Evidence-Based Series 21-3-5- EDUCATION AND INFORMATION 2013

The Role of IMRT in Lung Cancer

A. Bezjak, R.B. Rumble, G. Rodrigues, A. Hope, 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: November 22, 2010

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PBC Cancer Screening page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/clin-program/radther/

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process

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


The Role of IMRT in Lung Cancer: Guideline Recommendations

A. Bezjak, R.B. Rumble, G. Rodrigues, A. Hope, P. Warde
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QUESTION
What is the advantage, if any, of intensity-modulated radiation therapy (IMRT) compared with three-dimensional conformal radiation therapy (3DCRT) in treating early stage or locally advanced lung cancer (both small cell and non-small cell)?
The outcomes of interest included local control, overall survival, disease specific survival, acute esophagitis, acute pneumonitis, late esophagitis, and late pneumonitis.

TARGET POPULATION
The target population is comprised of all adult patients with lung cancer for whom treatment with radiation is being considered.

INTENDED USERS
This guideline is targeted for radiation oncologists, physicists, and dosimetrist.s. Administrators may find the report of value when considering the benefits of IMRT over standard 3DCRT for lung cancer.

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 around structures that are non-linear in shape 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 may be dose limiting (1). As a consequence, IMRT
theoretically may provide benefits in terms of increased tumour control through escalated dose and reduced normal tissue complications through OAR sparing. 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 reviews the published experience with IMRT in the treatment of lung cancer 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 on the use of IMRT for lung cancer informed by evidence.

<table>
<thead>
<tr>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are no published randomized trials comparing IMRT to 3DCRT in lung cancer. Two publications report on findings from retrospective cohort studies from the same cancer centre (3,4) that compared IMRT with 3DCRT. There is considerable overlap of the patients being reported on in these two publications. The study by Yom et al (4) reports more sparing of normal tissues in the IMRT patients, documented dosimetrically (e.g., lower V20 (IMRT, 35% versus [vs.] 3DCRT, 38%; p&lt;0.001) as well as clinically (a significant reduction in ≥ grade 3 treatment-related pneumonitis (TRP) 8% versus [vs.] 22% at six months, and 8% vs. 32% at 12 months, in favour of IMRT p=0.002). Similarly, the study by Liao et al (3) reported a significant difference in TRP in favour of treatment with IMRT compared with 3DCRT at both six and 12 months (p=0.017). In addition, Liao et al reported on disease-related outcomes, namely a difference in overall survival in favour of treatment with IMRT (p=0.039). However, IMRT-treated patients also had 4DCT for planning, whereas patients in the 3DCRT cohort had conventional CT planning. Thus, any survival benefit could not be attributed to IMRT, and these results are hypothesis-generating rather than proof of improved cancer outcomes with IMRT.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Qualifying Statements</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT may provide dosimetric and possibly clinical advantages in RT treatment to some (possibly most or even all) patients with non-small cell lung cancer (NSCLC) being considered for high-dose, potentially curative RT.</td>
</tr>
<tr>
<td>Current data are insufficient to fully determine the clinical, or even the dosimetric, advantage of IMRT versus traditional radiotherapy techniques. The only two publications comparing IMRT to 3DCRT include overlapping patient populations and are thus not independent observations, limiting the ability to generalize from their results. There are a number of reasons why IMRT may not be superior to 3DCRT in lung, including target definition, target motion, and the potential toxicity of low-dose RT to larger amounts of lung tissue. Other RT technological advances (e.g., positron emission tomography [PET]-based planning, 4DCT planning, respiratory motion management, image guided RT) are occurring in parallel with IMRT development and implementation, and they may also impact on rates of toxicity and local control and confound the ability to evaluate the benefits of IMRT.</td>
</tr>
<tr>
<td>It is not clear from the available literature what proportion of patients might benefit from IMRT, it may be some, most or even all patients being considered for high dose RT. Given the ability of IMRT to shape high-dose RT and provide sharp dose fall-offs, it would appear to be of particular benefit for the following situations involving patients with lung cancer:</td>
</tr>
<tr>
<td>Tumour in close proximity to an OAR (such as the spinal cord) where dose needs to be limited</td>
</tr>
</tbody>
</table>
| Tumour/Target volume in a location where CRT fields may include a large volume of
A careful and rigorous implementation of IMRT ought to proceed, with a systematic and comprehensive prospective assessment of the relevant outcomes, including tumour control and normal tissue toxicity. These data are clearly lacking in the literature and would be of great benefit in guiding the further implementation of IMRT in broader clinical practice.

RELATED GUIDELINES
REFERENCES


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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 may be dose limiting (1). As a consequence, IMRT may provide benefits in terms of increased tumour control through escalated dose and/or reduced normal tissue complications through OAR sparing. 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 reviews the published experience with IMRT in the treatment of lung cancer to quantify the potential benefits of this new technology and make recommendations for radiation treatment programs considering adopting this technique.
INTRODUCTION

Lung cancer is the leading cause of cancer deaths in Canada (3) and other industrialized countries, accounting for more deaths than breast, colon, and prostate cancers combined. One reason is the high prevalence of metastatic disease at presentation. In the case of non-small cell lung cancer (NSCLC), which accounts for approximately 80% of lung cancers, more than 30% of patients are discovered to have stage IV incurable disease at the time of initial diagnosis (4). In the case of small cell lung cancer (SCLC), the percentage of patients with clinically apparent metastatic disease at initial diagnosis is even higher, in the 55% range (4). For patients with stage IV or extensive-stage disease, improvements in thoracic radiotherapy may affect local symptoms and quality of life, and possibly length of survival, but are not likely to improve cure rates until a better way of dealing with metastatic disease is found. However, for the 60-70% of patients with NSCLC and 45% of patients with SCLC who present with tumours localized to the thorax (lung and/or adjacent lymph nodes, and/or mediastinal lymph nodes, i.e., stages I, II and III NSCLC/localized SCLC), achieving local control can improve the chance of cure. Some patients may already have occult metastatic disease even though staging investigations suggest that they are stage I-III; a proportion of them may be cured with a combination of effective locoregional therapy and chemotherapy to eradicate micrometastases. However, other patients may have developed metastatic disease as a result of persistent and/or uncontrolled locoregional disease; they may have an improved chance of cure if the thoracic disease is eradicated. The proof that a relationship does indeed exist between locoregional control and systemic disease in the context of locally advanced lung cancer is the better overall survival and lower proportion of systemic metastases in patients treated with a locally intensive radiation schedule of continuous hyperfractionated accelerated RT (CHART 54 Gy in 1.5 Gy three times a day over 12 days) as compared to conventional high-dose RT (60 Gy/2 Gy per fraction/6 weeks) in the CHART randomized trial (5). None of the patients in this randomized controlled trial (RCT) had any systemic chemotherapy as part of their initial treatment. Therefore, the reduction in systemic metastases was the result of improved local control with the more effective RT.

RT is an important, effective and very commonly employed treatment for lung cancer, and can provide a cure for a proportion of patients (6,7). Although both NSCLC and SCLC are moderately radiation-responsive tumours, local control is still not achieved in many patients, primarily because of the difficulties in delivering sufficiently high RT doses to the tumour due to concerns about toxicity development in normal tissue. The conventional technique for thoracic high-dose RT with curative intent is 3DCRT, using planning computerized tomography (CT) to outline the target (lung and lymph nodes involved by cancer, and possible areas of microscopic disease), and then conforming the fields to that target (typically with three or more beams that deliver the prescribed dose to the target, while respecting normal tissue tolerances, especially that of the spinal cord). The conventional RT dose is 60 Gy in 30 fractions, although there are efforts under way in many centres to deliver higher RT dose schedules. One randomized trial demonstrated that a higher RT dose (66 Gy) delivered only to areas of known involvement with cancer (i.e., primary tumour and involved lymph nodes) resulted in better outcomes than a somewhat lower RT dose (60 Gy) delivered to the known area as well as the potentially involved lymph nodes (elective nodal RT) (8).

There is evidence, albeit from non-randomized trials, that higher RT doses lead to a better chance of local control, as demonstrated by several dose-escalation studies (9-14) and the high rates of local control seen in the extremely hypofractionated stereotactic body RT (SBRT) protocols (15,16). However, normal tissue tolerances within the chest limit the ability to deliver sufficiently high doses of RT to most patients; this fact is dealt with further in the Discussion section.
IMRT can deliver higher doses of RT to the target, while sparing surrounding normal tissues from that high dose. Thus, it may improve the therapeutic ratio for lung cancers, increasing the beneficial effect, while minimizing the toxicity. However, there are several important potential problems with using IMRT for lung tumours, including target definition, target motion, and the potential toxicity of low-dose RT to larger amounts of lung tissue. These problems are also dealt with more extensively in the Discussion section. Given these potential concerns, one cannot extrapolate from the evidence of IMRT benefit in other cancer sites without carefully evaluating the potential drawbacks, therefore necessitating the systematic acquisition and analysis of relevant evidence that describes the potential therapeutic benefit of IMRT.

METHODS

The evidence-based series (EBS) guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (17). 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 lung cancer. The body of evidence in this review is primarily comprised of published reports of comparative studies between IMRT and 3DCRT. 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 Radiation Treatment Program (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 Programs is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE and Embase databases were searched for evidence on lung cancer and IMRT on March 8, 2010. In both databases keywords for “lung 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, 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.

Conference proceedings of the annual meetings of the American Society for Therapeutic Radiology and Oncology (ASTRO) were also searched from the year 2000 to current.
While a systematic review was not performed to obtain reports on dosimetric studies, specific papers were reviewed and summarized to facilitate the discussion (see Appendix 3).

**Study Selection Criteria**

**Inclusion Criteria**

All of the following publication types must include comparative data on IMRT versus 3DCRT in the treatment of early stage or locally advanced lung cancer (both small cell and non-small cell), and report on at least one of the outcomes of interest: local control, overall survival, disease specific survival, acute esophagitis, acute pneumonitis, late esophagitis, or late pneumonitis.

- CPGs, SRs, HTAs
- Randomized phase II or phase III trials
- Dose escalation studies, toxicity reports, quality of life (QoL) reports, and retrospective studies

In addition, the studies must be:

- Published in English
- Published in the year 2000 to current date

**Exclusion Criteria**

- Do not provide comparative data

**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 searches returned 142 and 165 potential articles, respectively. After removing those articles ineligible based on the title and abstract review, two remaining articles that met the inclusion criteria were ordered for full-text review (6,7). No other evidence was found in the NICE or the ASTRO Conference proceedings abstracts.

**Study Design**

The two papers obtained that met the inclusion criteria were reports of retrospective cohort studies from the same institution (6,7). Table 1 details the years on study, the total number of included patients, and the funding source for these two studies. The second report acknowledges that patients included in that series were previously reported on, but it is not clear exactly how many new patients were added to the second report. It is possible that all 290 patients from the Yom study (7) were included in the Liao study (6) (i.e., >70% of the patients in the latter study may have been previously reported on).

<table>
<thead>
<tr>
<th>Author, year published</th>
<th>Study period</th>
<th>Number of pts</th>
<th>Sponsorship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yom et al, 2007 (7)</td>
<td>2000-2005</td>
<td>290</td>
<td>UTMD Anderson Cancer Center</td>
</tr>
<tr>
<td>Liao et al, 2010 (6)</td>
<td>1999-2006</td>
<td>409</td>
<td>UTMD Anderson Cancer Center</td>
</tr>
</tbody>
</table>

Note: UTMD, University of Texas M.D. Anderson Cancer Center.

Table 2 describes certain 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 median follow-up, and what outcomes were reported.

### Table 2. Details of included studies.

<table>
<thead>
<tr>
<th>Author, year published</th>
<th>Comparison</th>
<th>Dose [median] (range)</th>
<th>Total N of pts</th>
<th>Disease stage</th>
<th>Follow-up [months] (range)</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yom et al, 2007 (7)</td>
<td>IMRT+Chemo</td>
<td>63 Gy/1.8 Gy/fr [50.4-76 Gy]</td>
<td>68</td>
<td>Stage II-IV (85% stage III)</td>
<td>8 (0-27)</td>
<td>V20, TRP</td>
</tr>
<tr>
<td></td>
<td>3DCRT+Chemo</td>
<td>63 Gy/1.8 Gy/fr [50.4-69.6 Gy]</td>
<td>222</td>
<td>Stage II-IV (90% stage III)</td>
<td>9 (0-56)</td>
<td></td>
</tr>
<tr>
<td>Liao et al, 2010 (6)</td>
<td>4DCT+IMRT+Chemo</td>
<td>63 Gy [50-72 Gy]</td>
<td>91</td>
<td>Stage I-III (80% stage III)</td>
<td>15.6 (1.2-38.4)</td>
<td>V20, TRP, LRP, DM, OS.</td>
</tr>
<tr>
<td></td>
<td>3DCRT++Chemo</td>
<td>63 Gy [50-73]</td>
<td>318</td>
<td>Stage I - III (87% stage III)</td>
<td>25.2 (1.2-94.8)</td>
<td></td>
</tr>
</tbody>
</table>

Note: N, number; IMRT, intensity-modulated radiation therapy; Chemo, chemotherapy comprised primary of carboplatin with a taxane; 3DCRT, 3-dimensional conformal radiotherapy; Gy, Gray; fr, fraction; V20, Percentage of lung volume that receives at least 20 Gy of radiation; TRP, treatment-related pneumonitis; 4DCT, four dimensional planning CT; LRP, locoregional progression; DM, distant metastasis; OS, overall survival.

* 3DCRT patients in Liao study (6) did not have 4DCT and were treated at an early time period than 4DCT + IMRT patients.

### Study Quality

The two retrospective cohort studies obtained (6,7) were assessed for quality according to criteria such as the balance between the treatment groups, identification of prognostic factors, and reporting of differences between baseline prognostic factors. Any other variances in study design that could affect the reliability of the study findings were also reported. Of note is the considerable overlap of the patients in the two studies, as described above.

In the study by Yom et al (7), the treatment groups were not in balance as the IMRT group (N=68) was smaller than the 3DCRT group (N=222). Prognostic factors were identified, and significant differences were reported between the groups for clinical stage in favour of 3DCRT (p=0.015, Stage IIIA: IMRT 25% versus [vs.] 3DCRT 39%; Stage IIIB: IMRT 60% vs. 3DCRT 51%); ECOG performance status in favour of 3DCRT (p<0.001); PS 0: IMRT 1% vs. 3DCRT 20% PS 2 IMRT 29% vs. 3DCRT 3%); and gross tumour volume (GTV) in favour of 3DCRT (p=0.011; median tumour volume 194 ml for IMRT, 142 ml for 3DCRT; GTV 0-200mL: IMRT 47% vs. 3DCRT 64%). No adjustments were possible due to the study design.

In the study by Liao et al (6), the treatment groups were not in balance, the IMRT group (n=91) being smaller than the 3DCRT group (n=318). Patients in the IMRT group received 4DCT that allowed for a more accurate assessment of respiratory motion at the planning and assignment of appropriate set-up margins (planning target volume [PTV]). In addition, patients in the IMRT cohort were treated in a more recent time period (2004-2006) than were 3DCRT patients (1999-2006). Prognostic factors were identified, and significant differences were reported between the groups for smoking history (Never/ex, 3DCRT: 75% vs. IMRT: 59%; Current, 3DCRT: 25% vs. IMRT: 37%; Unknown, 3DCRT: 3% vs. IMRT: 3% [p=0.007]), and pre-radiation treatment positron emission tomography (PET) (No, 3DCRT: 51% vs. IMRT: 15%; Yes, 3DCRT: 49% vs. IMRT: 82%; Unknown, 3DCRT: 0 vs. IMRT: 2% [p<0.0005]). The difference in PET might imply that more patients in the IMRT cohort had a correct stage assignment (i.e., 3DCRT patients might have been at a more advanced stage). No adjustments were possible due to the study design.
Outcomes: Dosimetric and Disease-Related

The paper by Yom et al (7) reported on the dosimetric comparisons of the IMRT and 3DCRT cohorts and on preliminary disease-related outcomes for the IMRT cohort only (six and 12 month rates of local control and overall survival) (Table 3a). V20 and most other lung volumes were significantly different between the groups (p<0.001), in favour of IMRT (median V20 in IMRT cohort 35% (range 20-48%) vs. 38% (range 8-78%) for 3DCRT. Of note, V5 was higher for the IMRT cohort (median 63% vs. 57%, p = 0.011). In the study by Liao et al (6) V20, locoregional progression, distant metastasis, and overall survival were reported in numerical or graphic format (as such, some data could not be extracted numerically) (Table 3b). There was a difference in overall survival in favour of treatment with IMRT (p=0.039). The distant metastases rate was no different between the two groups, suggesting that stage migration was not the likely explanation for the results. However, the two technological advances of IMRT and 4DCT were both introduced at around the same time; thus, any survival benefit could not be attributed to one over the other, and these results are thus hypothesis-generating rather than proof of improved cancer outcomes with IMRT. As well, the fact that there is a large overlap of patients reported means that the conclusions of the two papers are not independent and are likely to be two reports of the same findings.

Table 3a. Dosimetric and disease-related outcomes: Yom et al.

<table>
<thead>
<tr>
<th>Author, year published</th>
<th>Comparison</th>
<th>V20 (Median)</th>
<th>Local control (%)</th>
<th>Disease-free survival (%)</th>
<th>Overall survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yom et al, 2007 (7)</td>
<td>IMRT+Chemo 3DCRT+Chemo</td>
<td>35% (3-48) 38% (8-78)</td>
<td>p&lt;0.001</td>
<td>93.5 55.3</td>
<td>66.7 32.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 month 12 month</td>
<td>6 month 12 month</td>
<td>6 month 12 month</td>
</tr>
</tbody>
</table>

Note: IMRT, intensity-modulated radiation therapy; 3DCRT, 3-dimensional conformal radiotherapy; V20, Percentage of lung volume that receives at least 20 Gy of radiation.

Table 3b. Dosimetric and disease-related outcomes: Liao et al.

<table>
<thead>
<tr>
<th>Author, year published</th>
<th>Comparison</th>
<th>V20 (Median)</th>
<th>Locoregional progression-free rate (%)</th>
<th>Distant metastasis-free rate (%)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liao et al (6)</td>
<td>IMRT+Chemo 3DCRT+Chemo</td>
<td>34.4% (33-36) 37% (36-38) p=0.0013</td>
<td>NR (estimated as approx 78% at 2 yrs)</td>
<td>NR (estimated as approx 48% at 2 yrs)</td>
<td>16.8 10.2 p=0.039</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=ns</td>
<td></td>
</tr>
</tbody>
</table>

Note: IMRT, intensity-modulated radiation therapy; 3DCRT, 3-dimensional conformal radiotherapy; V20, Percentage of lung volume that receives at least 20 Gy of radiation.

Outcomes: Adverse Effects

The only adverse effect reported in the study by Yom et al (7) was grade ≥3 TRP, and a statistically significant difference was detected between IMRT and 3DCRT in favour of IMRT at 12 months (IMRT 8% vs. 3DCRT 32%; p=0.002). No significant difference was detected at six months. The study by Liao et al (6) reported a significant difference in favour of treatment with IMRT compared with 3DCRT in TRP at both six and 12 months (p=0.017), although the
precise incidence of TRP was not reported (Figures suggest it to be approximately 90% freedom from grade ≥3 TRP at 12 months with IMRT vs. approximately 75% with 3DCRT). Results appear in Table 4.

Table 4. Treatment-related pneumonitis (TRP).

<table>
<thead>
<tr>
<th>Author, year published</th>
<th>Comparison</th>
<th>Grade ≥ 3 TRP 6 months</th>
<th>Grade ≥ 3 TRP 12 months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yom et al, 2007 (7)</td>
<td>IMRT</td>
<td>8% (4-19)</td>
<td>22% (17-29%)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>3DCRT</td>
<td>8% (4-19)</td>
<td>32% (26-40)</td>
<td></td>
</tr>
<tr>
<td>Liao et al (6)</td>
<td>IMRT+Chemo</td>
<td>NR (HR&lt;1)</td>
<td>NR (HR&lt;1)</td>
<td>p=0.002</td>
</tr>
<tr>
<td></td>
<td>3DCRT+Chemo</td>
<td>NR</td>
<td>NR</td>
<td>p=0.017</td>
</tr>
</tbody>
</table>

Note: IMRT, intensity-modulated radiation therapy; 3DCRT, 3-dimensional conformal radiotherapy; NS, non-significant; HR, Hazard rate.

ONGOING TRIALS

The U.S. National Institutes of Health online directory of clinical trials (located at http://www.clinicaltrial.gov) was searched on September 17, 2009 for listings of relevant trials. The details of the relevant trial appear in Table 5.

Table 5. Ongoing trials.

A Randomized Trial to Compare Time to Common Toxicity Criteria for Adverse Effect (CTC AEC) 3.0 Grade. 3 Treatment Related Pneumonitis (TRP) in Patients With Locally Advanced Non-Small Cell Lung Carcinoma (NSCLC) Receiving Concurrent Chemoradiation Radiation Treated With 3-Dimensional Conformal Radiation Therapy (3D CRT, ARM 1) Versus Intensity Modulated Radiation Therapy (IMRT, ARM 2) Using 4-Dimensional CT Planning and Image Guided Adaptive Radiation Therapy (IGART)

<table>
<thead>
<tr>
<th>Phase:</th>
<th>Phase II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type:</td>
<td>Interventional</td>
</tr>
<tr>
<td>Status:</td>
<td>Active, not recruiting.</td>
</tr>
<tr>
<td>Age:</td>
<td>18 Years to 80 Years</td>
</tr>
<tr>
<td>Sponsor:</td>
<td>M.D. Anderson Cancer Center</td>
</tr>
<tr>
<td>Protocol IDs:</td>
<td>2006-0222, NCT00520702</td>
</tr>
<tr>
<td>Description:</td>
<td>To compare intensity-modulated radiation therapy (IMRT) with three-dimensional conformal radiation therapy (3D CRT) in the ability to decrease the risk of treatment-related pneumonitis (TRP).</td>
</tr>
</tbody>
</table>

DISCUSSION
Importance of Normal Tissue Toxicity in Thoracic RT

As touched upon in the Introduction section, normal tissue toxicity is a major clinical concern, limiting the ability to deliver sufficiently high doses of radiation to lung tumours. One of the normal tissues most sensitive to the effect of radiation is the lung, with damage seen even with a fractionated delivery of 20-25 Gy, a dose that is much lower than the therapeutic goal of 66-74 Gy or more. The most important variable that influences the severity and clinical manifestation of the RT damage to the lung is the volume factor. If 20 Gy is uniformly delivered to both lungs, the resulting damage will be universal, severe, and fatal, but if it is delivered to a very small volume, it may not be noticeable at all. In most cases of radical RT, it is delivered to a portion of the lung—some parts get a much higher dose, some get a lower dose (e.g., 5-10 Gy), and some parts get no dose at all. Depending on the volume of the lung receiving the dose, as well as a number of other factors (e.g., lung reserve, radiobiological factors, concurrent therapy), patients may experience no acute
symptoms and only an asymptomatic lung fibrosis in the RT field (typically 12 months or more post-therapy), transient mildly symptomatic RT pneumonitis (typically two to six months post-therapy), or a more symptomatic, severe, or even fatal RT pneumonitis. Thus, volumetric parameters such as V20 (volume of the lung receiving 20 Gy or more), mean lung dose (the average dose that both lungs have received), and lung volumes getting lower doses (e.g., V5 [% lung volume getting 5 Gy or more] and V10 [% lung volume getting 10 Gy or more]) have been shown to be the strongest predictors of the severity of RT-induced lung toxicity (7,18-20). Unless one can ensure that the RT plan delivers tolerable RT doses, i.e., doses that are associated with a modest risk of clinically significant RT pneumonitis, it is not likely that a certain “radical” plan will deliver sufficiently high RT doses to eradicate a tumour in most patients.

Lung is the most sensitive organ to RT damage but by no means the only dose-limiting organ that restricts RT dose escalation within the thorax. The spinal cord, esophagus, and heart also limit the ability to deliver higher RT doses to lung cancers. The spinal cord needs to be carefully protected from doses higher than 50 Gy, and cord-sparing techniques needed to deliver higher doses to the centrally-located tumours in turn expose a larger volume of lung to RT. Moreover, some tumours in close proximity to the cord (for example, those involving the vertebral body or the proximal aspect of the rib adjacent to the intravertebral foramen) cannot be safely exposed to sufficiently high doses due to the inability of 3DCRT to deliver plans that have a sufficiently sharp dose drop-off. The esophagus doesn’t have the critical dose threshold of the spinal cord, but acute RT damage, as can be seen with even modest doses of RT (and worsened, with increasing volume of esophageal tissue receiving high doses) can cause significant morbidity to patients (e.g., pain, dehydration, weight loss) and frequently limits the ability to dose-escalate RT. This is especially the case when RT is delivered concurrently with chemotherapy and when large volumes of esophageal tissue are incidentally exposed to RT in order to treat the mediastinal tumour volume (10,21).

Potential Concerns about IMRT in Lung Tissue

IMRT can deliver higher doses of RT to the target, while sparing surrounding normal tissues from a high dose. Thus, it may improve the therapeutic ratio for lung cancers, increasing the beneficial effect while minimizing the toxicity. However, there are several important potential problems when using IMRT for lung tumours, including target definition, target motion, and the potential toxicity of low-dose RT to larger amounts of lung tissue. In 3DCRT, although the fields are designed to conform to the outline of the target (e.g., the PTV), other mediastinal lymph nodes that have not been identified as targets but that are in the path of the RT beams will also receive significant RT doses (22,23). This “incidental irradiation” has been postulated to have a potentially therapeutic effect on small volume microscopic cancer that may be present in those nodes (24). In contrast, since IMRT typically uses a greater number of beams, and the RT dose across the beam is modulated significantly, the tissues in the path of the beam will receive a lower dose of RT when compared to that with 3DCRT. Thus, only the tissues identified as the target will likely get the therapeutic dose. There are great challenges in accurately defining the tissues that contain clinically obvious and especially microscopic cancer, with significant intra- and interobserver differences in contouring GTV, and special challenges seen if atelectasis is present. The incorporation of PET scan information reduces, but doesn’t eliminate, the contouring uncertainty and variability (25). Thus, how GTV is outlined, what expansion is made for clinical target volume (CTV) (e.g., uncertainty, risk of microscopic disease, potential routes of spread), and what expansion is further made for set-up and day-to-day positioning variations is going to be more critically important for IMRT plans. It is possible that IMRT will
result in better local control of the tumour but coupled with higher rates of regional failure in lymph nodes that have not been recognized as containing cancer.

Target motion is another challenge for the optimal delivery of thoracic IMRT. Typically, RT is planned and delivered with the patient breathing normally. 4DCT-based planning incorporates the extent of tumour motion into the planning, by designing patient-specific margins to incorporate the tumour motion within the internal target volume (ITV). Currently, motion information is not utilized when dose calculations are performed. Plans are created on a static data set (possibly from a certain phase of breathing, e.g., exhalation, or from the average free-breathing scan, or from the slightly blurred helical planning CT). In addition, the dose to any structure (target or OAR) will be influenced by the amount of tissue or lung surrounding it (using heterogeneity correction, since lung transmits RT in a way very different from that of solid tissue). However, in another phase of breathing cycle, the amount of solid tissue and lung at that point may be very different. This is a critical issue for spinal cord tissue, as there is a critical maximum dose that should not be exceeded (typically 50 Gy), and if the calculations demonstrate the dose to be just below that, the effect of tumour motion may lead to a higher dose actually being delivered, one exceeding normal tissue tolerance. 3DCRT techniques are usually not as sensitive to target motion, as the dose delivered is more uniform, and sharp dose gradients are not common. Thus, the planned IMRT doses may not represent the doses delivered. The greater the target motion, the larger the potential risk of a mismatch between the planned and delivered doses. This is such a critical factor that some multicentre protocols (e.g., RTOG 0617) that utilize IMRT for lung RT planning only allow patients whose tumour motion is <1cm; in cases with a greater amount of tumour motion, abdominal compression, gating, or other measures are required to reduce the amount of respiratory motion.

Finally, although IMRT can reduce the dose to OAR, especially to spinal cord and esophageal tissues, the integral dose remains constant, and thus, the dose needs to be deposited somewhere. Either some volumes get a higher dose, or larger volumes get a lower dose. In particular, in many IMRT plans, low-dose RT is distributed to larger volumes of the lung. Thus, V20 may be improved, but at the expense of V5 or V10. These were not particularly relevant parameters of lung toxicity in the 3DCRT era, as V10 was usually quite similar to V20, e.g., 30-35% for an acceptable plan, as a few beams would transverse lung tissue. It was thought that 5 or 10 Gy was within the tolerance range of lung tissue. However, in IMRT plans, V20s may be in the 30% range, but V10 may be 50% and V5 may be 65%, i.e., larger lung volumes would be spared higher dose RT but greater lung volumes would receive a lower dose RT (often due to the larger number of RT beams utilized in IMRT plans). Case reports have raised the issue of caution, with the need to pay attention to these larger volumes of lung that previously received non-relevant lung doses, as fatal RT pneumonitis has been reported with high V10 values in post-pneumonectomy cases (21,26-28). Thus, non-traditional lung toxicity parameters may be more clinically relevant, and IMRT plans may ironically be more, rather than less, toxic, even in the absence of dose escalation.

Evidence for Lung IMRT

There is a paucity of good quality data at the present time regarding the clinical impact of IMRT versus 3DCRT in lung cancer RT. There are no RCTs and very few cohort studies. The two studies described above are from the same centre, and the majority of patients in the second study were already reported on in the first study; thus, they cannot be treated as independent pieces of evidence but as highly correlated and interdependent results. The cohort studies are challenging to undertake, as clinical outcomes are influenced by a variety of confounding variables. Local control is influenced by tumour size/bulk, grade, stage, and type of staging tests utilized (e.g., PET scan) as well as other treatments (e.g.,
chemotherapy). RT toxicity is influenced by the patient baseline status (e.g., respiratory reserve, chronic obstructive pulmonary disease [COPD], other comorbidities), other treatments (e.g., chemotherapy, steroids, other medications), field size and RT doses used, intrinsic RT response (e.g., transforming growth factor [TGF] beta response to RT), frequency of follow-up, and methodological rigor in assessing the toxicity and frequency of radiological and clinical follow-up, among other variables. It is no wonder that clinical studies are few and far between. Even the dosimetric studies are few in number, and such reports are based on very few patients. Those studies report different dosimetric endpoints. Some of those studies are included in Appendix 3, but a systematic review of dosimetric studies was beyond the scope of this guideline.

However, despite the great limitations of the existing studies, it is notable that all the studies reached virtually identical conclusions—there appears to be a benefit to IMRT in terms of its sparing of normal tissues (at least in terms of sparing them from higher doses of RT)—but there is a need to monitor the effects of lower dose spillage. This finding in turn allows for RT dose escalation, thus permitting the potential (but as of yet unproven) improved local control of tumours, theoretically without an increase in normal tissue toxicity. However, given the concerns about the problems with lung IMRT, including target definition, target motion, and the potential toxicity of low-dose RT to larger amounts of lung, as detailed in the Introduction section, it would not be appropriate to advocate for the full implementation of IMRT for lung RT without some regard to its potential limitations, since they were not fully studied in the reported literature. IMRT may be appropriate if sufficient attention is given to tumour identification and contouring, the identification of areas of potential microscopic disease, tumour motion, and other factors that influence normal tissue toxicity as well as local control.

Who Would Benefit from Lung IMRT?

It is not clear from the available literature what proportion of patients might benefit from IMRT—it might be some, most, or even all the patients being considered for high-dose RT. Given the ability of IMRT to shape high-dose RT and provide sharp dose follow-ups, it would appear to be of particular benefit for the following situations involving patients with lung cancer:

- Tumour in close proximity to an OAR (such as the spinal cord) where the dose needs to be limited
- Tumour/Target volume in a location where CRT fields may include a large volume of OAR (e.g., bilateral nodal volume, where the target would include a large volume within the thorax)
- A situation where dose escalation would be beneficial, while trying to avoid an increase in normal tissue toxicity

While the first two would apply to only a proportion of NSCLC pts, the third may potentially apply to many, if not all, patients, as it is not clear which patients have a good chance of local control with current doses of conventionally fractionated RT. Moreover, IMRT may allow for the treatment of patients who currently cannot be safely exposed to radical doses with 3DCRT.

CONCLUSIONS

IMRT may provide dosimetric and possibly clinical advantages in RT treatment to some (possibly most or even all) patients with NSCLC being considered for high-dose potentially curative RT. The current data is insufficient for fully determining the clinical or even the dosimetric advantage of IMRT, except that all data seem to point towards the advantage of IMRT over 3DCRT. This would suggest that a careful and rigorous implementation of IMRT
ought to proceed, with a systematic and comprehensive prospective assessment of the
relevant outcomes, including tumour control and normal tissue toxicity. Health services
research may inform and enrich such work. These data are clearly lacking in the literature
and would be of great benefit in guiding the further implementation of IMRT in broader
clinical practice.

CONFLICT OF INTEREST
None declared.

JOURNAL REFERENCE
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- Bezjak A, Rumble RB, Rodrigues G, Hope A, Warde P; Members of the IMRT Indications

ACKNOWLEDGEMENTS
The IMRT Indications Expert Panel would like to thank Dr. Andrea Bezjak, Mr. R. Bryan
Rumble, Dr. George Rodrigues, and Dr. Andrew Hope for taking the lead in drafting this
systematic review.
REFERENCES


Steering Panel

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<tbody>
<tr>
<td>Dr. Padraig Warde</td>
<td>Provincial Head, Radiation Treatment Program, Cancer Care Ontario</td>
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Expert Panel

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<tr>
<td>Dr. Anthony Whitton</td>
<td>Radiation Treatment Program, Cancer Care Ontario</td>
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<tr>
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<td>Radiation Therapy Representative, Peel Regional Cancer Program</td>
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<td>Ms. Lisa Favell</td>
<td>Capital Project Representative, Cancer Care Ontario</td>
</tr>
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<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

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<tr>
<td>Dr. Andrea Bezjak</td>
<td>Radiation Oncologist, Princess Margaret Hospital</td>
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<tr>
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<td>Radiation Oncologist, London Regional Cancer Program</td>
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<td></td>
<td>Associate Scientist, Lawson Health Research Institute</td>
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<tr>
<td>Dr. Andrew Hope</td>
<td>Radiation Oncologist, Princess Margaret Hospital</td>
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<tr>
<td></td>
<td>Assistant Professor, Department of Radiation Oncology, University of Toronto</td>
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Appendix 2. Literature search strategies.
MEDLINE:
Database: Ovid MEDLINE(R) <1996 to May Week 4 2009>
Search Strategy:

1 lung cancer.mp. or exp Lung Neoplasms/ (63841)
2 exp Radiotherapy, Intensity-Modulated/ or imrt.mp. (2671)
3 brachytherapy.mp. or exp Brachytherapy/ (8631)
4 exp Protons/ or proton therapy.mp. (11583)
5 biological marker.mp. or exp Biological Markers/ (315041)
6 gene therapy.mp. or exp Gene Therapy/ (33428)
7 children.mp. or exp Child/ (540336)
8 pediatric cancer.mp. (675)
9 childhood cancer.mp. (1894)
10 exp Quality Assurance, Health Care/ or quality assurance.mp. (139162)
11 treatment plan comparison.mp. (5)
12 aperture optimization.mp. (29)
13 independent dose calculation.mp. (13)
14 EPID dosimetry.mp. (14)
15 set up errors.mp. (87)
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 (1016244)
17 1 and 2 (184)
18 1 and 16 (9638)
19 17 not 18 (162)
20 limit 19 to (english language and humans and yr="2000 - 2009") (141)
21 from 20 keep 1-141 (141)

EMBASE:
Database: Ovid EMBASE(R) <1996-2009 week 22>

1 lung cancer.mp. or exp Lung Cancer/ (74380)
2 imrt.mp. or exp Intensity Modulated Radiation Therapy/ (3457)
3 brachytherapy.mp. or exp Brachytherapy/ (10986)
4 proton therapy.mp. or exp Proton Therapy/ (713)
5 biological marker.mp. or exp Biological Marker/ (32990)
6 gene therapy.mp. or exp Gene Therapy/ (35072)
7 Child/ or child.mp. or children.mp. (466670)
8 quality assurance.mp. or exp Quality Control/ (112351)
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10 aperture optimization.mp. (31)
11 independent dose calculation.mp. (12)
12 EPID dosimetry.mp. (15)
13 set up errors.mp. (89)
14 exp Childhood Cancer/ or pediatric cancer.mp. (10072)
15 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (650239)
16 1 and 2 (254)
17 1 and 15 (5456)
18 16 not 17 (200)
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20 from 19 keep 1-165 (165)
## Appendix 3. Selected historical studies focusing on dosimetric comparisons of IMRT and 3DCRT, or IMRT alone.

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<td>Marnitz et al., 2002</td>
<td>10</td>
<td>Locally advanced NSCLC</td>
<td>IMRT: 73 Gy</td>
<td>Median lung V20: IMRT: 38.5% 3DCRT: 44.5%</td>
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<td>3DCRT: 63 Gy</td>
<td>Median maximum esophageal dose: IMRT: 75.4 Gy 3DCRT: 68.6 Gy</td>
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<td>Grills et al., 2003</td>
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<td>Stage I-IIIB locally advanced NSCLC</td>
<td>70 Gy/35</td>
<td>Mean PTV dose: IMRT: 89.9 Gy 3DCRT: 82.7 Gy</td>
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<td>70 Gy/35</td>
<td>Mean lung V20: IMRT: 23.6% 3DCRT: 24.0%</td>
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<td>Underwood et al., 2003</td>
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<td>NSCLC</td>
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<td>Mean PTV median dose: IMRT: 70.8 Gy 3DCRT: 72.2 Gy</td>
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<td>IDE</td>
<td>Mean lung V20: IMRT: 22.3% 3DCRT: 34.6%</td>
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<td>Amanie et al., 2004</td>
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<td>Mean 95% PTV dose: IMRT: 72.2 Gy 3DCRT: 75.7 Gy</td>
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<td>Mean esophageal mean dose: IMRT: 18.0 Gy 3DCRT: 27.5 Gy</td>
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<td>Mean maximum spinal cord dose: IMRT: 35.4 Gy 3DCRT: 34.9 Gy</td>
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<td>Study</td>
<td>Total dose</td>
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<td>Locally advanced NSCLC</td>
<td>Improved conformity index with IMRT of 1.37 (p=0.012)</td>
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<td>Liu et al., 2004 (33)</td>
<td>63Gy/35</td>
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<td>NR</td>
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<td>Murshed et al., 2004 (34)</td>
<td>63 Gy/35</td>
<td>Stage III-IV and recurrent NSCLC</td>
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<td>Mean Minimum PTV Dose: IMRT: 55.8 Gy 3D CRT: 56.5 Gy p=0.06</td>
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<td>Manon et al., 2005 (35)</td>
<td>16% (PTV1), 24% (PTV2), 13% (PTV3) lower with IMRT compared with 3D CRT</td>
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<td>Schwartz et al., 2005 (36)</td>
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<td>Pts 5-10: 65.3-100.9 Gy (mean dose) Pts 1-4: 64.8-101.25 Gy</td>
<td>Generalized Mean Equivalent Uniform Dose: IMRT coplanar: 73.5 Gy IMRT noncoplanar: 73.6 Gy</td>
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<td>Christian et al, 2007 (38)</td>
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<td>Mayo et al, 2008 (39)</td>
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Evidence-Based Series 21-3-5: Section 3

The Role of IMRT in Lung Cancer: EBS Development Methods and External Review Process

A. Bezjak, R.B. Rumble, G. Rodrigues, A. Hope, 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: November 22, 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 Evidence-based Series (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 evidence-based series 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 and 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 lung cancer guideline was presented to members of the IMRT Expert Panel (n=27), and feedback was obtained on the quality and comprehensiveness of the evidence and the recommendations. Results are as follows:

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<tr>
<th>I would recommend this guideline for use in practice.</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>
<td>N</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>15</td>
<td>6</td>
<td>27</td>
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<td>0</td>
<td>22.2</td>
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<td>22.2</td>
<td>99.5</td>
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**RECOMMENDATIONS**
1. **Insufficient evidence was obtained in this systematic review; therefore, it is not possible to propose recommendations on the use of IMRT for lung cancer informed by evidence.**
Response 1.Strongly disagree 2. 3. 4. 5.Strongly agree TOTALS Missing
N 0 1 2 15 9 27 0
% 0 3.7 7.4 55.6 33.3 100 0

Do you agree with this Recommendation?
Response Yes No Unsure TOTALS Missing
N 24 1 2 27 0
% 89 3.7 7.4 100 0

Additionally, the following feedback was also obtained ():

What are the barriers to the implementation of this guideline report?
- Lack of resources, including equipment and personnel
- Concerns about respiratory motion

Comments About the Recommendation:
- The fact that treatment with IMRT allows for dose escalation, which has been demonstrated to improve outcomes, while 3DCRT does not in all instances needs to be reinforced in the qualifying statements. There exists a sub-group of patients that will only be suitable for treatment with IMRT.
- Should make a stronger recommendation using lower level of evidence
- Should state “there is weak evidence supporting the use of IMRT”

Other Comments:
- There needs to be an RCT comparing IMRT with 3DCRT in lung cancer (mentioned by several attendees)
- Prospective data on IMRT are needed but an RCT may not be appropriate
- Other technological improvements are occurring in parallel with IMRT development and may impact on the ability to evaluate the benefits of IMRT (PET-based planning, gated CT simulation, gated delivery, other motion management strategies)

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) for review on May 25, 2010. The RAP is comprised of two members, including an oncologist, with expertise in clinical and methodological issues.

Key issues raised by the RAP included:
- The authors have not found the theoretical benefits of IMRT to be sufficient to recommend adoption, in contrast to the other IMRT documents in this series. Reasons should be better explained.
- The two studies that are summarized have an overlap of patients - that should be highlighted and discussed in more detail.
- Further work in evaluating IMRT may need to include health services research
- Some parts (Recommendation and Key Evidence in Part 1, Introduction in Part 2) should be rewored more succinctly and/or moved (to Discussion).
- It may be useful to add a short section on the role of RT in a disease site.

In response to the RAP review feedback, the following was added to the guideline:
- Section 1: Qualifying Statement now includes the statement “There are a number of reasons why IMRT may not be superior to 3DCRT in lung, including target definition, target motion, and the potential toxicity of low-dose RT to larger amounts of lung tissue” to explain why the theoretical benefits of IMRT were not deemed sufficient to recommend widespread adoptions without tracking the outcomes.
• Several changes were made to emphasize the overlap of patients in the two studies:
  o Section 1: Qualifying Statement, “The only two publications comparing IMRT to 3DCRT include overlapping patient populations and are thus not independent observations. This limits the ability to generalize their results.”
  o Section 2: Results, under Study Design, “It is possible that all 290 patients from the Yom study were included in the Liao study, i.e., that >70% of the patients in the latter study were previously reported on;” under Study Quality, “Of note is the considerable overlap of the patients in the two studies, as described above;” under Outcomes: Dosimetric and Disease-specific, “As well, the fact that there is a large overlap of patients reported means that the conclusions of the two papers are not independent but are more likely to be two reports of the same finding;” and in Discussion “The two studies described above are from the same centre, and the majority of patients in the second study were already reported on in the first study, thus, they cannot be treated as independent pieces of evidence but as highly correlated and interdependent results.”
• A statement was added to Section 2: Conclusions: “Health services research may inform and enrich such work.”
• In Section 2, large sections of the Introduction were moved to the Discussion under the headings “Importance of Normal Tissue Toxicity in Thoracic RT” and “Potential Concerns about IMRT in Lung.” Other sections in the Discussion now have subheadings as well. Section 1, Evidence was shortened by eliminating study details
• In Section 2, the following statement was added to address the role of RT in lung cancer: “Radiotherapy is an important, effective, and very commonly employed treatment for lung cancer, and can provide cure for a proportion of patients”

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 11 submitted responses (9% response rate). Results are as follows:

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<th>1. Rate the overall quality of the guideline report</th>
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<th>2. I would make use of this guideline in my professional decisions</th>
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4. What are the barriers or enablers to the implementation of this guideline report?
   Barriers:
   • Time consumed by IMRT set up far more than for 3DCRT.
   • The major barrier to wide acceptance of the use of IMRT in this setting is inconclusive data (N=2).
• Provincial mandate to treat a certain proportion of patients via IMRT in Ontario may lead to inappropriate or at least rushed implementation of IMRT for lung patients in Ontario.
• Organ motion and the potential for missing some microscopic disease with IMRT (N=2).
• Different planning software has different tools/processes for IMRT planning. It can be challenging finding the best templates for IMRT lung planning given minimal recommendation provided to us from the developer. The software providers need to have their IMRT lung planning recommendations ready for new developing centres.

Enablers:
None submitted.

5. Additional comments.
• Given concerns about heterogeneity correction and target motion during lung RT, it might be helpful to include detailed technical recommendations on minimum field size, minimum MU/segment, V5-10-20, etc. in the document.
• In the Background section it is implied that IMRT allows for the creation of steeper dose gradients and sharper fall off than 3DCRT plans. This is not actually correct, as while IMRT allows for more conformity around structures that are non-linear in shape, you can’t have a steeper gradient than that which could be created with a half beam block on a LINAC. IMRT does not change the laws of physics, it simply allows sculpting of dose gradients around curvilinear targets. The gradients around such structures are not as steep as that which can be obtained with a hard single beam edge but the distribution is better because of the conformity that IMRT can achieve.
• There should be a CCO sponsored province-wide, web-based database for collecting outcomes data on patients treated with IMRT.

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REFERENCES
