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

The Role of IMRT in Head & Neck Cancer

B. O'Sullivan, 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: January 12, 2011

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Journal Citation (Vancouver Style): O'Sullivan B, Rumble RB, Warde P; Members of the IMRT Indications Expert Panel. Intensity-modulated radiotherapy in the treatment of head and neck cancer. Clin Oncol. 2012;24:474-87. doi:10.1016/j.clon.2012.05.006.

Guideline Citation (Vancouver Style): O'Sullivan B, Rumble RB, Warde P; Members of the IMRT Indications Expert Panel. The role of IMRT in head and neck cancer. Toronto (ON): Cancer Care Ontario; 2011 Jan 12. Program in Evidence-based Care Evidence-based Series No.: 21-3-3.

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

The Role of IMRT in Head & Neck Cancer: Guideline Recommendations

B. O'Sullivan, R.B. Rumble, P. Warde,
and members of the IMRT Indications Expert Panel

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QUESTION(S)

1. In the treatment of nasopharyngeal cancer (NPC), is there a benefit in local control, adverse effects, and quality of life measures associated with the use of intensity-modulated radiation therapy (IMRT) compared with two-dimensional external beam radiotherapy (2D EBRT)?
2. In the treatment of locally advanced head and neck (H&N) cancer, is there a benefit in local control, adverse effects, and quality of life measures associated with the use of IMRT compared with 2D EBRT?

The outcomes of interest include local control, overall survival, xerostomia, osteoradionecrosis (specifically, mandible), optic nerve preservation, dysphagia, and quality of life.

TARGET POPULATION

The target population is comprised of all adult patients with head and/or neck cancer for whom treatment with radiation is being considered.

INTENDED USERS

This guideline is targeted for radiation oncologists, physicists, and radiation therapists/dosimetrists. Administrators may find the report of value when considering the benefits of IMRT over standard 2D EBRT for H&N 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 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 an 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 H&N cancer and prostate cancer. This evidence-based series reviews the published comparative evidence between IMRT and the standard treatment of 2D EBRT in the treatment of H&N cancer to summarize the potential benefits and/or harms of this new technology and to make recommendations for radiation treatment programs considering adopting this technique.

RECOMMENDATIONS AND KEY EVIDENCE

If the reduction of xerostomia and improved quality of life are the main outcomes of interest, then IMRT is the recommended treatment for all nasopharyngeal, oropharyngeal, hypopharyngeal, laryngeal, oral cavity, and unknown primary cancers where lymph node regions requiring inclusion in the treatment volume would result in irreparable damage to salivary function if 2D EBRT or 3D EBRT were used due to their inability to maintain salivary doses within their tolerance limits (<26 Gy mean dose). The data provided are applicable to locally advanced disease but are equally applicable to early-stage disease and rare sites (e.g. salivary gland tumours) requiring RT that would otherwise damage these normal structures. In addition, these principles hold for skin malignancy where advantages in sparing normal tissue while achieving target coverage are also relevant.

Evidence

Three randomized clinical trials comparing IMRT with 2D EBRT (3-5) and other supporting evidence, including two single-arm, Phase II trials (6,7) and other studies with or without comparative data (8-15).

If blindness is to be minimized or avoided, IMRT is indicated in the definitive or adjuvant RT setting for nasal and paranasal sinus cancers or other sites where the disease is juxtaposed to the optic apparatus. The latter would include diseases such as skin malignancy and sarcomas, in addition to epithelial cancers, since ocular toxicity is often a major barrier to safe treatment planning for lesions in these locations.

Evidence

One retrospective study (9) with comparative data spanning five decades and a recent non-comparative report in paranasal sinus cancer suggesting that blindness can be virtually eliminated, while treatment efficacy seems to be improved (16). Despite the lower quality study design upon which this recommendation is based, this all-or-none outcome is considered clinically compelling and equivalent to what otherwise would be considered the highest and most compelling level of evidence (Level 1) (17).

If osteoradionecrosis is to be minimized or avoided, IMRT is indicated in the definitive or adjuvant RT of tumours in the oral cavity, oropharynx, paranasal sinuses, and nasopharynx where significant doses of RT are required and would be applied to the mandible if 2D EBRT or 3D EBRT were used.

Evidence

One retrospective study (9) with comparative data spanning five decades and two recent reports (18,19) without comparative data.

If treatment-related outcomes (local control, overall survival) are the main outcomes of interest, there are no randomized data to support or refute a recommendation of IMRT over 2D EBRT or 3D EBRT in any head and neck site. However, NPC should ordinarily be treated with IMRT based on treatment-related outcomes as should nasal and paranasal sinus cancer.

Evidence

In the two randomized trials (3,4) addressing nasopharyngeal cancer, locally advanced disease was not included, potentially based on the safety limitations associated with treating such tumours with non-IMRT techniques (as non-IMRT techniques are unable to avoid critical nearby structures). Single institution data (20,21) and numerous similar reports from other institutions (not cited for purposes of brevity) and a multicentre phase II trial report (6) by the Radiation Therapy Oncology Group (RTOG) consistently indicate that local control exceeds 90% in nasopharynx cancer and significantly exceeds the control rates achieved by any group with non-IMRT techniques. One retrospective study (9) with comparative data spanning five decades and a recent non-comparative study (16) both report improved treatment efficacy compared to other reports on patients not treated with IMRT in paranasal sinus cancers.

Key Evidence

A total of 15 papers were included in this systematic review, including four randomized controlled trial (RCT) reports on three RCTs (3-5,22), one prospective cohort study (8), eight retrospective cohort studies (9,10,13-15,23-25), one case-control study (12), and one cross-sectional study (11). Additionally, two prospective non-randomized phase II trials (6,7) performed by the RTOG and reports of dramatically improved locoregional control in nasopharynx cancer, or reduction of significant important toxicity that included blindness in paranasal sinus cancer and osteoradionecrosis in several sites, are also considered. As with the RTOG phase II trials, these reports do not contain comparative data (and therefore, did not meet the inclusion criteria for this review), in part because the centres reporting the results did not treat with non-IMRT techniques. While they are not included in the formal systematic review, the contribution of these reports has shaped the current practice of H&N RT significantly, and they are described in Section 2, Introduction.

Qualifying Statement

The evidence obtained reported predominantly on reductions in late toxicities (specifically, xerostomia, blindness, and osteoradionecrosis of the mandible) that are also important in addressing QoL. Treatment-related outcomes are not convincingly improved, but there is no indication that these outcomes are compromised as a result of IMRT. In general, the trend is toward an improvement in treatment-related outcomes. It should be noted that, in some situations, trials cannot be performed because of the inability to treat disease without danger to critical anatomy where damage could have catastrophic consequences. This is particularly applicable to the treatment of NPC and paranasal sinus cancers.

FUTURE RESEARCH

Controlled clinical trial entry should be encouraged, although accrual and allocation may be challenging due to the certainty of exposing patients to unnecessary harm through normal tissue injury (especially salivary damage) in the head and neck. New studies should focus on additional normal tissue protection, specifically addressing early acute sequelae such as the exclusion of healthy mucosal surfaces from the high-dose volume and potential late-onset toxicities. We do not intend discussing the latter in detail, but their prevention involves swallowing function preservation, middle and inner ear protection (especially in patients receiving concurrent chemotherapy), brachial plexus protection, brain avoidance,

carotid artery avoidance (to minimize stroke risk), and optimizing the efficiency and accuracy of IMRT planning and delivery procedures. The treatment of recurrent H&N cancer is also an important emerging field that often combines the use of IMRT with surgery, chemotherapy, and brachytherapy. In addition, obtaining longer follow-up data should be encouraged.

RELATED GUIDELINES

- Whitton A, Warde P, Sharpe M, Oliver TK, Bak K, Leszczynski K, et al. Organisational standards for the delivery of intensity-modulated radiation therapy in Ontario. Clin Oncol. 2009;21(3):192-203.

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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Evidence-Based Series 21-3-3: Section 2

The Role of IMRT in Head & Neck Cancer: Evidentiary Base

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QUESTIONS

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The outcomes of interest include local control, overall survival, xerostomia, osteoradionecrosis (specifically, mandible), optic nerve preservation, dysphagia, and quality of life.

BACKGROUND

IMRT is a newer method of delivering radiation to target structures that differs from the 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 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 H&N cancer and prostate cancer. This evidence-based series reviews the published comparative evidence between IMRT

and the standard treatment of 2D EBRT in the treatment of H&N cancer to summarize the potential benefits and/or harms of this new technology and to make recommendations for radiation treatment programs considering adopting this technique.

INTRODUCTION

RT, either alone or in combination with surgery or chemotherapy, is commonly used in H&N cancer, but its use is fraught with challenges due to the need for high-dose delivery to treatment targets adjacent to critical structures. Many of these critical structures present absolute barriers to delivering a therapeutic dose of RT using traditional techniques, especially where the disease involves the region of the skull base in close proximity to the spinal cord, brainstem, and optic apparatus. In other situations, significant QoL deficits are anticipated if traditional RT is inadvertently administered to the structures that govern saliva production, taste, oral function, hearing, speech, and pharyngeal function (e.g., swallowing). Theoretically, IMRT is particularly suited to treating H&N cancers, allowing the potential for dose escalation or avoidance of vulnerable anatomy compared with standard RT techniques, with no plausible reason to believe that IMRT would reduce the dose to the tumour or local control.

In this systematic review of the literature, only reports that provided comparative data with sufficient cases were included in the Results section (as outlined in the Methods); however, to ensure that all relevant information was included, a summary of important historical and contemporary non-comparative evidence follows.

2D EBRT Alone or With 3D CRT Boost

While RT alone has shown efficacy in local control for early-stage nasopharyngeal carcinoma (3-9), 2D EBRT was associated with recurrence rates from a low of 16% at five years (10) to a high of 51% for all the years on study (8). Even large experienced centres, such as the Hong Kong study reported by Lee et al (6), achieved local control rates of only 61% in 5,037 patients treated over a 10-year period. Several factors might be contributing to these low reported local control rates, but an inadequate dose to the primary site (5) and the treatment of more advanced stage disease are both associated with recurrence (5,7,8). In a Washington University study, an observation was made that increasing the radiation doses resulted in nasopharynx tumour control in 80% of patients receiving 66 to 70 Gy and in 100% of those receiving over 70 Gy in the T1, T2, and T3 tumours. However, the tumour control rate did not rise above 55% even for doses over 70 Gy in the T4 lesions (7), illustrating the problem of larger more complex lesions being more difficult to treat without the risk of damage to critical structures. That study also reported improvements in tumour control associated with RT quality-assurance initiatives. In one of the previously noted studies (10), 171 consecutive patients were accrued over nine years (1990-1999), and the authors reported a five-year local control rate of 84% but at a cost of higher adverse effects: 44% of these patients had grade 3 xerostomia, 33% had grade 3 dental damage, and 11% had grade 3 hearing loss.

For overall survival, 2D EBRT alone is associated with rates of 48%, 34%, and 18% at five, 10, and 20 years, respectively, as was observed in a series of 378 patients treated between 1954 and 1992 at the MD Anderson Cancer Center (8).

One study (11) performed at Memorial Sloan Kettering, investigating the role of 3D CRT as an RT boost along with 2D EBRT, found no benefit from the addition of conformal radiation, although the authors attributed this to the fact that computerized tomography (CT) planning was used for only a fraction of the total dose administered.

IMRT

Local control rates greater than 90% have been reported in various H&N cancers (in nasopharynx cancer as reported by Sultanem et al (12), by Lee et al (13), and by numerous other centres since), and in oropharyngeal cancer as reported by Eisbruch et al, 2010 (14), as well as others. A study on blindness (15), performed on patients with paranasal sinus tumours at the University of Ghent, reported the virtual elimination of this high-risk adverse effect for these patients. Two reports on osteoradionecrosis (16,17) both reported rates lower than 2% in patients with various H&N cancers. The study on xerostomia (14) reported a grade ≥2 in 55% of patients at six months, but that dropped to 25% and 16% at 12 and 24 months, respectively, in a group of oropharyngeal cancer patients.

Studer et al (18) reported on patients with oral cavity cancer (69% of these patients presented with locally advanced or recurrent lesions) who underwent postoperative or definitive radiation. Their findings were that postoperative IMRT was associated with two-year local control rates of 92% compared to 70%-80% without IMRT. Another study reported by the same authors (19) in a heterogeneous group of H&N cancer patients who received postoperative IMRT found higher rates for local and regional control in patients receiving IMRT compared to a historical 3D EBRT series (postoperative IMRT, two-year local and regional control: 95% versus [vs.] non-IMRT, 82% [altered fractionation] and 68% [conventional fractionation]). In addition, researchers at the University of Ghent (20) reported on a small series of patients with cervical lymph node metastases from unknown primary cancers and compared the results obtained with IMRT against a historical control group treated with 2D EBRT. The findings were that IMRT was associated with lower toxicity than was conventional RT but with similar efficacy. Grade 3 acute dysphagia was significantly lower in the IMRT group compared to the 2D EBRT group (4.5% vs. 50%, p=0.003), and after six months, the grade 3 xerostomia rate was 12% with IMRT vs. 53.4% with 2D EBRT (p=0.03). No grade 3 dysphagia or skin fibrosis was observed after IMRT, but these adverse outcomes were noted after 2D EBRT (27%, p=0.01). These data support the conclusion that IMRT is not inferior to other forms of RT with respect to disease control.

Based on the potential benefits with IMRT suggested by this prior research, a systematic review of the comparative evidence between IMRT and the standard treatment of 2D EBRT was warranted.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (21). 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 (see Appendix 1 for membership) 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 H&N cancer. The body of evidence in this review is primarily comprised of published reports of comparative studies between IMRT and other methods of radiation delivery. 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 RTP are 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.

Literature Search Strategy

The MEDLINE and EMBASE databases were searched for evidence on H&N cancer and IMRT on March 20, 2009. In both databases, keywords for "head cancer" and "neck 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. (See Appendix 2 for the search results.)

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.

Conference proceedings of the annual meetings of the American Society of Radiation Oncology (ASTRO) and the American Society of Clinical Oncology (ASCO) were also searched from the year 2000 to current.

Study Selection Criteria

Inclusion Criteria

All of the following publication types must include comparative data on IMRT versus 2D EBRT and report on at least one of the outcomes of interest, including local control, osteoradionecrosis (specifically, mandible), xerostomia, optic nerve preservation, dysphagia, or QoL.

- CPGs, SRs, HTAs
- Randomized phase II or phase III trials
- Dose escalation studies, toxicity reports, QoL reports, and retrospective studies

In addition, the publications:

- Must 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
- Does not provide comparative data
- Reports on fewer than 50 patients
- Published prior to 2000

Synthesizing the Evidence

No statistical analyses were planned in this systematic review but would be considered if data allow.

RESULTS

Literature Search Results

The MEDLINE and EMBASE searches returned 150 and 159 potential articles, respectively. After removing articles determined to be ineligible based on a title and abstract review, 13 eligible articles were ordered from the MEDLINE results, and two from the EMBASE results (15 articles in total were ordered for full-text review). Of the 15 fully published papers, the two submitted papers, and the two abstracts that were ordered for full-text review, only 10 of the fully published papers were retained (22-31), along with both the author-submitted papers (32,33), and both the abstracts (34,35). One of the abstract reports (34) was an update of a previously published paper (36), and this paper was also obtained for completeness. These 15 papers comprise the evidence in this systematic review. Appendix 3 contains a table of the excluded evidence, including the reasons for exclusion.

Study Design

The 15 papers retained included four randomized controlled trial (RCT) reports on three RCTs (27,34-36), one prospective cohort study (22), eight retrospective cohort studies (23,25,28-33), one case-control study (26), and one cross-sectional study (24). Table 1 details the years on study, the disease site(s), the total number of included patients, and the funding source where reported.

Table 1. Study design of included evidence.

Author, year published	Years on study	Disease Site	Total included n	Sponsorship
Randomized controlled trials				
Kam et al, 2007 (27)	2001-2003	Nasopharyngeal carcinoma	56	Hong Kong Research Grants Council
Kwong et al, 2008 (34) [abstract]	2000-2005	Nasopharyngeal carcinoma	82	Committee on Research and Conference Grants, University of Hong Kong
Nutting et al, 2009 (35) [abstract]	2003-2007	Oropharyngeal, hypopharyngeal	94	NHS (U.K.)
Prospective cohort studies				
Braam et al, 2006 (22)	1996-2005	Oropharyngeal	56	Dutch Cancer Society
Retrospective cohort studies				
Duthoy et al, 2005 (33)	1998-2003	Adenocarcinoma of the ethmoid sinus	58	Belgische Federatie tegen Kanter, University of Ghent
Lee et al, 2006 (28)	1998-2004	Locally advanced oropharyngeal	112	NR
Chen et al, 2007 (32)	1960-2005	Sinonasal carcinoma	127	NR
Fang et al, 2007 (23)	1998-2003	Nasopharyngeal carcinoma	237	NR
Hodge et al, 2007 (25)	1995-2005	Oropharyngeal	195	NR
Rades et al, 2007 (29)	1999-2005	Oropharyngeal, hypopharyngeal, larynx, oral cavity	148	No funding received
Yao et al, 2007 (31)	1997-2005	Oropharyngeal squamous cell carcinoma	53	NIH

Van Rij et al, 2008 (30)	1999-2003	Hypopharyngeal, larynx, nasopharyngeal, oral cavity, oropharyngeal, thyroid, other	163	Netherlands Cancer Institute
Case-control studies				
Jabbari et al, 2005 (26)	1999-2002	Oral tongue, base of tongue, retromolar trigone and alveolar ridge, tonsil, pyriform sinus, supraglottic larynx	40	NIH Duke Family Head and Neck Cancer Research Fund
Cross-sectional studies				
Graff et al, 2007 (24)	2001-2005	Oral cavity, nasopharyngeal-oropharyngeal, hypopharyngeal-larynx	134	French League Against Cancer

Note: NR, not reported; NHS, National Health Services (U.K.); NIH, National Institutes of Health (U.S.).

Table 2 describes 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 the outcomes that were reported.

Table 2. Details of included studies.

Author, year published	Comparison	Dose	Total n	Disease Stage	Median follow-up (months)	Outcomes reported
Randomized controlled trials						
Kam et al, 2007 (27)	IMRT 2D RT	32.2Gy* 61.5Gy*	28 28	T1-2,N0-1,M0	Minimum 1 year	AE
Kwong et al, 2008 (34) [abstract]	IMRT 2D RT	41Gy** 41Gy**	42 40	T2	54	AE
Nutting et al, 2009 (35) [abstract]	IMRT 2D RT	65Gy/2f 65Gy/2f	47 47	T1-4,N0-3,M0	31.9 (IQR: 26.6-38.8)	AE
Prospective cohort studies						
Braam et al, 2006 (22)	IMRT 2D RT	33.7Gy* 48.1Gy*	30 26	T1-4	NR	AE
Retrospective cohort studies						
Duthoy et al, 2005 (33)	IMRT 2D RT 3D CRT	70Gy/2f (60-70) 66Gy/2f (54-66)	28 30	T2-4b T1-4	31 (9-67)	TRO
Lee et al, 2006 (28)	IMRT 2D RT with concomitant boost	70Gy 70Gy	41 71	T3-4	31 (20-64) 46 (3-93)	TRO, AE
Chen et al, 2007 (32)	IMRT	70Gy (66-72)	23	T1-4	44	TRO, AE

	2D RT 3D CRT	63Gy (50-74) 66Gy (50-73)	59 45		52 59	
Fang et al, 2007 (23)	IMRT 2D RT 2D RT plus 3D CRT boost 3D CRT	NR NR NR NR	52 61 91 33	T1-4	NR	QoL
Hodge et al, 2007 (25)	IMRT 3D CRT 2D RT	70Gy (65.1-70.4) 72Gy (60-78) NR	52 41 105	Tis-4,N0-3	23.8 (3-52.9) 54.1 (3.3-165.8)	TRO
Rades et al, 2007 (29)	IMRT 3D CRT 2D RT	52-63Gy 51-60Gy 54-58Gy	18 26 104	T1-4, N0	NR	TRO
Yao et al, 2007 (31)	IMRT 2D RT	54-70Gy/1.8-2f 70Gy/2f	26 27	T1-4	NR	QoL
Van Rij et al, 2008 (30)	IMRT 2D RT	69Gy/2f 70Gy/2f	75 88	T1-4,N0-2,M0	31.2	QoL
Case-control studies						
Jabbari et al, 2005 (26)	IMRT 2D RT	65.3Gy (60-78) 70Gy (63-76.8)	30 10	NR	Minimum one year	AE, QoL
Cross-sectional studies						
Graff et al, 2007 (24)	IMRT 2D RT	Minimum 45Gy all patients	67 67	T1-4,N0-3	Minimum one year	QoL

Note: T, tumour; N, node; M, Metastases; AE, adverse effects; f, fraction; TRO, treatment-related outcomes; NR, not reported; QoL, quality of life; Tis, in situ.
* Mean dose
**Dose to parotid gland

Study Quality: RCTs

The four reports (27,34-36) on the three RCTs obtained were assessed for quality using the following indicators: reporting of randomization details, reporting of blinding details, reporting of analysis details, stating the expected effect size and describing the power calculation, reporting the length of follow-up, and reporting any differences in patient characteristics. The trial by Kam et (27) was well reported, with only blinding details not disclosed. The trials by Kwong et al (34) and Pow et al (36) were also well reported, but the method of randomization and differences in patients characteristics were not disclosed. The abstract report by Nutting et al (35) was less completely reported, disclosing only randomization and median follow-up, and the final paper is awaited. Table 3 describes the components of quality for the RCTs.

Table 3. Study quality: RCTs.

Author, year published	Kam et al, 2007 (27)
Randomization	Performed at the central office of the Comprehensive Cancer Trial Unit, stratified into bilateral or unilateral parotid sparing groups and then randomized to either 2D RT or IMRT.
Blinding	NR
Analysis details	X^2 and the t-test were used to detect any differences in proportion and mean. Paired t-test was used to observe the change in saliva flow-rates over time. Spearman's Rho correlation was used to describe relationships between radiation dose, saliva flow rates, and xerostomia scores. All tests performed were 2 sided with a set level of significance of 5%.
Expected effect size and power calculation details	Powered at 80% to detect a 40% difference in favour of IMRT. An allowance for up to 10% drop-out was added to the final sample size.
Length of follow-up (months)	Minimum one year
Differences in patient characteristics	Patient groups were well-balanced for age, sex, ECOG performance status, parotid gland volume, laterality of sparing, and baseline whole saliva production.
Author, year published	Kwong et al, 2008 (34) [abstract]; Pow et al, 2006 (36)
Randomization	NR
Blinding	Assessors of quality of life were blinded to treatment
Analysis details	Repeated measures ANOVA to compare differences in quality of life and salivary parameters between time points and treatment groups. Univariate measures were used to test within-subjects effects. All tests performed were 2 sided with a set level of significance of 5%.
Expected effect size and power calculation details	Powered at 90% to detect a mean difference as determined by previous research on salivary flow.
Length of follow-up (months)	Minimum one year
Differences in patient characteristics	NR
Author, year published	Nutting et al, 2009 (35) [abstract]
Randomization	Method of randomization NR, but was stratified by tumour site and centre
Blinding	NR
Analysis details	NR
Expected effect size and power calculation details	NR
Length of follow-up (months)	31.9 months median follow-up (IQR: 26.6-38.8)
Differences in patient characteristics	NR

Note: ECOG, Eastern Cooperative Oncology Group; NR, not reported; ANOVA, analysis of variance; IQR, interquartile range.

Study Quality: Non-Randomized Studies

The non-randomized study reports were assessed for quality according to criteria such as the balance between the treatment groups, identification and reporting of differences in baseline prognostic factors between treatment groups, and whether or not any adjustments were made when differences in the baseline prognostic factors were detected. Other variances in study design that could affect the reliability of the study findings were also reported. Of the 12 studies, only five (22,24,30,31,33) included groups with similar patient proportions. Ten of the included studies (22-26,28-32) reported on baseline prognostic factors, and of these ten, four (22,24,30,31) reported significant differences in at least one comparison. Two of the studies (24,30) reported that adjustments were made because of

significant differences in baseline prognostic factors, but two of the studies that did report differences in baseline characteristics did not report any adjustments (22,31). Table 4 describes the components of quality for the non-randomized studies.

Table 4. Study quality: non-randomized studies.

Author, year published	Balance between treatment groups (yes/no: details)	Identification and reporting of differences in baseline prognostic factors between groups (yes/no: details)	Were any adjustments made to account for any differences in baseline prognostics factors if found? (yes/no: details)
Prospective cohort studies			
Braam et al, 2006 (22)	Yes	Yes, but sig. more patients in the 2D RT group received post-op radiation treatment (20 vs. 5; $p<0.005$)	No
Retrospective cohort studies			
Duthoy et al, 2005 (33)	Yes	No	No
Lee et al, 2006 (28)	No, groups were not in balance (71 vs. 41)	Yes, no differences were reported between groups	No, groups were well balanced for baseline prognostic factors
Chen et al, 2007 (32)	No, groups were not in balance (59 vs. 45 vs. 23)	Yes	No
Fang et al, 2007 (23)	No, groups were not in balance (61 vs. 91 vs. 33 vs. 52)	Yes, X^2 test used to analyze baseline prognostic factors	No
Hodge et al, 2007 (25)	No, groups were not in balance (105 vs. 41 vs. 52)	Yes, Pearson's X^2 test used to analyze baseline prognostic factors	No
Rades et al, 2007 (29)	No, groups were not in balance (104 vs. 26 vs. 18)	Yes	No, groups were well balanced for baseline prognostic factors
Yao et al, 2007 (31)	Yes	Yes, sig. differences reported in age, disease stage, and use of concurrent chemotherapy	No
Van Rij et al, 2008 (30)	Yes	Yes, sig. differences reported in nodal status, tumour stage, whether or not chemotherapy was also given, whether surgery was prior to radiotherapy, and questionnaire response time	Yes, adjustments were made due to the identified differences
Case-control studies			
Jabbari et al, 2005 (26)	No, groups were not in balance (30 vs. 10)	Yes, no differences were reported as patients were matched	No, as this was a matched case-control study
Cross-sectional studies			
Graff et al, 2007 (24)	Yes	Yes, sig. differences were reported in gender and employment status	Yes, patients were matched on tumour stage and on the delay between RT and study invitation

Note: 2D RT, two-dimensional radiotherapy; vs., versus; X^2, Chi square.

Outcomes: Treatment Related

Five of the obtained papers reported on treatment-related outcomes (25,28,29,32,33). All were retrospective cohort studies, including a total of 640 patients. None of the studies detected a significant difference between treatment groups (which included 2D RT, 3D CRT, and IMRT) for either local control or overall survival for periods of follow-up between two and five years. Treatment-related outcomes appear in Table 5.

Table 5. Treatment-related outcomes.

Author, year published	Comparison	Local control rates	Overall survival
Retrospective cohort studies			
Duthoy et al, 2005 (33)	IMRT	2 year: 69% 4 year: 63%	2 year: 65% 4 year: 58%
	2D RT 3D CRT	2 year: 70% 4 year: 63% p=0.72	2 year: 83% 4 year: 66% p=0.25
Lee et al, 2006 (28)	IMRT	3 year: 95%	3 year: 91%
	2D RT with concomitant boost	3 year: 85% p=0.17	3 year: 81% p=0.10
Chen et al, 2007 (32)	IMRT	5 year: 65%	5 year: 47%
	2D RT	5 year: 59%	5 year: 51%
	3D CRT	5 year: 62% p>0.05	5 year: 57% p=0.60
Hodge et al, 2007 (25)	IMRT	3 year: 96.1%	NR
	3D CRT	3 year: 78.1%	
	2D RT	3 year: 81.1% p>0.05	
Rades et al, 2007 (29)	IMRT	2 year: 86%	2 year: 89%
	3D CRT	2 year: 80%	2 year: 79%
	2D RT	2 year: 74% p=0.30	2 year: 78% p=0.34

Note: IMRT, intensity-modulated radiotherapy; 2D RT, two-dimensional radiotherapy; 3D CRT, three-dimensional radiotherapy.

Outcomes: Adverse Effects

Seven (22,26-28,32,34,35) of the 10 obtained studies reported on adverse events and included a total of 567 patients. All seven reported on some aspect of xerostomia, but only the retrospective cohort study by Chen et al (32) reported on osteoradionecrosis and optic nerve preservation. None of the obtained studies reported on dysphagia. Of the seven studies reporting on xerostomia outcomes between IMRT and 2D RT, five studies, totalling 400 patients, detected significant benefits in favour of IMRT. However, two of the studies obtained did not report any differences between IMRT and 2D RT for xerostomia, the retrospective cohort study by Chen et al (32), with 127 patients (p=not reported [NR]), and the case-control study by Jabbari et al (26), with 40 patients (p=0.70). For osteoradionecrosis outcomes as reported by Chen et al (32), only IMRT treatment was associated with no events, as both 2D RT and 3D CRT reported 5.5% and 3.9%, respectively. This same study by Chen et

al (32) also reported a significant benefit favouring treatment with IMRT compared with 2D RT or 3D CRT for optic nerve preservation (grade 3 or higher toxicity, IMRT: 0, 2D RT: 20%, 3D CRT: 9%; p=0.01). Table 6 describes the adverse effects reported.

Table 6. Adverse effects.

Author, year published	Comparison	Xerostomia	Osteoradionecrosis	Optic nerve preservation	Dysphagia
Randomized controlled trials					
Kam et al, 2007 (27)	IMRT 2D RT	1 year: 39.3% 1 year: 82.1% p=0.001	NR	NR	NR
Kwong et al, 2008 (34) [abstract]	IMRT 2D RT	1 year: 114%[1] 1 year: 26%[2] 1 year: 0[1] 1 year: 5%[2] p<0.05[1] p<0.05[2]	NR	NR	NR
Nutting et al, 2009 (35) [abstract]	IMRT 2D RT	1 year: 74% 1 year: 40% p=0.005	NR	NR	NR
Prospective cohort studies					
Braam et al, 2006 (22)	IMRT 2D RT	6 month: 56%[3] 6 month: 81%[3] p=0.04	NR	NR	NR
Retrospective cohort studies					
Lee et al, 2006 (28)	IMRT 2D RT with concomitant boost	+20 months: 12% +20 months: 67% p<0.002	NR	NR	NR
Chen et al, 2007 (32)	IMRT 2D RT 3D CRT	Grade 3+: 13% Grade 3+: 17% Grade 3+: 16% p=NR	0 5.5% 3.9%	Grade 3+: 0 Grade 3+: 20% Grade 3+: 9% p=0.01	NR
Case-control studies					
Jabbari et al, 2005 (26)	IMRT 2D RT	2 year: p=0.01[4] 2 year: p=0.53[4] [IMRT vs. 2D RT: p=0.7]	NR	NR	NR

Note: p, probability; NR, not reported; IMRT, intensity-modulated radiotherapy; 2D RT, two-dimensional radiotherapy.
1 stimulated parotid production
2 whole salivary production
3 mean parotid complication rate
4 xerostomia improvement over time (24 month)

Outcomes: Quality of Life

Six of the obtained studies reported on QoL measures (23,24,26,30,31,36): the RCT by Pow et al (36); the three retrospective cohort studies reported by Fang et al (23), Yao et al (31), and Van Rij et al (30); the single case-control study reported by Jabbari et al (26); and the cross-sectional study reported by Graff et al (24). In total, these six studies comprised 672 patients. For the six studies, all but the case-control study reported by Jabbarri et al (26) (with 40 patients and median 12-month Health-Related [HR] QoL Questionnaire results,

p=ns) detected significant benefits in favour of treatment with IMRT. In the RCT reported by Pow et al (36), significant benefits in favour of treatment with IMRT were detected in role-physical, body pain, speech problems, and swallowing indices. The retrospective cohort study reported by Fang et al (23) detected benefits favouring conformal RT over non-conformal RT for 11 of 14 of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 comparisons, with the remaining comparisons being non-significant. This same study also detected significant benefits favouring conformal RT over non-conformal RT for 12 of 13 of the EORTC H&N35 comparisons, with the remaining comparison also being non-significant. The retrospective cohort study reported by Yao et al (31) detected a significant benefit at 12 months favouring IMRT over 2D RT for eating (p=0.007), but the remaining comparisons were all non-significant. The retrospective cohort study reported by van Rij et al (30) detected significant benefits favouring treatment with IMRT in 5 of 8 of the questions related to xerostomia at rest (all but change in saliva amount, problems with gums, and difficulty sleeping due to dry mouth) and 7 of 9 of the questions related to xerostomia while eating (all but solid/grounded/liquid diet and more frequent swallowing), with the remaining comparisons being nonsignificant. The cross-sectional study reported by Graff et al (24) detected significant differences favouring treatment with IMRT for physical function and dyspnea on the EORTC QLQ-C30, and in pain, swallowing, social eating, teeth, opening mouth, dry mouth, and sticky saliva on the EORTC H&N35 scale. Where differences were reported for all the included studies, the benefits were always in favour of treatment with IMRT, with no exceptions. All the included studies reported 100% response rates for the QoL data, except for the study reported by van Rij et al (30), where the IMRT group had a 97% response rate and the 2D EBRT group had a 77% response rate. Table 7 describes the quality of life outcomes reported.

Table 7. Quality of life.

Author, year published	Comparison	Quality of life outcomes
Randomized controlled trials		
Pow et al, 2006 (36)	IMRT vs. 2D RT	12 month EORTC SF-36 Significant differences in favour of IMRT for: Role-physical (p=0.011) Bodily pain (p=0.044) No significant differences for any of the other comparisons EORTC QLQ-C30 For all measures, IMRT was associated with higher functional scores and lower symptom scores (all p=ns) EORTC H&N35 Significant differences were detected in favour of IMRT for: Speech problems (p<0.05) Swallowing (p<0.05)
Retrospective cohort studies		
Fang et al, 2007 (23)	IMRT vs. 2D RT vs. 2D RT plus 3D CRT boost vs. 3D CRT	EORTC QLQ-C30 Conformal RT vs. non-conformal RT: Significant benefits detected for all five functional scales and 6/9 symptom scales (all but constipation, diarrhea, financial problems) in favour of conformal RT

<table>
<tr><td></td><td></td><td>EORTC H&N35
Conformal RT vs. non-conformal RT:
Significant benefits detected for 12 of 13 scales (all but sexuality) in favour of conformal RT

No significant differences were detected for 2D RT vs. 2D RT+3D CRT boost or 3D CRT vs. IMRT.</td></tr>
<tr><td>Yao et al, 2007 (31)</td><td>IMRT vs. 2D RT</td><td>12 month HRQoL<table><tr><td></td><td>IMRT</td><td>2D RT</td><td>p-value</td></tr><tr><td>Eating</td><td>55.4</td><td>39.0</td><td>0.007</td></tr><tr><td>Speech</td><td>83.2</td><td>74.3</td><td>0.059</td></tr><tr><td>Aesthetics</td><td>90.4</td><td>79.3</td><td>0.069</td></tr><tr><td>Social disruption</td><td>86.1</td><td>78.8</td><td>0.115</td></tr></table></td></tr>
<tr><td>Van Rij et al, 2008 (30)</td><td>IMRT vs. 2D RT</td><td>Xerostomia-related quality of life:
Questions related to xerostomia symptoms at rest:
5/8 factors significant benefits in favour of treatment with IMRT, 3/8 no difference (change in saliva amount, problems with gums, difficulty sleeping with a dry mouth)

Questions related to xerostomia symptoms during meals:
7/9 factors significant benefits in favour of treatment with IMRT, 2/9 no difference (solid/grounded/liquid diet, more frequent swallowing)</td></tr>
<tr><td colspan="3">Case-control studies</td></tr>
<tr><td>Jabbari et al, 2005 (26)</td><td>IMRT vs. 2D RT</td><td>Median 12 month HRQoL:
IMRT: 17 (2-67)
2D RT: 68 (7-93)
p>0.05</td></tr>
<tr><td colspan="3">Cross-sectional studies</td></tr>
<tr><td>Graff et al, 2007 (24)</td><td>IMRT vs. 2D RT</td><td>EORTC QLQ-C30
Physical function:
IMRT: 87.1±16.9
2D RT: 78.9±18.7
p=0.01

Dyspnea:
IMRT: 19.4±27.9
2D RT: 31.3±31.4
p=0.01

EORTC H&N35:
Significant differences in favour of treatment with IMRT in pain, swallowing, social eating, teeth, opening mouth, dry mouth, and sticky saliva. The benefits of IMRT were most significant in dry mouth and sticky saliva.</td></tr>
</table>

Note: IMRT, intensity-modulated radiotherapy; 2D RT, two-dimensional radiotherapy; EORTC, European Organization for the Research and Treatment of Cancer; SF-36, 36-item Short Form questionnaire; QLQ-C30, 30-item quality-of-life questionnaire; H&N35, 35-item head and neck questionnaire; HRQoL, Health-related Quality of Life questionnaire.

Ongoing Trials

The U.S. National Institutes of Health online directory of clinical trials (located at http://www.clinicaltrial.gov) was searched on September 21, 2009 for listings of relevant trials. The details of the four relevant trials appear in Table 8.

Table 8. Ongoing trials.

Study of 3-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiotherapy (IMRT) for head and neck squamous cell carcinoma (HNSCC) Phase: Phase II Type: Interventional Status: Ongoing, closed to accrual Age: 18 years to 65 years Sponsor: Tata Memorial Hospital Protocol IDs: H&N_3DCRT_IMRT07, NCT00652613 Description: A phase II study of 3-dimensional conformal radiotherapy (3D CRT) vs. intensity-modulated radiotherapy (IMRT) for squamous cell carcinoma of the head and neck (HNSCC)
IMRT plus cisplatin versus conventional radiotherapy plus cisplatin in stage III-IV HNSCC Phase: Phase III Type: Interventional Status: Open, recruiting Age: 18 years of age+ Sponsor: Groupe Oncologie Radiotherapie Tete et Cou Protocol IDs: GORTEC 2004-01, NCT00158678 Description: A multicentric, randomized, phase III trial comparing intensity-modulated radiotherapy (75 Gy) plus cisplatin versus conventional radiotherapy (70 Gy) plus cisplatin in patients with stage III-IV squamous cell carcinoma of oral cavity, oropharynx or hypopharynx. The main end points are the rate of locoregional control and the rate of xerostomia at 2 years.

DISCUSSION

The case for IMRT in H&N cancer can be broadly outlined as follows:

1) The data identified in this review as well as the earlier historical data described in the Introduction support the contention that IMRT is, at worst, not inferior to 2D CRT with respect to disease control.
2) The data identified in this review as well as the earlier historical data support the contention that with IMRT, there are clinically relevant and statistically significant differences in adverse event rates and QoL compared to 2D CRT.

These two points together provide a compelling justification for the use of IMRT in H&N cancer. This is especially true in the case of the elimination of blindness, as demonstrated in the Chen et al (32) study, where, prior to treatment with IMRT, patients could expect five-year rates of blindness of approximately 20% with 2D EBRT and none with IMRT. This specific result can be considered the equivalent of level 1 evidence (37), in that it does not require a randomized study to demonstrate the complete elimination of an adverse event when there is no plausible reason to suspect inferior efficacy. A similar effect also appears in the context of an apparent dramatic reduction in rates of osteoradionecrosis (16,17,32).

In fact, the definitive early results described in the Introduction explain the lack of randomized data comparing IMRT with 2D EBRT regimens. Once a clear advantage in favour of IMRT was generally accepted in the radiation oncology community, clinical equipoise was no longer considered present, and IMRT came to be considered as the standard of care in jurisdictions where it could be provided. Therefore, the allocation of patients to any non-

IMRT treatment is no longer considered ethical by many radiation oncologists if IMRT can be provided, which means that, in jurisdictions where IMRT capability exists, it is unlikely that there will be further randomized trials of IMRT compared to 2D EBRT.

IMRT is ideally suited to the treatment of H&N cancer. Improved dose conformality allows for the delivery of high doses to target volumes harbouring disease, with sharp dose gradients allowing the protection of adjacent normal structures. The opportunities created by this capability have been outlined earlier and include, in broad terms, protection of normal tissue function, such as salivary function, that was frequently obliterated in regular, traditional head and neck RT practice prior to the advent of IMRT. The disturbance of the integrity of other structures (e.g., mandible, swallowing mechanism, hearing apparatus) can also result from the effects of RT and, to date, some of these have only been partially solved in the nascent period of IMRT introduction.

In truth, these problems and adverse sequelae traditionally resulted in large part from acceptance of the fact that collateral damage to tissues considered of lesser importance from the perspective of a catastrophic event could be considered a reasonable price for a cure when an alternative was not available. In contrast, in some diseases (e.g., NPC) the inability to protect critical normal anatomy where damage would not have been acceptable resulted in deliberate underdosage of the necessary target volume (38). This was also regarded as a reasonable trade off at the time, since not all patients succumbed to disease using 2D EBRT in this setting, but the chance of control was still significantly less than that reported for IMRT-related outcome in this disease (13,39).

With the introduction of IMRT, we now have the capability of addressing what were traditional contradictory goals of ensuring relatively good normal tissue protection, including those tissues traditionally regarded as relatively less important, while disease targets can now be treated adequately without compromise to the most critical normal structures. The latter is best exemplified by diseases in proximity to the skull base and spine.

The studies described in this document cover a wide array of specific sites of cancer in the head and neck but leave some gaps in knowledge of specific, rarer sites. However, given the overall advantages already identified and the fact that all sites in the head and neck face the same issues regarding protection of crucial structures from damage, these data are generalizable to other head and neck sites, and support the use of IMRT over other RT methods in any patient with H&N cancer of any type where RT would be considered valuable.

Despite the intention and purpose of introducing IMRT in H&N cancer, practitioners must be aware of the pitfalls in its use and deployment. Numerous potential problems exist in IMRT planning and delivery and probably reach their zenith in its application in H&N cancer due to the number of anatomic targets to be treated and the variety of critical structures to be protected. One of the most vulnerable elements in the chain is in the design of the treatment target volumes that are entirely dependent on manual delineation by physicians. An appreciation of the behaviour and potential routes of spread of the disease being treated is mandatory for radiation oncologists practicing in this area, as is knowledge of clinical and radiographic anatomy, to avoid a geographic or marginal miss. Collaboration and consultation with other specialist colleagues is essential and should form a regular component of the IMRT-planning process; these colleagues should include diagnostic radiologists in all complex cases, and indeed this process will often enhance the management of less difficult presentations as well. Similar discussions at the RT-contouring workstations are advisable with head and neck surgeons when treating unusually complicated postoperative cases with IMRT. Finally, there should also be a process of consistent quality assurance of target delineation among peers to ensure an ever-present culture of education that includes the use of regimented standards that address disease assessment and target design to avoid inadequate dosimetric consequences to tumour and normal tissue objects at all costs.

Examples of the early implementation problems with IMRT are evident from the pioneering work at the University of Michigan (40,41) when these authors examined the outcome of 80 patients with oropharyngeal cancer treated with IMRT. Although a three-year locoregional control of 94% was obtained, four marginal recurrences became evident after the first analysis of these data, prompting the authors to change their contouring strategy for the nodal clinical target volume. No further marginal recurrences resulted once this change was instituted. In this case, the issue of concern related to the most superior area of the regional nodal volumes. Another report highlighted recurrences in underdosed parotid regional lymph nodes in NPC due to the decision to protect salivary function (42). Here, the authors courageously acknowledged that re-evaluation of the pretreatment imaging revealed the presence of small nonspecific periparotid nodules that showed no hypermetabolic activity on positron emission tomography but still represented culprit targets.

Therefore, if one undertakes head and neck IMRT, the existence of a learning curve that embodies many different diagnostic and treatment domains must be appreciated, and a resolute culture of quality must prevail to ensure that treatment outcome improves as the experience of the team using IMRT increases. Experience in centres with a tradition of delivering head and neck IMRT on a consistent basis indicates that this is achievable provided the necessary investments are made.

CONCLUSIONS

The potential benefits of IMRT for H&N cancer are now well known, and a rapidly expanding literature suggests that IMRT will help to improve disease control and reduce toxicity. Leading this evidence is the undoubted benefit in protecting salivary function throughout virtually all head and neck practice and the ability to deliver adequate doses to RT targets, especially in the vicinity of the skull base, that could not be adequately treated before.

What is needed additionally is the attention to properly designed clinical and technical studies in order to comprehensively deploy and use this complex, emerging treatment strategy. So far, studies have tended to comprise heterogeneous descriptions with respect to the site and stage of the tumour, contain relatively small numbers of patients, and, generally, suffer from short follow-up. IMRT is also significantly more time consuming and complex than conventional RT and requires a complete change in department workflow procedures to permit its efficient deployment for H&N cancer treatment. Due to the complexity of the different elements and tasks, requirements would probably be achieved most reliably in institutions having a significant focus on quality and training so that IMRT is provided to H&N cancer patients in the safest manner possible.

CONFLICT OF INTEREST

None declared.

JOURNAL REFERENCE

The following article has been published in *Clinical **Oncology*** (Crown Copyright © 2012 Published by Elsevier Ltd on behalf of The Royal College of Radiologists; http://www.journals.elsevier.com/clinical-oncology/).

- O'Sullivan B, Rumble RB, Warde P; Members of the IMRT Indications Expert Panel. Intensity-modulated radiotherapy in the treatment of head and neck cancer. Clin Oncol. 2012;24:474-87. doi:10.1016/j.clon.2012.05.006.

ACKNOWLEDGEMENTS

The IMRT Indications Expert Panel would like to thank Dr. Brian O'Sullivan and Mr. R. Bryan Rumble for taking the lead in drafting this systematic review.

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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Appendix 1. Members of the IMRT Indications Expert Panel and the Head & Neck Cancer Working Group.

Steering Panel

Dr. Padraig Warde Provincial Head, Radiation Treatment Program, Cancer Care Ontario
Mr. Eric Gutierrez Program Manager, Radiation Treatment Program, Cancer Care Ontario
Ms. Kate Bak Project Coordinator, Radiation Treatment Program, Cancer Care Ontario
Mr. Bryan Rumble Research Coordinator, Program in Evidence-Based Care, Cancer Care Ontario

Expert Panel

Dr. Anthony Whitton Radiation Treatment Program, Cancer Care Ontario
Ms. Sarah Etheridge Radiation Therapy Representative, Peel Regional Cancer Program
Ms. Lisa Favell Capital Project Representative, Cancer Care Ontario
Ms. Katrina Fleming Radiation Therapy Representative, Grand River Regional Cancer Centre
Ms. Esther Green Chief Nursing Officer and Director of Health Human Resource Planning, Cancer Care Ontario
Dr. Konrad Leszczynski Physics Representative, Northeastern Ontario Regional Cancer Centre
Dr. Michael Sharpe Physics Representative, Princess Margaret Hospital

Working Group

Dr. Brian O'Sullivan Radiation Oncologist, Head and Neck Cancer Program Leader, Princess Margaret Hospital Professor, Department of Radiation Oncology, University of Toronto

Appendix 2. Literature search strategies.

Database: Ovid MEDLINE(R) <1996 to March Week 2 2009>

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1 exp "Head and Neck Neoplasms"/ (79466)
2 imrt.mp. or exp Radiotherapy, Intensity-Modulated/ (2549)
3 brachytherapy.mp. or exp Brachytherapy/ (8490)
4 exp Protons/ or proton therapy.mp. (11375)
5 biological marker.mp. or exp Biological Markers/ (308241)
6 gene therapy.mp. or exp Gene Therapy/ (32926)
7 children.mp. or exp Child/ (529379)
8 pediatric cancer.mp. (657)
9 childhood cancer.mp. (1926)
10 exp Quality Assurance, Health Care/ or quality assurance.mp. (136493)
11 treatment plan comparison.mp. (5)
12 aperture optimization.mp. (27)
13 independent dose calculation.mp. (13)
14 EPID dosimetry.mp. (13)
15 set up errors.mp. (85)
16 planning.mp. (80527)
17 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 or 16 (1059158)
18 1 and 2 (660)
19 1 and 17 (15662)
20 18 not 19 (173)
21 limit 20 to (english language and humans and yr="2000 - 2009") (150)
22 from 21 keep 1-150 (150)

Database: EMBASE <1996 to 2009 Week 11>

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1 head cancer.mp. or exp Head Cancer/ (964)
2 neck cancer.mp. or exp Neck Cancer/ (12573)
3 1 or 2 (12732)
4 imrt.mp. or exp Intensity Modulated Radiation Therapy/ (3312)
5 brachytherapy.mp. or exp Brachytherapy/ (10760)
6 proton therapy.mp. or exp Proton Therapy/ (680)
7 biological marker.mp. or exp Biological Marker/ (31873)
8 gene therapy.mp. or exp Gene Therapy/ (34502)
9 child/ or child.mp. or children.mp. (457760)
10 childhood cancer.mp. or exp Childhood Cancer/ (10051)
11 quality assurance.mp. or exp Quality Control/ (110835)
12 treatment plan comparison.mp. (5)
13 aperture optimization.mp. (28)
14 independent dose calculation.mp. (12)
15 EPID dosimetry.mp. (14)
16 set up errors.mp. (88)
17 exp Planning/ or planning.mp. (125942)
18 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (743702)
19 3 and 4 (506)
20 3 and 18 (2219)
21 19 not 20 (180)
22 limit 21 to (human and english language and yr="2000 - 2009") (159)
23 from 22 keep 1-159 (159)

Appendix 3. Excluded papers (n=5).

Title	Reason(s) for exclusion
Retrospective cohort studies	
Gomez D, Hoppe B, Wolden S, Zhung J, Patel S, Kraus D, et al. Outcomes and prognostic variables in adenoid cystic carcinoma of the head and neck: a recent experience. Int J Radiat Oncol Biol Phys. 2008;70(5):1365-72.	No comparative data provided
Kent ML, Brennan MT, Noll JL, Fox PC, Burri SH, Hunter JC, et al. Radiation-induced trismus in head and neck cancer patients. Support Care Cancer. 2008;16:305-9.	No outcomes of interest reported on
Munter MW, Hoffner S, Hof H, Herfarth KK, Haberkorn U, Rudat V, et al. Changes in salivary gland function after radiotherapy of head and neck tumors measured by quantitative pertechnetate scintigraphy: comparison of intensity-modulated radiotherapy and conventional radiation therapy with and without amifostine. Int J Radiat Oncol Biol Phys. 2007;67(3):651-9.	No outcomes of interest reported on
Rudat V, Munter M, Rades D, Grotz KA, Bajrovic A, Haberkorn U, et al. The effect of amifostine or IMRT to preserve the parotid function after radiotherapy of the head and neck region measured by quantitive salivary gland scintigraphy. Radiother Oncol. 2008;89:71-80.	No outcomes of interest reported on
Case-series	
Madani I, Bonte K, Vakaet L, Boterberg T, and De Neve W. Intensity-modulated radiotherapy for sinonasal tumors: Ghent University Hospital update. Int J Radiat Oncol Biol Phys. 2009;73(2):424-32.	No comparative data provided

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program in evidence-based care | programme de soins fondé sur des preuves

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

The Role of IMRT in Head & Neck Cancer: EBS Development Methods and External Review Process

B. O'Sullivan, 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: January 12, 2011

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/Radiation Treatment Program (RTP). The series is a convenient and up-to-date source of the best available evidence on the role of IMRT in H&N 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 H&N cancers guideline was presented to the Expert Panel members (N=26), 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?					
Response	Yes	No	Unsure	TOTALS	Missing
n	8	18	0	26	0
%	30.8	69.2	0	100	0

Rate the overall quality of the guideline report.							
Response	1.Lowest	2.	3.	4.	5.Highest	TOTALS	Missing
n	0	0	0	8	17	25	1
%	0	0	0	32	68	100	3.8

I would make use of this guideline in my professional decisions.							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
n	0	1	0	1	21	23	3
%	0	4.4	0	4.4	91	99.8	11.5

I would recommend this guideline for use in practice.							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
n	0	1	0	4	21	26	0
%	0	3.8	0	15.4	80.8	100	0

RECOMMENDATIONS

1. If xerostomia and quality of life are the main outcomes of interest, then IMRT is the recommended treatment for all nasopharyngeal, oropharyngeal, hypopharyngeal, laryngeal, oral cavity and unknown primary cancers where lymph node regions requiring inclusion in the treatment volume would result in irreparable damage to salivary function if 2D EBRT or 3D EBRT were used due to their inability to maintain salivary doses within their tolerance limits (<26 Gy mean dose). The data provided are applicable to locally advanced disease but are equally applicable to early stage disease

and rare sites (e.g. salivary gland tumours) requiring radiotherapy that would otherwise damage these normal structures.							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
n	0	0	0	6	20	26	0
%	0	0	0	23.1	76.9	100	0

Do you agree with this Recommendation?					
Response	Yes	No	Unsure	TOTALS	Missing
n	22	1	3	26	0
%	84.6	3.9	11.5	100	0

2. If blindness is to be minimized or avoided, IMRT is indicated in the definitive or adjuvant radiotherapy setting for nasal and paranasal sinus cancers or other sites where disease is juxtaposed to the optic apparatus.							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
n	0	0	1	4	21	26	0
%	0	0	3.8	15.4	80.8	100	0

Do you agree with this Recommendation?					
Response	Yes	No	Unsure	TOTALS	Missing
n	22	1	3	26	0
%	84.6	3.9	11.5	100	0

3. If osteoradionecrosis is to be minimized or avoided, IMRT is indicated in the definitive or adjuvant radiotherapy of tumours in the oral cavity, oropharynx, paranasal sinuses, and nasopharynx where significant doses of radiotherapy are required and would be applied to the mandible if 2D EBRT or 3D EBRT were used.							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
n	0	0	1	5	20	26	0
%	0	0	3.9	19.2	76.9	100	0

Do you agree with this Recommendation?					
Response	Yes	No	Unsure	TOTALS	Missing
n	23	0	3	26	0
%	88.5	0	11.5	100	0

4. If treatment-related outcomes are the main outcomes of interest, there are no randomised data to support or refute a recommendation of IMRT over 2D EBRT or 3D EBRT in any head and neck site. However, nasopharyngeal cancer should ordinarily be treated with IMRT based on treatment-related outcome as should nasal and paranasal sinus cancer.							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
n	0	0	0	12	14	26	0
%	0	0	0	46.1	53.9	100	0

Do you agree with this Recommendation?					
Response	Yes	No	Unsure	TOTALS	Missing
n	23	0	3	26	0
%	88.5	0	11.5	100	0

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?
• Consider adding commentary to Section 2 that includes treatment delivery efficiency of H&N IMRT as well as elimination of a known failure mode/weakness of 2D/3D EBRT (field match failures) with H&N IMRT.
Comments Recommendation One:
• More explicit statement in introduction as to historical rates of these complications of local failure with non-IMRT techniques. • Make the recommendation stronger (Change to "recommended").
Comments Recommendation Two:
• Add in a more explicit statement in the Introduction as to historical rates of these complications of local failure with non-IMRT techniques. • Make the recommendation stronger (Change to "recommended").
Comments Recommendation Three:
• The recommendation should not extend it to other sites unless evidence is present. • Make the recommendation stronger (Change to "recommended").
Comments Recommendation Four:
• Make the recommendation stronger (Change to "recommended").
Other Comments:
• None obtained.

Report Approval Panel

Following the presentation of this EBS draft report for Expert Panel review, the report was submitted on June 15, 2010 to the PEBC Report Approval Panel (RAP) for review. The RAP is comprised of two members, including an oncologist, with expertise in clinical and methodological issues.

Key issues raised by the RAP included:

1. There is a large amount of selected non-comparative evidence in the Introduction that was not included in the Results section. Considering the volume of relevant comparative evidence that was included in the Results section, this material does not significantly add to the document and raises questions regarding how it was selected, and should either be removed or included with the Results following a proper quality appraisal.
2. Considering the outcomes of interest, and the limitations of the RCT evidence available, the lack of cohort studies, case series, and studies demonstrating the biological effectiveness of IMRT in this setting was questioned.
3. As this guideline is intended to cover the use of IMRT in all H&N sites, but the evidence was separated by type and location, a discussion on the generalizability of results should be added.
4. More information needs to be given on the studies that reported on QoL as a major outcome.
5. It was suggested that a meta-analysis of the non-randomized data be included.

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

1. The majority of this material was either removed or collapsed into part of the historical narrative in the Introduction section.
2. As determined in the initial planning stages, the intent was to only look at comparative evidence.
3. The generalizability of IMRT to the H&N site along with relevant limitations now appears in the revised Discussion section.

4. Response rates and other relevant outcomes are now reported with the QoL data.
5. The lead author did not see the merit of performing a meta-analysis when there was no ambiguity of the results.

In addition to the above major points, various minor editing changes were made throughout the document.

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 14 submitted responses (11% response rate) were received. Results are as follows:

1. Rate the overall quality of the guideline report							
Response	1. Lowest	2.	3.	4.	5. Highest	TOTALS	Missing
n	0	0	1	6	7	14	0
%	0	0	7	43	50	100	0
2. I would make use of this guideline in my professional decisions							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
n	0	0	1	6	7	14	0
%	0	0	7	43	50	100	0
3. I would recommend this guideline for use in practice							
Response	1.Strongly disagree	2.	3.	4.	5.Strongly agree	TOTALS	Missing
n	0	0	1	5	8	14	0
%	0	0	7	36	57	100	0

4. What are the barriers or enablers to the implementation of this guideline report?

   Barriers:
   - Infrastructure costs and expertise in utilizing these new technologies.
   - Linac wait times.
   - Shortage of physicists and dosimetrists.

   Enablers:
   - CCO initiatives for mentorship.
   - IMRT sponsored educational activities.

5. Additional comments.

   No additional comments were received.

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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