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Practice Guideline Report 5-6b EDUCATION AND INFORMATION 2012

Hyperfractionated Radiotherapy for Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Report Date: January 2003

An assessment conducted in December 2012 put Evidence-based Series (EBS) 5-6b in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

PG 5-6b consists of a Summary and a Full Report and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Head and Neck Cancer Disease Site Group page at:
https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/head-neck-ebs/

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/
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Cancer Care Ontario Practice Guidelines Initiative

Sponsored by: Cancer Care Ontario
Ontario Ministry of Health and Long-Term Care

Hyperfractionated Radiotherapy for Locally Advanced Squamous Cell Carcinoma of the Head and Neck

Practice Guideline Report #5-6b

ORIGINAL GUIDELINE: November 27, 2000
MOST RECENT LITERATURE SEARCH: January 2003
NEW EVIDENCE ADDED TO GUIDELINE REPORT: January 2003

New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

SUMMARY

Guideline Questions
Does hyperfractionated radiotherapy improve loco-regional control or survival compared with conventionally fractionated radiotherapy in patients with newly diagnosed, locally advanced (stage III-IV) squamous cell carcinoma of the head and neck who are deemed suitable for radiotherapy with curative intent? What is the toxicity associated with hyperfractionation? Can these novel regimens enhance the therapeutic ratio comparing benefits to toxicity?

Target Population
These recommendations apply to adult patients with newly diagnosed, locally advanced (stage III-IV) squamous cell carcinoma of the head and neck who are deemed suitable for radical radiotherapy with curative intent.

Recommendations

Key Recommendations

- This group of patients should be considered for concomitant chemotherapy and conventional radiotherapy as recommended in Cancer Care Ontario Practice Guidelines Initiative guideline #5-6a.
- Hyperfractionated radiotherapy cannot be recommended as routine clinical practice at this time.

Qualifying Statement

- Although the improvements in loco-regional control and survival are promising, longer

follow-up and more complete information on late complications will be needed to meaningfully compare these results to those achieved with concomitant chemoradiation in locally advanced SCCHN.

Methods

The literature was searched using MEDLINE (1966 through January 2003), CANCERLIT (1983 through October 2002), the Cochrane Library (Issue 4, 2002), the Physician Data Query database, the Canadian Medical Association Infobase, the National Guideline Clearinghouse, and abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1997-2002), and the American Society for Therapeutic Radiology and Oncology (1999-2002). Article bibliographies and personal files were also searched to January 2003 for evidence relevant to this practice-guideline-in-progress report.

Evidence was selected and reviewed by two members of the Cancer Care Ontario Practice Guidelines Initiative's Head and Neck Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Head and Neck Cancer Disease Site Group, which comprises medical and radiation oncologists, surgeons, and a community representative.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee. The Cancer Care Ontario Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This process consists of a periodic review and evaluation of the scientific literature and, where appropriate, the integration of this literature with the original guideline information.

Key Evidence

- Hyperfractionated radiotherapy (multiple fractions per day) yields higher rates of acute toxicity compared with conventional radiotherapy (one fraction per day, five days per week).
- Data on the incidence and severity of late complications associated with hyperfractionation are incomplete. It is premature to conclude that hyperfractionation with dose escalation does not increase late tissue complications.
- Conclusions regarding loco-regional control are limited by the quality of the published data. To date, only three of seven randomized controlled trials have provided convincing evidence of improved loco-regional control with hyperfractionation compared with conventional radiotherapy. In one of these three studies, improved loco-regional control was accompanied by an increase in overall survival. Two other randomized controlled trials have documented improved overall survival with hyperfractionation, but both studies have been criticized for failing to report complete data.

Related Guidelines

- Please refer to companion guidelines on concomitant chemotherapy and radiotherapy (#5-6a) and accelerated radiotherapy (#5-6c) in locally advanced (stage III-IV) squamous cell carcinoma of the head and neck.

Prepared by the Head and Neck Cancer Disease Site Group

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PREAMBLE: About Our Practice Guideline Reports

The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) is a project supported by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by Disease Site Groups of the CCOPGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are a convenient and up-to-date source of the best available evidence on a clinical topic, developed through systematic reviews, evidence synthesis and input from a broad community of practitioners.

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

The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This includes a regular review and evaluation of the scientific literature and, where appropriate, integration with the original guideline report.

Reference:

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
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Disclaimer

Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgement in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation nor warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

FULL REPORT

I. QUESTIONS

Does hyperfractionated radiotherapy improve loco-regional control or survival compared with conventionally fractionated radiotherapy in patients with newly diagnosed, locally advanced (stage III-IV) squamous cell carcinoma of the head and neck (SCCHN) who are deemed suitable for radiotherapy with curative intent? What is the toxicity associated with hyperfractionation? Can these novel regimens enhance the therapeutic ratio comparing benefits to toxicity?

II. CHOICE OF TOPIC AND RATIONALE

Conventional fractionation of the radiotherapy treatment schedule yields suboptimal results in patients with newly diagnosed, locally advanced squamous cell carcinoma of the head and neck when used as the definitive modality with curative intent. Published rates of local control range from 5% to 64%. The reported overall five-year survival rate seldom exceeds 40% (1).

Conventionally fractionated radiotherapy regimens have been empirically derived. They are based on clinical observations of acceptable levels of acute and chronic adverse effects on normal tissue for daily fractions of approximately 180 to 250 cGy, five days per week, to total doses of 50 to 70 Gy over four to seven weeks.

Prompted by radiobiologic observations and preclinical experimental results, there has been increasing interest in the potential benefits of altered fractionation. This guideline report will present the results achieved with hyperfractionation.

Over the course of the development of the practice guideline below, there been a noticeable increase in the clinical dissatisfaction with the results of standard management that includes standard fractionation of the radiotherapy in the treatment of advanced head and neck cancer. In many places in Canada and North America, current practice has now changed, generally to concomitant chemo-radiotherapy. Some institutions and research agencies are continuing to investigate the results of acceleration of the radiation course. The Cancer Care Ontario Practice Guideline Initiative (CCOPGI) Head and Neck Disease Site Group considers that future research efforts for this group of patients should concentrate on altered fractionation with and without chemotherapy versus concomitant chemotherapy and conventional radiation.

Hyperfractionation

In contrast to conventional radiotherapy, hyperfractionated protocols deliver a higher total dose using multiple fractions per day and smaller doses per fraction over the same overall treatment time. The rationale for hyperfractionation is based on the observation that late responding tissues are more sensitive to changes in dose per fraction than early responding tissues (2). As a result, decreasing the dose per fraction could be expected to decrease the incidence of late complications. Because squamous cell carcinomas of the head and neck behave like early responding tissues, this observation permits dose escalation using small fractions without increasing the risk of late toxicity. The use of small fractions with short inter-fraction intervals may also influence cell cycle redistribution (3) and re-oxygenation of tumour clonogens (4), but the experimental evidence for these claims is not as convincing.

Most hyperfractionation regimens are based on small fractions of 1.0 to 1.2 Gy delivered twice daily (BID) or three times daily (TID). An example is 80.5 Gy delivered as 1.15 Gy BID in 70 fractions over seven weeks, which is the regimen used in the European Organization for Research and Treatment of Cancer (EORTC) trial 22791 (5).

Interfraction Interval

Repair of sub-lethal damage is slower in most late responding tissues than in early responding

tissues (6). In practice, this means that the interval between multiple daily fractions must be sufficiently long to permit normal tissue recovery. Sequential studies by the Radiation Therapy Oncology Group (RTOG) have suggested that the interfraction interval should be no less than six hours (7). For a critical structure like the spinal cord, which is characterized by a relatively slow rate of sublethal damage repair, the interval should be at least eight hours.

Therapeutic Index

The therapeutic index is defined as the ratio of tumour control to treatment toxicity. A meaningful improvement in the therapeutic index in SCCHN requires an improvement in tumour control with either no increase or a minimal increase in toxicity. Given the transient and manageable nature of most acute reactions, the evaluation of toxicity has focused on the chronic permanent side effects of treatment. Unfortunately, late adverse effects are difficult to evaluate and are poorly reported in most trials.

Given that most regimens involving multiple daily fractions are resource intensive and more complex to schedule, a convincing increase in the therapeutic index will probably be necessary before altered fractionation replaces conventional fractionation in the treatment of SCCHN.

III. METHODS

Guideline Development

This guideline was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) using the methodology of the Practice Guidelines Development Cycle (8). Evidence was selected and reviewed by two members of the CCOPGI's Head and Neck Cancer Disease Site Group (DSG) and methodologists. This guideline is a convenient and up-to-date source of the best available evidence on hyperfractionated radiotherapy for locally advanced SCCHN, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. It is intended to enable evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Practitioner feedback was obtained through a mailed survey consisting of items asking for ratings on the quality of the draft practice guideline, and whether the draft recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC). The CCOPGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Literature Search Strategy

MEDLINE (1966 to November 2000), CANCERLIT (1983 to September 2000) and the Cochrane Library (Issue 3, 2000) were searched with no language restrictions. "Head and neck neoplasms" (Medical Subject Heading [MeSH]) and "carcinoma, squamous cell" (MeSH) were combined with "fractionation" (MeSH), "dose fractionation" (MeSH), "radiotherapy dosage" (MeSH) and "hyperfraction:" used as a text word. These terms were then combined with the search terms for the following study designs or publication types: practice guidelines, meta-analyses, randomized controlled trials. The citation lists of all retrieved articles were reviewed to identify additional trials. The proceedings of the 1999 and 2000 annual meetings of the American Society of Clinical Oncology (ASCO) and the 1999 annual meeting of the American Society for Therapeutic Radiology and Oncology (ASTRO) were searched for reports of new trials. On-going trials were identified through the Physician Data Query (PDQ) clinical trials database (http://cnetdb.nci.nih.gov/trialsrch.shtml).

Update
The original literature search has been updated using MEDLINE (through January 2003), CANCERLIT (through October 2002), the Cochrane Library (Issue 4, 2002), the Physician Data Query database, the Canadian Medical Association Infobase, the National Guideline Clearinghouse, and abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2001,2002), and the American Society for Therapeutic Radiology and Oncology (2000-2002).

Inclusion Criteria
The systematic review was limited to randomized trials and meta-analyses of randomized trials that compared hyperfractionated radiotherapy with a control arm using conventional radiotherapy (daily Monday to Friday). Three-arm trials investigating the addition of chemotherapy or radiosensitizers were included if there was a comparison of hyperfractionated radiotherapy versus conventional treatment and relevant and complete information could be extracted. Overall survival and loco-regional control were the primary outcomes of interest. Change in the therapeutic ratio comparing benefits to toxicity was also considered.

Synthesizing the Evidence
Pooling of data was not attempted because of the small number of trials with complete information and the methodological problems inherent in several of the studies. Of the seven randomized controlled trials comparing hyperfractionation with conventional fractionation (5,9-14), two trials have been reported only in abstract form (10,13), two trials (10,11) did not report whether or not prognostic factors were balanced between treatment groups and one trial (11) included results for only the complete responders. In another trial (9), the total dose in the hyperfractionated radiotherapy arm was not higher than in the conventional radiotherapy arm. No data on overall survival were reported for one trial (10). Data on rates of acute and late toxicity were also not reported for this trial (10). Reports of two other trials (12,13) did not include data on late complication rates. This left two studies (EORTC trial 22791 (5) and RTOG trial 9003 (14)) which were fully published with mature follow-up, delivered an increase in total dose in the hyperfractionated radiotherapy arm compared with the conventional therapy arm, and reported data on survival, loco-regional control and acute and late adverse effects.

IV. RESULTS

Literature Search Results
Seven randomized controlled trials (two reported in abstract form) of hyperfractionated radiotherapy compared with conventional radiotherapy met the inclusion criteria (5,9-14) (Table 1). Data on loco-regional response, loco-regional control and survival are summarized in Table 2. The four-arm RTOG trial 9003 (14) deserves special consideration because of the simultaneous comparison of accelerated, hyperfractionated and conventionally fractionated regimens (Table 3).

The results of a published meta-analysis of randomized controlled trials of hyperfractionated radiotherapy (15) are included in this report, but this pooled analysis was weakened by the methodological problems inherent in several of the studies. Of note, the data on mortality and relapse-free survival from one of the trials included in the pooled analysis pertained to only the complete responders (11).

Update
Since the original guideline was completed in November 2000, limited evidence has become available from two meeting abstracts (1u,2u) and one published report (3u).

An abstract by Bourhis et al for the 2002 ASTRO meeting presented results of a relevant

individual-patient-data meta-analysis, but it is unclear which randomized trials were included in the analysis of hyperfractionated versus conventional radiotherapy. Confidence limits on the hazard ratios for death (0.78) and loco-regional failure (0.76) were not reported (1u).

Another ASTRO abstract provided additional information about the RTOG 90-03 trial included in the original guideline report (14). Fisher et al reported that quality of life was "related to the intensity of RT" but did not provide any data (2u).

One additional randomized trial has been published since completion of the original guideline. Bartelink et al (3u) reported loco-regional control, survival and toxicity data from a randomized phase II trial that compared conventional and hyperfractionated radiotherapy, both of which were given with concomitant cisplatin. This was a small trial (N=53) that was designed to assess the feasibility of hyperfractionated radiotherapy (three fractions per day of 1.6 Gy each during weeks 1, 4 and 7, total dose 72 Gy) plus 10 mg/m^2 of cisplatin given between the first and second radiotherapy sessions, rather than the effect of hyperfractionation on clinical outcomes.

Table 1. Randomized controlled trials of hyperfractionated versus conventional radiotherapy in locally advanced squamous cell carcinoma of the head and neck.

Study Year (Reference)	Site (n)	Stage* (n)	# Randomized (# Analyzed)	Treatment Groups	Follow-up
RTOG 79-13/ Marcial et al 1987 (9)	Oropharynx (87) Hypopharynx (30) Oral cavity (28) Nasopharynx (15) Supraglottic larynx (15) Glottic larynx (5) Sinuses (7)	T1 (8) T2 (27) T3 (83) T4 (69) N0 (54) N1 (32) N2 (42) N3 (59)	210 (187)	Cfx (n=93): 66-73.8 Gy in 33-41 fractions over 7-8 weeks Hfx (n=94): 60 Gy in 2 fractions of 1.2 Gy per day over 5 weeks	Appears to be 2-6 years (survival curves to 30 months)
Datta et al 1989 (10) ABSTRACT	NR	NR but included T2 T3 N0 N1	212 (176)	Cfx(n=85): 66 Gy in 33 fractions over 6½ weeks Hfx(91): 79.2 Gy in 2 fractions of 1.2 Gy per day over 6½ weeks	2 years
Sanchiz et al 1990 (11)	Larynx (203) Oral cavity (175) Hypopharynx (73) Nasopharynx (57) Other (51)	T3 (350) T4 (209) N0 (138) N1 (33) N2 (205) N3 (183)	586 (559)	Cfx (n=277): 60 Gy in 30 fractions over 6 weeks Hfx (n=282): 70.4 Gy in 2 fractions of 1.1 Gy per day over 6.4 weeks (a third arm received Cfx plus 5-fluorouracil)	Range: 1-10 years
Pinto et al 1991 (12)	Oropharynx: -base of tongue (28) -other sites (70)	T1/T2 (14) T3 (78) T4 (6) N0/N1 (49) N2 (24) N3 (25) Stage III (46) Stage IV (52)	112 (98)	Cfx (n=48): 66 Gy in 33 fractions over 6½ weeks Hfx (n=50): 70.4 Gy in 2 fractions of 1.1 Gy per day over 6½ weeks	Median: 25 months Range: 7-42 months
EORTC 22791/ Horiot et al 1992 (5)	Oropharynx (lesions arising from base of tongue excluded)	T2N0 (143) T2N1 (69) T3N0 (52) T3N1 (61) (N1: < 3 cm)	356 (325)	Cfx (n=176): 70 Gy in 35 fractions over 7 weeks Hfx (n=180): 80.5 Gy in 2 fractions of 1.15 Gy per day over 7 weeks	Range: 4-8 years
Cummings et al 2000 (13) ABSTRACT	Oropharynx (138) Larynx (133) Hypopharynx (65)	T1 (22) T2 (72) T3 (13) T4 (109) N0 (127) N1 (74) N2 (117) N3 (18)	336 (331)	Cfx: 51 Gy in 20 fractions over 4 weeks Hfx: 58 Gy in 2 fractions of 1.45 Gy per day over 4 weeks	NR

RTOG 9003/ Fu et al 2000 (14)	Oral cavity (110) Oropharynx (649) Hypopharynx (141) Supraglottic larynx (173)	T1 (64) T2 (288) T3 (406) T4 (315) N0 (239) N1 (214) N2 (494) N3 (126)	1113 (1073)	Cfx (n=268): 70 Gy in 35 fractions over 7 weeks Hfx (n=263): 81.6 Gy in 2 fractions of 1.2 Gy per day over 7 weeks Afx-s (n=274): 67.2 Gy in 42 fractions over 6 weeks with 2-week rest after 38.4 Gy Afx-c (n=268): 72 Gy in 42 fractions over 6 weeks with 1.8 Gy fractions per day to large field plus 1.5 Gy per day to boost field for last 12 treatment days	Median: 41.2 months

Note: Afx-c, accelerated fractionation using a concomitant boost; Afx-s, accelerated fractionation with split course; Cfx, conventional fractionation; Hfx, hyperfractionation; NR, not reported.
*Marcial et al used American Joint Commission on Cancer (AJCC) staging criteria and Sanchiz et al and Pinto et al used the 1978 International Union Against Cancer (UICC) staging criteria.

Table 2. Results of randomized controlled trials of hyperfractionated versus conventional radiotherapy in locally advanced squamous cell carcinoma of the head and neck.

Study (Reference)	Loco-regional Response		Loco-regional Control at 5 years		Overall Survival (median)	
	Cfx	Hfx	Cfx	Hfx	Cfx	Hfx
RTOG 79-13/ Marcial et al 1987 (9)	55%	52%	NR (29% at 2 years)	NR (30% at 2 years)	11 months*	13 months*
Datta et al 1989 (10)	72.9%	85.7%	NR (32.9% at 2 years)	NR (62.7% at 2 years)	NR	NR
			p<0.02			
Sanchiz et al 1990 (11)	67.8% (188/277)	90% (254/282)	22%* †	47%* †	3.2 years*	7 years*
			p<0.001 (data reported only for complete responders)		p<0.001 (data reported only for complete responders)	
Pinto et al 1991 (12)	52% (25/48)	62% (31/50)	NR (relapse-free survival‡ was 20% at 2 years*)	NR (relapse-free survival ‡ was 30% at 2 years*)	13.5 months*	21 months*
			p=0.079		p=0.03	
EORTC 22791/ Horiot et al 1992 (5)	86%	86%	40%	59%	2.5 years*	3 years*
			p=0.02			
Cummings et al 2000 (13)	NR	NR	37%	45%	NR (30% at 5 years)	NR (40% at 5 years)
			p=0.010		p=0.013	
RTOG 9003/ Fu et al 2000 (14)	NR	NR	NR (46% at 2 years)	NR (54.4% at 2 years)	NR (46.1% at 2 years)	54.5% at 2 years)
			p=0.045		p>0.05	

Note: Cfx, conventional radiotherapy; Hfx, hyperfractionated radiotherapy; NR, not reported.
* Calculated from survival curves.
† Estimated loco-regional control rates were 14.4% with conventional radiotherapy versus 41.5% with hyperfractionated radiotherapy when calculated using data on progression-free survival adjusted to take into account the missing data on the non-responders.
‡ It was unclear if relapse-free survival included both loco-regional and distant failures. However, one of the objectives of the trial was to determine the efficacy of hyperfractionated radiotherapy by comparing the rate of loco-regional control between the treatment groups, and only relapse-free survival rates were reported.

Table 3. Results of the Radiation Therapy Oncology Group trial 9003.

Treatment	Number of Patients	Loco-regional Control (p-value*)	Disease-free Survival (p-value)	Overall Survival (p-value)	Grade 3+ Acute Toxicity	Grade 3+ Late Toxicity (p-value)
Cfx	268	46.0%	31.7%	46.1%	35.0%	26.8%
Hfx	263	54.4% (p=0.045)	37.6% (p=0.067)	54.5% (p=0.13)	54.5% (p<0.0001)	28.0% (p=NS)
Afx-s	274	47.5% (p=0.55)	33.2% (p=0.26)	46.2% (p=0.86)	50.4% (p=0.0002)	27.6% (p=NS)
Afx-c	268	54.5% (p=0.05)	39.3% (p=0.054)	50.9% (p=0.40)	58.8% (p<0.0001)	37.2% (p=0.011)

Note: Afx-c, accelerated fractionation using a concomitant boost; Afx-s, accelerated fractionation with split course; Cfx, conventional fractionation; Hfx, hyperfractionation; NS, not statistically significant.
*P-value for comparison of treatment versus conventional radiotherapy. Log-rank p-values are reported for loco-regional control, disease-free survival and overall survival.

Survival

Data on overall survival were reported for six of the seven trials of hyperfractionated radiotherapy compared with conventional radiotherapy (Table 2). Three trials detected a significant survival benefit favouring hyperfractionated radiotherapy (11-13). Sanchiz et al (11) reported results only for the complete responders and did not report on prognostic factor balance at baseline.

In 1997, Stuschke and Thames (15) published a meta-analysis of survival data from three randomized controlled trials (5,11,12). RTOG trial 79-13 (9) was not included because of its failure to increase the total dose in the hyperfractionation arm beyond that used in the control arm. Stuschke and Thames (15) performed some calculations to try to compensate for the missing data on non-responders in the trial by Sanchiz et al (11). Specifically, they assumed the non-responders died within two years. The meta-analysis detected a significant reduction in the mortality odds ratio (OR) favouring hyperfractionated radiotherapy compared with conventional radiotherapy (OR, 0.48; 95% confidence interval [CI], 0.40 to 0.58; p<0.0001). The meta-analysis was weakened by the methodological problems in the trial by Sanchiz et al (11).

Loco-regional Control

Reports of all seven trials of hyperfractionated radiotherapy provided data on loco-regional control (Table 2). Excluding the trial by Sanchiz et al (11), who reported data for only the complete responders, four trials (5,10,13,14) demonstrated significantly improved loco-regional control favouring hyperfractionated radiotherapy. Since the positive results reported by Datta et al (10) and Cummings et al (13) have never been fully published and there was no information regarding prognostic factor balance, EORTC trial 22791 (5) and RTOG trial 9003 (14) represent the best of the currently available evidence in favour of hyperfractionated radiotherapy. The distribution of Karnofsky performance status and T and N stages was balanced between the study arms in both trials (p-values not reported). EORTC trial 22791 (5) demonstrated a 19% absolute improvement in loco-regional control at five years favouring hyperfractionation (59% versus 40%; p=0.02). An 8.4% absolute improvement in loco-regional control at two years with hyperfractionation was detected in RTOG trial 9003 (54.4% versus 46%; p=0.045).

Stuschke and Thames (15) pooled data from four trials (5,10-12) and reported a significant improvement in loco-regional control favouring hyperfractionated radiotherapy compared with conventional radiotherapy (OR, 0.35; 95% CI, 0.28 to 0.45; p<0.0001). Data on the probability of loco-regional control at five years (5), relapse-free survival at two or five years (10,11) and the number of patients with loco-regional failure as the site of first treatment failure (12) were combined in this meta-analysis. Data on relapse-free survival from the trial by Sanchiz et al (11) were provided for only the complete responders.

An unplanned subset analysis of EORTC trial 22791 showed that loco-regional control for

T2 tumours was 60% for both treatment groups. However, loco-regional control for T3 tumours was increased from 18% in the conventional arm to 51% in the hyperfractionated arm. The authors of this trial concluded that hyperfractionation was superior treatment for T3 but not T2 tumours.

Adverse Effects

Acute toxicity

Data on acute mucosal and/or skin toxicity were available from six trials of hyperfractionated versus conventional radiotherapy (Table 4). Hyperfractionated radiotherapy was associated with increased mucosal and skin toxicity compared with conventional radiotherapy (p-values were not often reported). In RTOG trial 9003 (14), grade 3 or worse acute toxicity was increased significantly with hyperfractionation compared with conventional fractionation (54.5% versus 35%; p<0.0001). Datta et al (10) did not report any data on toxicity, but stated that acute complications were more severe with hyperfractionated radiotherapy compared with conventional radiotherapy.

Table 4. Acute toxicity in five of seven randomized trials of hyperfractionated versus conventional radiotherapy in locally advanced squamous cell carcinoma of the head and neck.

Study	Mucosal Toxicity			Skin Toxicity		
	Scale	Cfx	Hfx	Scale	Cfx	Hfx
RTOG 79-13/ Marcial et al 1987 (9)	Mucositis: patients rated as "severe"	13%	23%	Patients rated as "severe"	7%	6%
Sanchiz et al 1990 (11)	Mucositis graded according to WHO criteria*: Grade 3	14/277 (5%)	11/282 (4%)	Skin toxicity graded according to WHO criteria‖: Grade 3	1/277 (0.4%)	4/282 (1.4%)
Pinto et al 1991 (12)	Mucosal reaction graded using study specific criteria†: Grade 4	17/48 (35%)	24/50 (48%)	Skin reaction graded using study specific criteria¶: Grade 3	10/48 (21%)	14/50 (28%)
EORTC 22791/ Horiot et al 1992 (5)	Objective mucosal reaction graded according to EORTC scale‡: Grade 3 Functional mucosal reaction graded according to EORTC scale§: Grade 4	78/158 (49%) 17/158 (11%)	108/162 (67%) 26/162 (16%)	Not Measured		
Cummings et al 2000 (13) ABSTRACT	Mucosal toxicity graded according to RTOG scale: Grade 3	43%	57%	Not Reported		
RTOG 9003/ Fu et al 2000 (14)	Mucosal toxicity graded according to RTOG scale: Grade 3 or 4	67/268 (25%)	110/263 (42%)	Skin toxicity graded according to RTOG scale: Grade 3 or 4	20/268 (7%)	30/263 (11%)

Note: Cfx, conventional radiotherapy; Hfx, hyperfractionated radiotherapy.

* 1=soreness/erythema; 2=erythema/ulcers; 3=ulcers (liquid diet only); 4=alimentation not possible

† 1=faint erythema, 2=brisk erythema, 3=punctiforme mucositis, 4=confluent mucositis

‡ 1=mild mucositis; 2=patchy mucositis; 3=diffuse mucositis

§ 1=mild irritation; 2=moderate irritation; 3=liquid diet only; 4=oral alimentation impossible

‖ 1=erythema; 2=dry desquamation, vesiculation, pruritus; 3=moist desquamation, ulceration; 4=exfoliative dermatitis; necrosis requiring surgical intervention

¶ 1=erythema; 2=dry desquamation; 3=moist desquamation; 4=slough

Late toxicity

Data on the incidence of late adverse effects were available for four trials (5,9,13,14), all of which demonstrated no statistically significant differences in late toxicity. In RTOG trial 9003 (14), 28% of patients in both the conventional and hyperfractionated radiotherapy arms experienced grade 3 or worse late adverse effects. In RTOG trial 79-13 (9), late treatment

effects with conventional radiotherapy versus hyperfractionated radiotherapy were severe in 10% versus 22% and life threatening in 6% versus 8% of patients. The incidence of late side effects in EORTC trial 22791 (5) was over 50% in both arms. Additional information on EORTC trial 22791 (5) revealed that the incidence in grade 3 reactions was doubled in the hyperfractionated arm (actuarial, 14% versus 27%; p=0.37; crude, 7% (8/118) versus 12% (16/135); p=0.17) (16). This large, though statistically non-significant, difference was only apparent after six years of follow-up. A final report with long-term follow-up on sufficiently large patient numbers is required before firm conclusions can be drawn concerning late complications. The grade 3 or 4 late toxicity rates at five years in the trial by Cummings et al (13) were 8% with hyperfractionation compared with 14% with conventional radiotherapy (p=0.31). Reports of two other trials also indicated no statistically significant differences in late toxicity, but no data were reported (10,12). Sanchiz et al (11) reported moderate xerostomia in 42% of patients, skin elastoses in 19% and bone necroses in 11%, but did not indicate whether the late treatment effects differed between the groups.

V. INTERPRETIVE SUMMARY

Loco-regional control and survival

Conclusions regarding the relative merits of hyperfractionation are limited by the quality of the published data. Of the seven randomized controlled trials comparing hyperfractionation with conventional fractionation, two have been published only as abstracts (10,13) and two have provided incomplete data with respect to non-responders and prognostic factor balance (11) and late complication rates (11,12). The three remaining trials, RTOG trial 79-13 (9), EORTC trial 22791 (5), and RTOG trial 9003 (14) are viewed as well conducted intergroup studies with reasonable follow-up. However, the published results are inconsistent. RTOG trial 79-13 was a negative study. It has been criticized as a poor example of hyperfractionation for failing to deliver an increase in total dose and was excluded from the published meta-analysis for this reason (15). In contrast, EORTC trial 22791 and RTOG trial 9003 have both reported a statistically significant improvement in loco-regional control favouring hyperfractionation. Interestingly, the dramatic 19% absolute improvement reported by the EORTC has not escaped criticism. Rudoltz and Mohiuddin have suggested that the difference in tumour control might be due to the poor performance of the conventional arm rather than the benefits of hyperfractionation (17). The conventional arm in the RTOG study fared somewhat better reducing the benefits accruing to hyperfractionation to a modest absolute gain of 8.4%. In both trials this benefit has not yet translated into improved disease-free or overall survival.

Subset Analysis

Are there subgroups of patients that might benefit from hyperfractionated radiotherapy? The subset analysis of EORTC trial 22791 suggested that the apparent advantage of hyperfractionation over conventional fractionation was limited to larger (i.e. T3) lesions. A subset analysis addressing this question has not been reported in the updates of other hyperfractionation trials.

Therapeutic Gain

Conclusions regarding a possible therapeutic gain for hyperfractionation have been limited by methodological problems. Tumour control has been most often reported as actuarial data whereas late complications have been reported as crude data. This tends to underestimate late complication rates. It is premature to conclude that hyperfractionation with dose escalation does not increase clinically important late tissue complications (16).

Qualitative reviews of the randomized controlled trials of hyperfractionated radiotherapy have reached differing conclusions. Beck-Bornholdt et al (16) concluded that hyperfractionation

with adequate dose escalation does not lead to improved tumour response without increasing late complications. They could not rule out the possibility that the same results might be achieved simply by escalating the total dose delivered by conventional protocols. Baumann et al (18) critiqued the meta-analysis published by Stuschke and Thames (15) and the review by Beck-Bornholdt et al (16). Baumann concluded that, despite the methodologic problems identified by Beck-Bornholdt et al, the evidence supported a therapeutic gain for hyperfractionation compared with conventional radiotherapy. Recently, Olmi and Fallai (19) reviewed five randomized controlled trials of hyperfractionated radiotherapy (5,9-12) and concluded that there is insufficient evidence to recommend hyperfractionation as routine clinical practice. The subsequent publication of the study by Cummings et al (13) and RTOG trial 9003 (14) is unlikely to change this view.

VI. ONGOING TRIALS

There are no on-going trials of hyperfractionated radiotherapy versus conventional radiotherapy involving patients with stage III-IV SCCHN, however, there are two on-going trials in stage II disease:

(i) RTOG-9512 (Trotti). Phase III randomized study of hyperfractionation (twice daily) versus conventional fractionation (once daily) radiotherapy for stage II (T2 NO) squamous cell carcinoma of the true vocal cord. Local response rate, acute and late toxic effects, and overall and disease-free survival will be assessed. Projected accrual is 240 patients (status: open).

(ii) EORTC-22962 (Bernier, Horiot). Phase III study of conventional versus hyperfractionated radiotherapy in stage II (T2a/b NO) head and neck squamous cell carcinoma with or without concomitant chemotherapy. Progression-free survival in 994 patients will be measured in this four-arm trial which is also intended to assess the benefits of concomitant chemotherapy and radiotherapy as well as the difference between conventional and hyperfractionated radiotherapy schedules (status: closed).

VII. DISEASE SITE GROUP CONSENSUS PROCESS

A draft report on altered fractionation in locally advanced SCCHN was submitted to the Head and Neck Cancer DSG. Subsequent feedback from DSG members suggested that there was too much information to be considered in a single guideline. Therefore, two guidelines were developed, one addressing hyperfractionated radiotherapy and the second addressing accelerated radiotherapy. It was suggested that both guidelines include a reference to the recently completed guideline on concomitant chemotherapy and radiation in the same group of patients.

Despite the publication of seven randomized controlled trials comparing hyperfractionated radiotherapy with conventional (daily fractionated) radiotherapy, the DSG expressed concern regarding the quality of the available data. Two of the studies had been published only as abstracts (10,13). Information reported by Sanchiz et al (11) and Datta et al (10) was incomplete with respect to the balance of prognostic factors. In addition, Sanchiz et al reported results only for complete responders. There was concern regarding the generalizability of the Brazilian study reported by Pinto et al (12). Ultimately, only two trials (EORTC 22791 and RTOG 9003) provided convincing evidence of improved loco-regional control. The DSG noted that this benefit was not accompanied by improved disease-free or overall survival. A recent update of a third trial (13) demonstrated significantly improved loco-regional control and survival with hyperfractionation, but the result have been reported only in abstract form. There was concern regarding the completeness of reporting of the incidence and severity of late complications in all trials. The DSG members noted the paucity of data on salvage surgery in this group of patients. The group felt that it was premature to conclude that hyperfractionation

with dose escalation does not increase late tissue complications.

In comparing the relative merits of hyperfractionation and accelerated fractionation in patients with locally advanced disease, the DSG members noted that there was evidence for improved loco-regional control for both strategies. However, the group rated modestly accelerated regimens somewhat higher because they could improve the therapeutic index without undue pressure on departmental resources. In general, fractionation regimens utilizing two or more fractions per day require more personnel, more machine time, and are more difficult to schedule than conventional daily fractionation. Hyperfractionation leads to a dramatic increase in the number of fractions. In all but one of the published hyperfractionation trials, the number of radiation treatments was doubled in the experimental arm. Because hyperfractionation is resource intensive, DSG members felt that the implementation of hyperfractionation would be difficult in Ontario, particularly in centres where a shortage of machine time contributes to waiting lists.

The DSG members concluded that current information does not support the use of hyperfractionated radiotherapy in adults with locally advanced squamous cell carcinoma of the head and neck at this time. Given the strength of the data supporting concomitant chemoradiation as summarized in the CCOPGI practice guideline on concomitant chemotherapy and radiotherapy in SCCHN (#5-6a), the DSG members concluded that concomitant chemoradiation should be regarded as the treatment of first choice in patients with locally advanced SCCHN.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence above, the Head and Neck Cancer DSG drafted the following recommendations. At the time that the draft recommendations were developed, the results of RTOG 9003 (14) were published only in abstract form and only preliminary results were available for the trial by Cummings et al (13).

Target Population

These draft recommendations apply to adult patients with newly diagnosed, locally advanced (stage III-IV) squamous cell carcinoma of the head and neck who are deemed suitable for radical radiotherapy with curative intent.

Recommendations

- Hyperfractionated radiotherapy cannot be recommended as routine clinical practice at this time.
- This group of patients should be considered for concomitant chemotherapy and conventional radiotherapy as recommended in Cancer Care Ontario Practice Guidelines Initiative guideline #5-6a.

Key Evidence

- Hyperfractionated radiotherapy (multiple fractions per day) yields higher rates of acute toxicity compared with conventional radiotherapy (one fraction per day, five days per week).
- Data on the incidence and severity of late complications associated with hyperfractionation are incomplete. It is premature to conclude that hyperfractionation with dose escalation does not increase late tissue complications.

- Conclusions regarding loco-regional control are limited by the quality of the published data. To date, only one of seven randomized trials has provided convincing evidence of improved loco-regional control with hyperfractionation compared with conventional radiotherapy. In this study, improved loco-regional control was not accompanied by an increase in overall survival.
- Only two of seven randomized trials have documented improved overall survival with hyperfractionation. Both studies have been criticized for failing to report complete data.

Related Guideline

- Please refer to companion guideline #5-6c on accelerated radiotherapy in locally advanced (stage III-IV) squamous cell carcinoma of the head and neck.

Practitioner Feedback

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

Methods

Practitioner feedback was obtained through a mailed survey of 112 practitioners in Ontario (15 medical oncologists, 25 radiation oncologists and 72 surgeons). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey have been reviewed by the Head and Neck Cancer Disease Site Group.

Results

Key results of the practitioner feedback survey are summarized in Table 5. Fifty-four (50%) surveys were returned. Eighteen (33%) respondents (11 radiation oncologists, six surgeons and one medical oncologist) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey. Of this latter sample, 72% agreed that the document should be approved as a practice guideline and 78% agreed that they would use it in their own clinical practice.

Table 5. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)*		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	17 (94%)	0	0
There is a need for a clinical practice guideline on this topic.	15 (83%)	2 (11%)	0
The literature search is relevant and complete.	16 (89%)	1 (6%)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	16 (89%)	1 (6%)	0
The draft recommendations in this report are clear.	17 (94%)	0	0
I agree with the draft recommendations as stated.	15 (83%)	2 (11%)	0
This report should be approved as a practice guideline.	13 (72%)	3 (17%)	1 (6%)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	14 (78%)	2 (11%)	2 (11%)

*percentages may not total 100% due to missing data.

Summary of Written Comments
Six (33%) respondents provided written comments. There was agreement that hyperfractionated radiotherapy should not be used as routine clinical practice, but two respondents thought that it may be used selectively. One respondent indicated a need for further studies to establish the role of hyperfractionated radiotherapy in head and neck cancer stratified on the basis of tumour site T2N stage.

Modifications/Actions
The results from practitioner feedback did not warrant modification of the draft recommendations. The guideline report was updated to reflect new evidence that emerged since the practitioner feedback survey was conducted.

Approved Practice Guideline Recommendations
The approved practice guideline recommendations in Section IX reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Systemic Treatment DSG and the Practice Guidelines Coordinating Committee.

Update
New evidence found by update searches since completion of the original guideline is consistent with the original recommendations.

IX. PRACTICE GUIDELINE

Target Population
These recommendations apply to adult patients with newly diagnosed, locally advanced (stage III-IV) squamous cell carcinoma of the head and neck who are deemed suitable for radical radiotherapy with curative intent.

Recommendations
- This group of patients should be considered for concomitant chemotherapy and conventional radiotherapy as recommended in Cancer Care Ontario Practice Guidelines Initiative guideline #5-6a.
- Hyperfractionated radiotherapy cannot be recommended as routine clinical practice at this time.

Qualifying Statement
- Although the improvements in loco-regional control and survival are promising, longer follow-up and more complete information on late complications will be needed to meaningfully compare these results to those achieved with concomitant chemoradiation in locally advanced SCCHN.

Related Guidelines
- Please refer to companion guidelines on concomitant chemotherapy and radiotherapy (#5-6a) and accelerated radiotherapy (#5-6c) in locally advanced (stage III-IV) squamous cell carcinoma of the head and neck.

X. JOURNAL REFERENCE

Mackenzie RG, Hodson DI, Browman GP, Zuraw L, and the members of the Head and Neck Cancer Disease Site Group. Hyperfractionated radiotherapy for locally advanced squamous cell carcinoma of the head and neck. *Curr Oncol* 2001;8:6-15.

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For a full list of members of the Cancer Care Ontario Head and Neck Disease Site Group, please visit the website of the Program in Evidence-based Care at: www.cancercare.on.ca/

REFERENCES

1. Munro AJ. An overview of randomized controlled trials of adjuvant chemotherapy in head and neck cancer. *Br J Cancer* 1995;71:83-91.
2. Withers HR, Thomas HD, Peters LJ. Differences in the fractionation response of acutely and late-responding tissues. In: Karcher KH, KogeInik HD, Reinartz G, editors. *Progress in Radio-Oncology.* Vol 2. New York: Raven Press;1982. p. 287-96.
3. Withers HR. Cell cycle distribution as a factor in multifraction irradiation. *Radiology* 1975;114:199-202.
4. Palcic B, Skarsgard LD. Reduced oxygen enhancement ratio at low doses of ionizing radiation. *Radiat Res* 1984;100:328-39.
5. Horiot J, Le Fur R, Nguyen T, Chenal C, Schraub S, Alfonsi S, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. *Radiother Oncol* 1992;25:231-41.
6. Withers HR. Biologic basis for altered fractionation schemes. *Cancer* 1985;55 Suppl 9:2086-95.
7. Cox J, Pajak T, Marcial V, Coia L, Mohiuddin M, Fu K, and the Radiation Therapy Oncology Group. ASTRO Plenary: Interfraction interval is a major determinant of late effects, with hyperfractionated radiation therapy of carcinoma of the upper respiratory and digestive tracts: results from RTOG protocol 8313. *Int J Radiat Oncol Biol Phys* 1991;20:1191-5.
8. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502-12.
9. Marcial V, Pajak T, Chu C, Tupchong I, Stetz J. Hyperfractionated photon radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity, pharynx, larynx and sinuses, using radiation therapy as the only planned modality (preliminary report) of the RTOG. *Int J Radiat Oncol Biol Phys* 1987;13:41-7.
10. Datta NR, Choudry AD, Gupta S, Bose AK. Twice a day versus once a day radiation therapy in head and neck cancer [abstract]. *Int J Radiat Oncol Biol Phys* 1989;17 Suppl 1:132-3. Abstract 35.
11. Sanchiz F, Milla A, Torner J, Bonet F, Artola N, Carreno L, et al. Single fraction per day versus two fractions per day versus radiochemotherapy in the treatment of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1990;19:1347-50.
12. Pinto L, Canary P, Araujo C, Bacelar S, Souhami L. Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stages III and IV oropharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 1991;21:557-62.
13. Cummings B, O'Sullivan B, Keane T, Pintilie M, Liu FF, McLean M, et al. 5-year results of 4 week/twice daily radiation schedule – the Toronto trial [abstract]. The 19th annual meeting of the European Society of Radiation Oncology (ESTRO). Istanbul, Turkey September 19-23, 2000. Abstract 22.
14. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000;48:7-16.
15. Stuschke M, Thames HD. Hyperfractionated radiotherapy of human tumours: overview of the randomized clinical trials. *Int J Radiat Oncol Biol Phys* 1997;37:259-67.
16. Beck-Bernholdt H, Dubber H, Leirtz-Petersen C, Willers H. Hyperfractionation: where do

we stand? *Radiother Oncol* 1997;43:1-21.
17. Rudoltz MS, Mohiuddin M. Is hyperfractionation really better? *Radiother Oncol* 1993;29:354-5.
18. Baumann M, Sentzen SM, Ang KK. Hyperfractionated radiotherapy in head and neck cancer: a second look at the clinical data. *Radiother Oncol* 1998;46:127-30.
19. Olmi P, Fallai C. Randomized trials on altered fractionation in head and neck cancer radiotherapy with conventional fractionation a control arm: another lap to go. *Tumori* 1998;84:160-6.

Update

This section includes all references obtained from the review and updating activities.

1u. Bourhis J, Syz N, Overgaard J, Ang KK, Dische S, Horiot J, et al. Conventional vs modified fractionated radiotherapy. Meta-analysis of radiotherapy in head & neck squamous cell carcinoma: a meta-analysis based on individual patient data [abstract]. *Int J Radiat Oncol Biol Phys* 2002;54 (2 Suppl.1):71-2**.**
2u. Fisher J, Scott C, Fu K, Trotti A, Spencer S, Garden A, et al. Treatment, patient and tumour characteristics impact quality of life in patients with locally advanced head and neck cancer: Report of the Radiation Therapy Oncology Group trial (RTOG) 90-03 [abstract]. *Int J Radiat Oncol Biol Phys* 2001;51(3 Suppl.1):1-2*.*
3u. Bartelink H, Van den Bogaert W, Horiot JC, Jager J, van Glabbeke M. Concomitant cisplatin and radiotherapy in a conventional and modified fractionation schedule in locally advanced head and neck cancer: a randomised phase II EORTC trial. *Eur J Cancer* 2002;38:667-73.