

**Report Approval Panel**

Following the presentation of this EBS draft report for Expert Panel review, the report was submitted to the PEBC Report Approval Panel (RAP) on March 8, 2010 for review. The RAP is comprised of two members, including an oncologist, with expertise in clinical and methodological issues.

Key issues raised by the Report Approval Panel included:

- As noted in the Qualifying Statement, the Schwartz study did not reach statistical significance but it was used as the justification for recommending treatment using IMRT if a reduction in adverse event rates is the intent.

In response to the RAP review feedback, the following was added to the guideline:

- The Qualifying Statement was reworded to “Although not statically significant, the data from Schwartz et al (3) reports a lower late adverse event rate with IMRT”.

No RAP resubmission was requested, and the guideline was approved on April 5, 2010.

**External Review: Professional Consultation**

On September 20, 2010, the RAP-approved document was distributed to clinicians practicing within the Province of Ontario as part of a Profession Consultation review process. A total of 126 clinicians were invited to participate, and a total of four submitted responses (3% response rate). Results are as follows:

<table>
<thead>
<tr>
<th>1. Rate the overall quality of the guideline report</th>
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<tbody>
<tr>
<td>Response</td>
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<tr>
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</tr>
<tr>
<td>N</td>
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<tr>
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</tbody>
</table>
2. I would make use of this guideline in my professional decisions

<table>
<thead>
<tr>
<th>Response</th>
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<th>4.</th>
<th>5. Strongly agree</th>
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<tr>
<td>N</td>
<td>1</td>
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<td>0</td>
<td>4</td>
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<tr>
<td>%</td>
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<td>0</td>
<td>75</td>
<td>0</td>
<td>100</td>
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</tbody>
</table>

3. I would recommend this guideline for use in practice

<table>
<thead>
<tr>
<th>Response</th>
<th>1. Strongly disagree</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5. Strongly agree</th>
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<td>75</td>
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</table>

4. What are the barriers or enablers to the implementation of this guideline report? None submitted.

5. Additional comments. None submitted.

Funding
The PEBC is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

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Phone: 905-527-4322, ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
REFERENCES

