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Practice Guideline Report 5-6c EDUCATION AND INFORMATION 2012

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

Report Date: November 27, 2000

An assessment conducted in December 2012 put Evidence-based Series (EBS) 5-6c 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 5-6c 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/

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

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Cancer Care Ontario Practice Guidelines Initiative

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

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

Practice Guideline Report # 5-6c

SUMMARY

Guideline Questions

Does accelerated 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 accelerated fractionation? 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 (SCCHN) 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 radiation as recommended in Cancer Care Ontario Practice Guideline Initiative guideline #5-6a.
- It would be reasonable to offer modestly accelerated radiotherapy to patients with locally advanced (stage III and IV) disease who are not candidates for concomitant chemotherapy and conventional radiation.
- Rapid acceleration of radical radiotherapy cannot be recommended as standard therapy.

Qualifying Statements

- The emerging evidence suggests that modestly accelerated radiotherapy can improve loco-regional control compared with conventional radiotherapy. Overall survival may be enhanced. 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

Entries to MEDLINE (1966 through November 2000), CANCERLIT (1983 through September 2000) and Cochrane Library (2000 Issue 3) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology were systematically searched for evidence relevant to this practice guideline 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

- Rapid acceleration of radical radiotherapy results in excessive normal tissue toxicity. This can be minimized by reducing the total dose (as in the continuous hyperfractionated accelerated radiotherapy [CHART] regimen) or introducing a treatment interruption (as in the split-course protocols of the European Organization for Research and Treatment of Cancer trial 22811 and the Radiation Therapy Oncology Group trial 9003) but at the expense of tumour control. These regimens have not proven superior to conventional fractionation in terms of survival and loco-regional control.
- Modest acceleration of radical radiotherapy without an accompanying reduction in total dose may be superior to conventional fractionation. A reduction in overall treatment time from seven weeks to six weeks achieved by delivering six fractions per week instead of five fractions per week, or by treating patients seven days a week instead of five days per week, or using a concomitant boost over the last 12 treatment days, yielded improved loco-regional control with increased but manageable acute toxicity. Full data on long-term effects are not yet available, but based on the limited evidence that is available from randomized trials the effects appear to be clinically acceptable.

Related Guidelines

- Please refer to companion guidelines on concomitant chemotherapy and radiotherapy (#5-6a) and hyperfractionated radiotherapy (#5-6b) in locally advanced (stage III-IV) squamous cell carcinoma of the head and neck.
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Prepared by the Head and Neck Cancer Disease Site Group
Report Date: November 27, 2000

The Cancer Care Ontario Practice Guidelines Initiative guidelines are reviewed and updated regularly. Please visit our Web site at http://www.cancercare.on.ca/ccopgi/ for the most up-to-date versions.

For further information about this practice guideline report, please contact: Dr. Ian Hodson, Chair, Head and Neck Cancer Disease Site Group, Hamilton Regional Cancer Centre, 699 Concession Street, Hamilton, Ontario, L8V 5C2; TEL (905) 387-9711, ext. 4702; FAX (905) 575-6326.

PREAMBLE: About Our Practice Guideline Reports

The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) is a project supported by Cancer Care Ontario and the 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 multi-disciplinary 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. They are intended to enable evidence-based practice.

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.

For more information about the Program or the CCOPGI, please visit our web page (http://www.cancercare.on.ca/ccopgi/) or contact us by telephone (905-525-9140, extension 22055) or fax (905-577-0017).

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

FULL REPORT

I. QUESTIONS

Does accelerated 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 accelerated fractionation? 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 newly diagnosed, locally advanced squamous cell carcinoma of the head and neck treated with curative intent. Published rates of local control range between 5% and 64%. The reported overall five-year survival 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 normal tissue toxicities 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 accelerated fractionation.

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.

Accelerated fractionation

In contrast to conventional radiotherapy, accelerated protocols deliver a similar total dose in less time by using six or more fractions per week. The rationale for accelerated fractionation is based on the observation that tumours, like acutely responding tissues, have the capacity to repopulate during an extended course of radiotherapy (2). Accelerated fractionation regimens aim to counteract the proliferation of tumour clonogens during treatment. Because late responding tissues are less sensitive to overall treatment time than acutely responding tissues, modest acceleration of treatment is not expected to increase late complications. However, excessive shortening of overall treatment time can lead to “consequential“ late effects unless there is a corresponding decrease in total dose.

There are two strategies to accelerate radiation treatment. Pure accelerated fractionation reduces the overall treatment time without concurrent changes in fraction size or total dose. The Vancouver regimen of 66 Gy delivered as 2.0 Gy BID (twice daily) in 33 fractions over three weeks is an example. Hybrid accelerated fractionation reduces the overall treatment time in conjunction with changes in other parameters such as fraction size and total dose, with and without planned breaks in treatment. Four variations of hybrid protocols have emerged in clinical practice. Continuous hyperfractionated accelerated radiotherapy (CHART) is the prototype of intensive short course treatment in which the overall duration of treatment is

markedly reduced with a corresponding decrease in total dose. Split-course BID protocols and concomitant boost regimens are examples of schedules in which the duration of treatment is more modestly reduced while the total dose is kept in the same range as conventional therapy. There is more limited experience with hybrid schedules in which the total dose delivered per week is progressively increased during the course of therapy.

Tumour Kinetics

Proliferation of tumour cells during radiotherapy may limit loco-regional control, especially in rapidly proliferating tumours. Pretreatment potential doubling times under five days have been recorded in some patients with SCCHN. In the future, these results may guide the choice of fractionation (3,4). To date, patients entered on trials of altered fractionation have not been selected on the basis of tumour kinetics.

Interfraction Interval

Repair of sub-lethal damage is slower in most late responding tissues than in early responding tissues (5). 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 (6). 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 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 (7). 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 accelerated 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 “accelerated” 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 clinical trials were identified through the Physician Data Query (PDQ) clinical trials database (http://cnetdb.nci.nih.gov/trialsrch.shtml).

Inclusion Criteria

The systematic review was limited to randomized trials and meta-analyses of randomized trials comparing accelerated 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 accelerated 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

The results for survival and loco-regional control were pooled in separate analyses using the Metaanalyst[0.998] software provided by Dr. Joseph Lau (Boston, MA). The Head and Neck Cancer DSG decided that it would be appropriate to conduct a pooled analysis because the patient populations were similar and the treatment groups were comparable. Data from the total randomized population were pooled if available. Otherwise, data from the evaluable patients were used. Data were abstracted from published reports. The random effects model was used as the more conservative estimate of effect (8). Results were expressed as risk ratios (RR) with 95% confidence intervals (CI). A RR less than 1.0 favours the experimental treatment (accelerated radiotherapy) and a RR greater than 1.0 favours the control (conventional radiotherapy).

IV. RESULTS

Literature Search Results

Eleven randomized trials (12 comparisons) of accelerated radiotherapy compared with conventional radiotherapy met the inclusion criteria (9-19). Five of these trials have been published only in abstract form (13-16,19) (Table 1). Data on loco-regional response, loco-regional control and survival are summarized in Table 2. The four-arm RTOG trial 9003 (18) deserves special consideration because of the simultaneous comparison of accelerated, hyperfractionated and conventionally fractionated regimens (Table 3).

Rapid acceleration of radiotherapy, which refers to an accelerated course of radiation that delivered radiation in four weeks or less or needed a split in the course to allow for tissue healing, was compared with conventional radiotherapy in eight trials (9-12,15,16,18,19). Modest acceleration of radiotherapy versus conventional radiotherapy was evaluated in four trials (13,14,17,18). Specifically, the overall treatment time was reduced from seven weeks to six weeks by treating patients for six or seven days per week instead of five days per week

(13,14,17) or by giving two fractions per day (concomitant boost) for the last 12 treatment days (18).

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

Study (Reference)	Site (n)	Stage* (n)	# Randomized (# Analyzed)	Treatment Groups	Follow-up
EORTC 22851/Horiot et al, 1997 (9)	Oropharynx (64%) oral cavity (16%) larynx (14%) other (6%)	T1 (1) T2 (168) T3 (200) T4 (128) N0 (213) N1 (117) N2 (93) N3 (76)	512 (500)	Cfx (n=255): 70 Gy in 35 fractions over 7 weeks Afx (n=257): 72 Gy in 45 fractions over 5 weeks (3 fractions of 1.6 Gy per day for 8 days,12-14 day rest, 3 fractions of 1.6 Gy per day for 17 days)	Median: 4.75 years
Dische et al, 1997 (10)	Larynx (424) Oropharynx (239) Oral cavity (126) Hypopharynx (87) Nasopharynx (29) Paranasal sinus (13)	T1 (28) T2 (412) T3 (296) T4 (181) N0 (601) N1 (140) N2 (123) N3 (54)	918 (918)	Cfx (n=366): 66 Gy in 33 fractions over 6.5 weeks Afx (n=552): 54 Gy in 36 fractions over 12 days (3 fractions of 1.5 Gy per day 7 days/week)	Appears to be 2-7 years (survival curves to 60 months)
EORTC 22811/van den Bogaert et al, 1995 (11)	Oropharynx (205) Tongue (83) Other oral cavity (52) Larynx (78) Hypopharynx (69)	T1 (11) T2 (22) T3 (354) T4 (100) N0 (131) N1 (85) N2 (43) N3 (228)	523 (498)	Cfx (n=168): 70 Gy in 35 fractions over 7 weeks or 75 Gy in 45 fractions over 9 weeks Afx (n=163): 67.2-72 Gy in 45 fractions of 1.6 Gy over 7 weeks given as 48 Gy over 2 weeks followed by a 4 week rest period and then 19.2 Gy over 4 days or 24 Gy over 5 days (3 fractions/day) A 3rd arm received multiple fractions/day plus misonidazole (n=167)	8.5 years
Jackson et al, 1997 (12)	Oral cavity (16) Larynx (21) Pharynx (45)	T1 (6) T2 (21) T3 (37) T4 (18) N0 (25) N1 (18) N2 (36) N3 (3)	82 (80)	Cfx (n=41): 66 Gy in 33 fractions over ~6-7 weeks Afx (n=41): 66 Gy in 33 twice daily fractions over ~3 weeks (2 fractions of 2 Gy per day, 5 days/week at least 6 hours apart)	NR

Table 1. Continued.

Study (Reference)	Site (n)	Stage* (n)	# Randomized (# Analyzed)	Treatment Groups	Follow-up
Overgaard et al, 2000 (13) ABSTRACT	Oral cavity Larynx Pharynx	NR	1485 (1485)	Cfx (n=NR): 66-68 Gy in 33-34 fractions (5/week) Afx (n=NR): 66-68 Gy in 33-34 fractions (6/week)	NR
Hliniak et al, 1999 (14) ABSTRACT	Glottis (292) Supraglottis (103)	T1 (65) T1a (104) T1b (16) T2 (171) T3 (38)	395 (383)	Cfx (n=195): 66 Gy in 33 fractions over 7 weeks Afx (n=188): 66 Gy in 33 fractions over 6 weeks	Median: 21 months
Dobrowsky et al, 1999 (15) ABSTRACT	Oral cavity (70) Oropharynx (95) Hypopharynx (39) Larynx (25)	T3/T4 (84%) N1-3 (79%)	229 (NR)	Cfx (n=NR): 70 Gy in 35 fractions over 7 weeks Afx (n=NR): 55.3 Gy in 33 fractions over 17 consecutive days 3rd arm of Afx + mitomycin C	Median: 48 months
Bourhis et al, 2000 (16) ABSTRACT	NR	NR	268 (NR)	Cfx (n=NR): 70 Gy over 7 weeks Afx (n=NR): 62-64 Gy, 2 Gy twice daily, over 3 weeks	Median: 28 months
Skladowski et al, 2000 (17)	Oral cavity (22) Oropharynx (28) Hypopharynx (9) Supraglottic larynx (41)	T2N0 (17) T2N1 (2) T3 N0 (26) T3N1 (21) T4N0 (16) T4N1 (18)	100 (100)	Cfx (n=49): 66-72 Gy, once daily fractions of 1.8-2 Gy, 5 days/week over 7 weeks Afx (n=51): 66-72 Gy, once daily fractions of 1.8-2 Gy, 7 days/week over 5 weeks	Median: 37 months
RTOG 9003/ Fu et al, 2000 (18)	Oral cavity (110) Oropharynx (649) Hypopharynx (141) Supraglottic larynx (173)	T1 (64) T2 (288) T3 (406) T4 (315) N0 (239) N1 (214) N3 (494) N3 (126)	1113 (1073)	Cfx (n=268): 70 Gy in 35 fractions over 7 weeks Hfx (n=263): 81.6 Gy, 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
TROG 91.01 Denham et al, 2000 (19) ABSTRACT	NR	NR	350 (NR)	Cfx (n=NR): 70 Gy in 30 daily fractions of 2 Gy over 47 days Afx (n=NR): 59.4 Gy in 33 twice daily fractions of 1.8 Gy over 24 days	18 month minimum follow-up

Note: Afx, accelerated fractionation; Afx-c, accelerated fractionation using a concomitant boost; Afx-s, accelerated fractionation with split course; Cfx, conventional fractionation; Hfx, hyperfractionation; NR, not reported TROG, Trans-Tasman Radiation Oncology Group.

* van den Bogaert et al used the 1978 (International Union Against Cancer (UICC) staging criteria.

Table 2. Results of randomized trials of accelerated fractionation versus conventional radiotherapy in locally advanced SCCHN.

Study (Reference)	Loco-regional Response		Loco-regional Control at 5 years		Overall Median Survival (Months)	
	Cfx	Afx	Cfx	Afx	Cfx	Afx
Horiot et al, 1997 EORTC 22851 (9)	46% (116/253)	56% (137/247)	46%	59%	24	21
			Hazard ratio=0.7; 95%CI 0.52 to 0.94, p=0.02			
Dische et al, 1997 (10)	74%	79%	43%*	44%*	36*	36*
van den Bogaert et al, 1995 EORTC 22811 (11)	61%*	66%*	28%*	23%*	13*	13*
Jackson et al, 1997 (12)	71% (29/41)	85% (35/41)	NR (recurrence-free survival was 44% at 3 years)	NR (recurrence-free survival was 49% at 3 years)	NR	NR
			p>0.05			
Overgaard et al, 2000 (13)	NR	NR	57%	66%	NR	NR
			p=0.01		not significant	
Hliniak et al, 1999 (14)	96.4% (187/199)	92.4% (175/196)	NR (79% at 2 years)	NR (85% at 2 years)	NR (83% at 2 years)	NR (81% at 2 years)
			one-sided p=0.03		one-sided p=0.29	
Dobrowsky et al, 1999 (15)	NR	NR	NR (31% at time of reporting)	NR (34% at time of reporting)	NR (27% at time of reporting)	NR (28% at time of reporting)
			p-value NR		p-value NR	
Bourhis et al, 2000 (16)	NR	NR	NR (34% at 2 years)	NR (58% at 2 years)	NR (25% at 2 years)	NR (38% at 2 years)
			p=0.01		p=0.13	
Skladowski et al, 2000 (17)	69%	88%	NR (37% at 3 years)	NR (82% at 3 years)	NR (32% at 3 years)	NR (78% at 3 years)
			p<0.0001		p<0.0001	
Fu et al, 2000 RTOG 9003 (18)	NR	NR	NR (46% at 2 years)	NR (47.5% for Afx-s and 54.5% for Afx-c at 2 years)	NR (46.1% at 2 years)	NR (46.2% for Afx-s and 50.9% for Afx-c at 2 years)
			p=0.05 for Cfx versus Afx-c		p>0.05 for Cfx versus Afx-c and Cfx versus Afx-s	
TROG 91.01 Denham et al, 2000 (19)	NR	NR	51%	54%	31%	37%
			p>0.1		p>0.5	

Note: Afx, accelerated fractionation; Afx-c, accelerated fractionation using a concomitant boost; Afx-s, accelerated fractionation with split course; Cfx, conventional radiotherapy; NR, not reported; TROG, Trans-Tasman Radiation Oncology Group.
*Calculated from survival curve.

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.

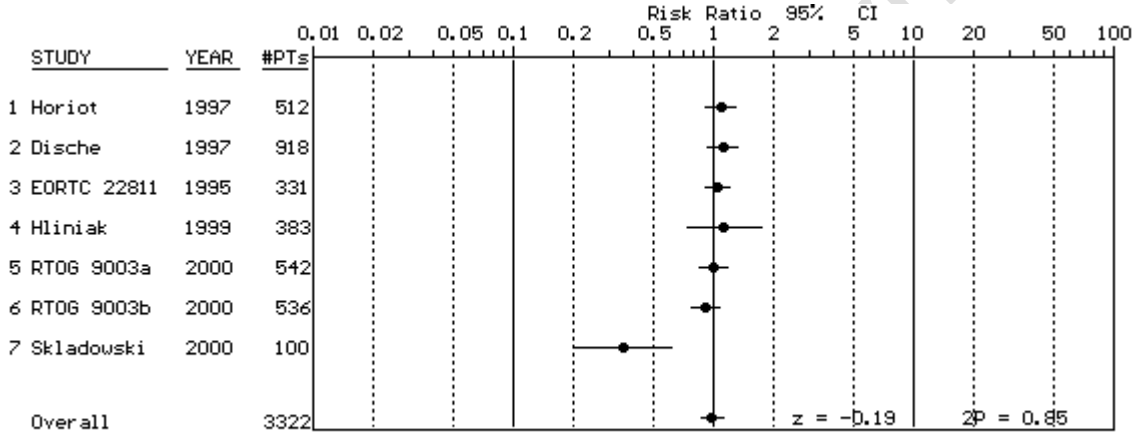
Survival

Data on overall survival were reported for nine of the 11 trials (12 comparisons) of accelerated radiotherapy (Table 2). One trial of modest acceleration of radiotherapy (i.e., treatment time was reduced by treating patients once daily for seven days a week instead of the conventional five days a week) demonstrated a significant survival benefit favouring accelerated fractionation (17). Complete information was available from six trials (seven comparisons) to facilitate pooling of data. This exercise did not include the trials reported by Jackson et al (12), Overgaard et al (13), Dobrowsky et al (15), Bourhis et al (16) or Denham et al (19) because of incomplete information on the number of patients and deaths in each arm. Pooling detected no significant difference in two-year survival rates for accelerated radiotherapy compared with conventional radiotherapy (RR, 0.99; 95% CI, 0.87 to 1.12; p=0.85) (Figure 1). There was significant heterogeneity across the trials (X^2=17.12; p<0.05), largely reflecting the disparate results reported by Skladowski et al (17). This trial is an outlier; the 95% confidence interval around the RR for this trial did not overlap with any of the other trials. Also, the small size of this trial may have led to an imbalance in prognostic factors favouring the accelerated radiotherapy group. In fact, there were more patients with oropharyngeal tumours (33% versus 22%) and node-negative disease (64% versus 53%) in the accelerated radiotherapy group, although Skladowski et al (17) reported that these differences were not significant (p-value not reported). Removing this trial reduced the overall heterogeneity (X^2=3.70; p>0.10) without altering the conclusions of the pooled analysis (RR, 1.03; 95% CI, 0.96 to 1.10; p=0.44).

Figure 1. Pooling of data on mortality at two years from six of eleven randomized trials of accelerated radiotherapy compared with conventional radiotherapy*.

Study	Accelerated Radiotherapy		Conventional Radiotherapy		Risk Ratio for Mortality (Random Effects)	95% Confidence Interval	
	Events	Total	Events	Total		Low	High
Horiot et al	134	257	122	255	1.09	0.92	1.30
Dische et al	226	552	135	366	1.11	0.94	1.31
EORTC 22811	117	163	116	168	1.04	0.90	1.20
Hliniak et al	36	188	33	195	1.13	0.74	1.74
RTOG 9003a (split)	148	274	145	268	1.00	0.85	1.17
RTOG 9003b (boost)	132	268	145	268	0.91	0.77	1.07
Skladowski et al	11	51	30	49	0.35	0.20	0.62
TOTAL	804	1753	726	1569	0.99	0.87	1.12

*The trials reported by Jackson et al (12), Overgaard et al (13), Dobrowsky et al (15), Bourhis et al (16) and Denham et al (19) could not be included in the pooled analysis because of incomplete information regarding number of patients and deaths in each study arm.



Favours Accelerated RT ≈ ≡ Favours Conventional RT
overall risk ratio = 0.99 (95% CI, 0.87 to 1.12; p=0.85)

Loco-regional Control

Data on loco-regional control were reported for all 11 trials of accelerated radiotherapy compared with conventional radiotherapy (Table 2). Six trials demonstrated improved loco-regional control with accelerated radiotherapy (9,13,14,16-18), but three of these trials (13,14,16) have been published only in abstract form. In four of the six positive trials, modest acceleration of radiotherapy was used (13,14,17,18). Specifically, the overall treatment time was reduced from seven weeks to six weeks by treating patients for six or seven days per week (13,14,17) or by using a concomitant boost over the last 12 treatment days (18).

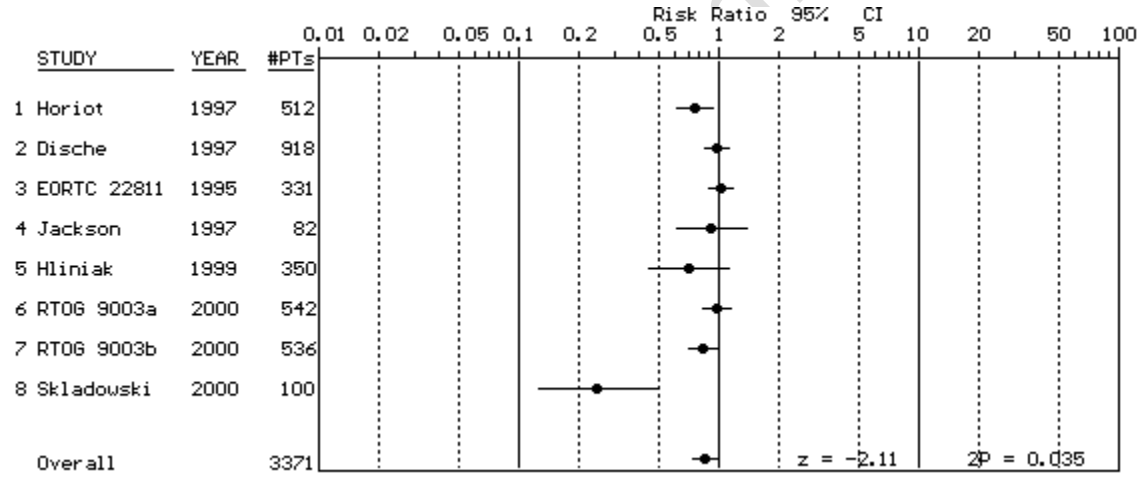
Complete information was available from seven trials (eight comparisons) to facilitate pooling of data. This exercise did not include the trials reported by Overgaard et al (13), Dobrowsky et al (15), Bourhis et al (16) or Denham et al (19) because of incomplete information on the number of patients and loco-regional failures in each arm. Pooling detected a significant improvement in local control favouring accelerated fractionation compared with conventional radiotherapy (RR, 0.86; 95% CI, 0.75 to 0.99; p=0.035) (Figure 2), but there was significant heterogeneity across the trials (X^2=24.65; p<0.05). The significant heterogeneity seems to be due to the extreme result by Skladowski et al (17), and removal of this trial reduced the overall

heterogeneity (X^2=9.85; p>0.10). However, the pooled analysis without Skladowski et al (17) detected only a nonsignificant trend towards improved loco-regional control with accelerated fractionation (RR, 0.92; 95% CI, 0.84 to 1.00; p=0.062).

Figure 2. Pooling of data on local recurrence at two years from seven of eleven randomized trials of accelerated radiotherapy compared with conventional radiotherapy.

Study	Accelerated Radiotherapy		Conventional Radiotherapy		Risk Ratio for Mortality (Random Effects)	95% Confidence Interval	
	Events	Total	Events	Total		Low	High
Horiot et al	98	257	128	255	0.76	0.62	0.93
Dische et al	276	552	187	366	0.98	0.86	1.11
EORTC 22811	119	163	119	168	1.03	0.90	1.18
Jackson et al	21	41	23	41	0.91	0.61	1.37
Hliniak et al	25	169	38	181	0.70	0.45	1.12
RTOG 9003a (split)	144	274	145	268	0.97	0.83	1.14
RTOG 9003b (boost)	122	268	145	268	0.84	0.71	1.10
Skladowski et al	8	51	31	49	0.25	0.13	0.49
TOTAL	813	1775	816	1596	0.86	0.75	0.99

*The trials reported by Overgaard (13) Dobrowsky (15), Bourhis (16) and Denham et al (19) could not be included in the pooled analysis because of incomplete information regarding number of patients and loco-regional failures in each arm.



Favours Accelerated RT ≈ ≡ Favours Conventional RT
overall risk ratio = 0.86 (95% CI, 0.75 to 0.99; p=0.035)

Adverse Effects

Acute toxicity

An increase in acute radiation reactions with accelerated radiotherapy compared with conventional radiotherapy was reported for ten trials (9-18). In RTOG trial 9003 (18), grade 3 or worse toxicity was increased significantly with accelerated fractionation using either the split-course regimen (50.4% versus 35%; p=0.0002) or the concomitant boost technique (58.8% versus 35%; p<0.0001) compared with conventional radiotherapy. Acute toxicity appeared to be most severe in trials with daily accumulated doses of 4 Gy or more and total doses of 66 Gy or more (9,11,12). Two of these trials (9,11) allowed an interfraction interval of four hours or less, which has been independently reported to lead to enhanced normal tissue toxicity (6).

Data on acute mucosal toxicity has been reported separately in six trials (Table 4). In each

trial, accelerated fractionation was associated with increased acute mucosal toxicity. Although data were not provided, the same finding has been reported in four other trials (11,13,15,16). Reports of two trials also provided data on acute skin toxicity (10,18). In RTOG trial 9003 (18), the incidence of acute skin reactions was 3% with split-course accelerated fractionation, 11% with accelerated fractionation using a concomitant boost and 7% with conventional fractionation (p-value not reported). Dische et al (10) reported that severe erythema and moist desquamation were observed more frequently with conventional radiotherapy than with CHART (39% versus 20% and 45% versus 28%, respectively; p-values not reported).

Table 4. Acute toxicity in accelerated versus conventional radiotherapy in locally advanced squamous cell carcinoma of the head and neck.

Study (Reference)	Mucosal Toxicity		
	Scale	Cfx	Afx
Horiot et al, 1997 EORTC 22851 (9)	Objective mucosal reaction graded according to EORTC/RTOG scale*: Grade 3 or 4 Functional mucosal reaction graded according to EORTC/RTOG scale†: Grade 3 or 4 (Grade 4)	50% 45% (5%)	67% 68% (17%)
Dische et al, 1997 (10)	Mucositis graded as none/patchy/confluent: confluent mucositis	43%	73%
Jackson et al, 1997 (12)	RTOG scale: Grade 3 or 4 reaction of skin or mucosa	20%	68%
Hliniak et al, 1999 (14)	Mucositis graded as none/ patchy/confluent: confluent mucositis at the end of treatment	56%	70%
Skladowski et al,2000 (17)	EORTC scale: Grade 3 or 4 mucosal reactions	71%	96%
Fu et al, 2000 RTOG 9003 (18)	RTOG scale: Grade 3 or 4 mucosal reactions	25%	41% (Afx-s) 47% (Afx-c)

Note: Afx, accelerated fractionation; Afx-s, accelerated fractionation with split course; Afx-c, accelerated fractionation using a concomitant boost; Cfx, conventional radiotherapy.
* 1=mild mucositis; 2=patchy mucositis; 3=diffuse mucositis
† 1=mild irritation; 2=moderate irritation; 3=liquid diet only; 4=oral alimentation impossible

Late toxicity

Four trials demonstrated increased late adverse effects with accelerated radiotherapy (9,11,12,14); three of these trials used rapid acceleration of radiotherapy (9,11,12). In EORTC trial 22851 (9), severe neurologic complications occurred only in the accelerated arm. Overall, late severe functional irradiation damage was observed in 14% of patients randomized to accelerated fractionation compared with 4% in the conventional radiotherapy group (p-value not reported). In EORTC trial 22811 (11), there was a statistically significant increase in the crude chronic toxicity rate for accelerated fractionation compared with conventional radiotherapy (39% versus 14%; p=0.00009). The combined grade 3 and 4 late effects were similar between treatment arms in the Vancouver trial (12), but there was a significantly higher proportion of grade 4 adverse effects in the accelerated arm, which led to discontinuation of the trial after 82 of the planned 226 patients had been randomized. Hliniak et al (14) reported significantly more telangiectasia six months after treatment with modestly accelerated fractionation compared with conventional radiotherapy (32% versus 18%; p=0.001).

Results of other studies suggest that accelerated radiotherapy does not increase late toxicity (10,13,16-19); three of these trials used modest acceleration of radiotherapy (13,17,18). The significant increase in late toxicity with accelerated fractionation using the concomitant boost technique (37.2% versus 26.8%; p=0.011) that was found in RTOG trial 9003 (18) was mostly transient. The frequency of grade 3 or worse late effects reported at six to 24 months after the start of radiotherapy did not differ significantly among the treatment groups.

Skladowski et al (17) reported that consequential late effects were not seen after the dose per fraction was reduced from 2 Gy to 1.8 Gy. The rate of grade 3 late toxicity (oedema, fibrosis and atrophy) was 8% with modestly accelerated radiotherapy (2 Gy plus 1.8 Gy groups combined) versus 4% with conventional radiotherapy. The p-value not reported but the difference was described as not significant. There were no grade 4 late normal tissue reactions with conventional radiotherapy compared with 10% with modestly accelerated radiotherapy (p-value not reported). Overgaard et al (13) reported no difference in the incidence of late edema or fibrosis, and Bourhis et al (16) reported no increase in late toxicity with accelerated radiotherapy, although no data were presented for either of these trials. Dische et al (10) reported a life table analysis revealing reduced severity of late morbidities in favour of CHART, especially for skin telangiectasia, superficial and deep mucosal ulceration and laryngeal edema. Late toxicity analysis documented osteoradionecrosis in only 0.4% of patients treated with CHART compared with 1.4% of patients treated with conventional treatment. The incidence of chondritis and cartilage necrosis was similar in both arms. Denham et al (19) reported reduced rates of EORTC/RTOG grade II or greater late skin toxicity (38% versus 75%; $p<0.025$), subcutaneous fibrosis (53% versus 68%; $p<0.025$) and late laryngeal morbidity (19% versus 34%; $p<0.05$) for the accelerated schedule. All other late normal tissue endpoints, including late mucosal toxicity, were similar in both arms.

V. INTERPRETIVE SUMMARY

Of the 11 randomized controlled trials (12 comparisons), six demonstrated a significant increase in loco-regional control (two of six trials of rapid acceleration and all four trials of modest acceleration) in favour of accelerated radiotherapy (9,13,14,16-18). One trial of modest acceleration demonstrated a significant increase in overall survival (17).

Although the pooled data reveal only a nonsignificant trend towards reduced loco-regional failure and no significant decrease in mortality with accelerated radiotherapy, the analysis is weakened by our inability to include the latest studies in the calculation because of the incompleteness of the published data. Because two of the four omitted studies favoured accelerated radiotherapy, the pooled analysis may underestimate the benefits of accelerated treatment.

A clinically significant but manageable increase in acute toxicity has been reported for all of the accelerated regimens. However, the late toxicity produced by rapid acceleration has proven unacceptable. Severe functional damage was recorded in 14% of patients treated with accelerated fractionation compared with 4% of patients treated with conventional fractionation in EORTC trial 22851 (9). The Vancouver trial (12) was closed prematurely because of an excess of grade 4 toxicity in the accelerated arm. If the rate of late complications is truly independent of the dose per fraction, then the explanation for the increase in late toxicity must be attributed to the accumulated daily dose, total dose or interfraction interval used in these trials.

The CHART (10) and Trans-Tasman Radiation Oncology Group (19) trials demonstrate that it is possible to dramatically shorten the overall treatment time without increasing late normal tissue toxicity. This appears to have been achieved by limiting the total dose to 54 Gy and 59.4 Gy, respectively. A lower total dose may also explain why the rate of loco-regional control in the accelerated arm was no better than that achieved with conventional treatment. The ability of these regimens to achieve equivalent tumour control is interesting, but the practical difficulties associated with multiple daily fractions makes it unlikely that many centres will drop conventional fractionation in favor of these short intensive protocols.

The evidence suggests that the clinical benefits of accelerated fractionation may be limited to regimens yielding modest reductions in overall treatment time with no corresponding reduction in total dose (13,17,18). Reducing overall treatment time from seven weeks to six

weeks by delivering six fractions per week as reported by Overgaard et al (13), by treating patients seven days a week as reported by Skladowski et al (17), or using a concomitant boost over the last 12 treatment days as reported by the RTOG (18), has yielded improved loco-regional control with acceptable acute toxicity. Skladowski et al (17) reported an accompanying improvement in overall survival. There are incomplete data on late toxicity making it difficult to evaluate changes in the therapeutic ratio. The delivery of six fractions per week Monday through Friday (as practiced by some of the centers participating in the trial by Overgaard et al) and the concomitant boost technique are well within the resources of most centres. Although the benefits attributed to the concomitant boost have not yet translated into improved cause-specific or overall survival, the regimen is considered sufficiently promising to be considered the conventional arm in upcoming RTOG trials.

The emerging evidence suggests that modestly accelerated radiotherapy can improve loco-regional control compared with conventional radiotherapy. Overall survival may be enhanced. 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.

VI. ON-GOING TRIALS

(i) CNR-ORO-93/01, EU-97007 (Olmi). Phase III study comparing bifractionated radiotherapy, conventional radiotherapy, and concomitant radiotherapy/chemotherapy for locally advanced (stage III or IV, excluding T1-T2 N1 tumours) oropharyngeal carcinoma. It is expected that 281 patients be accrued for this study. Conventional radiotherapy is delivered five days/week for seven weeks and bifractionated radiotherapy is delivered twice/day, four to six hours apart, five days/week, with a two-week break in the middle.

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.

The DSG members expressed regret that the trial of modest acceleration reported by Overgaard et al (13) could not be included in the pooled analysis because of incomplete information. The author has been contacted to obtain data on the number of patients and rate of loco-regional failure in each arm, but there has been no response to date. The pooled analysis, as presented in the guideline, probably underestimates the potential for improved loco-regional control with accelerated radiotherapy.

The DSG members agreed that rapid acceleration of radical radiotherapy produced unacceptable normal tissue toxicity and could not be recommended as standard therapy.

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. It was acknowledged that the delivery of daily radiation six or seven times per week could pose logistical difficulties in some Canadian centres.

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. It would be reasonable to offer modestly accelerated radiotherapy to patients with locally advanced disease who were not judged to be candidates for concomitant chemoradiation. For most centres, this goal could be most reliably achieved with the concomitant boost protocol of the RTOG.

VIII. 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 (18) and Skladowski et al (17) were published only in abstract form and results of the trials by Dobrowsky et al (15), Bourhis et al (16) and Denham et al (19) were not yet included in the guideline report.

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 (SCCHN) who are deemed suitable for radical radiotherapy with curative intent.

Recommendations

- Rapid acceleration of radical radiotherapy cannot be recommended as standard therapy.
- It would be reasonable to offer modestly accelerated radiotherapy to patients with locally advanced (stage III-IV) disease who are not candidates for concomitant chemotherapy and conventional radiation (Refer to Guideline #5-6a).

Qualifying Statements

- The emerging evidence favouring modestly accelerated fractionation over conventional fractionation has been published only in abstract form and must be regarded as preliminary. 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.

Key Evidence

- Rapid acceleration of radical radiotherapy results in excessive normal tissue toxicity. This can be minimized by reducing the total dose (as in the continuous hyperfractionated accelerated radiotherapy [CHART] regimen) or introducing a treatment interruption (as in the split-course protocols of the European Organization for Research and Treatment of Cancer trial 22811 and the Radiation Therapy Oncology Group trial 90-03) but at the expense of tumour control. These regimens have not proven superior to conventional fractionation in terms of survival and loco-regional control.
- Modest acceleration of radical radiotherapy without an accompanying reduction in total dose may be superior to conventional fractionation. A reduction in overall treatment time from seven weeks to six weeks achieved by delivering six fractions per week instead of five fractions per week, or by treating patients seven days a week instead of five days per week, or using a concomitant boost over the last 12 treatment days, yielded improved loco-regional control and survival with increased but manageable acute toxicity. Full data on long-term effects are not yet available but the effects appear to be clinically acceptable.

Related Guideline

- Please refer to companion guideline #5-6b on hyperfractionated radiotherapy in locally

advanced (stage III-IV) squamous cell carcinoma of the head and neck.

IX. PRACTITIONER FEEDBACK

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-one (47%) surveys were returned. Nineteen (37%) respondents (ten radiation oncologists, seven surgeons and two medical oncologists) indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey. Of the 19 clinicians who completed the survey, 79% agreed that the document should be approved as a practice guideline and 95% 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.	19 (100%)	0	0
There is a need for a clinical practice guideline on this topic.	16 (84%)	2 (10%)	1 (5%)
The literature search is relevant and complete.	16 (84%)	3 (16%)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	18 (95%)	1 (5%)	0
The draft recommendations in this report are clear.	19 (100%)	0	0
I agree with the draft recommendations as stated.	18 (95%)	1 (5%)	0
This report should be approved as a practice guideline.	15 (79%)	3 (16%)	0
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**
	18 (95%)	0	1 (5%)

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

Summary of Main Findings

Two (10%) respondents provided written comments. One respondent noted that the impact of altered fractionation on organ preservation is not addressed. The other respondent indicated that the guideline is not definitive, but that it is a reasonable assessment of the available data given that the data do not allow for a definitive conclusion.

Modifications/Actions

Practitioner feedback did not indicate a need to modify the draft recommendations. The guideline report was updated to reflect new evidence that emerged since the practitioner feedback survey was conducted.

X. 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 (SCCHN) who are deemed suitable for radical radiotherapy with curative intent.

Recommendations

- This group of patients should be considered for concomitant chemotherapy and conventional radiation as recommended in Cancer Care Ontario Practice Guideline Initiative guideline #5-6a.
- It would be reasonable to offer modestly accelerated radiotherapy to patients with locally advanced (stage III and IV) disease who are not candidates for concomitant chemotherapy and conventional radiation.
- Rapid acceleration of radical radiotherapy cannot be recommended as standard therapy.

Qualifying Statements

- The emerging evidence suggests that modestly accelerated radiotherapy can improve loco-regional control compared with conventional radiotherapy. Overall survival may be enhanced. 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.

Key Evidence

- Rapid acceleration of radical radiotherapy results in excessive normal tissue toxicity. This can be minimized by reducing the total dose (as in the continuous hyperfractionated accelerated radiotherapy [CHART] regimen) or introducing a treatment interruption (as in the split-course protocols of the European Organization for Research and Treatment of Cancer trial 22811 and the Radiation Therapy Oncology Group trial 9003) but at the expense of tumour control. These regimens have not proven superior to conventional fractionation in terms of survival and loco-regional control.
- Modest acceleration of radical radiotherapy without an accompanying reduction in total dose may be superior to conventional fractionation. A reduction in overall treatment time from seven weeks to six weeks achieved by delivering six fractions per week instead of five fractions per week, or by treating patients seven days a week instead of five days per week, or using a concomitant boost over the last 12 treatment days, yielded improved loco-regional control with increased but manageable acute toxicity. Full data on long-term effects are not yet available, but based on the limited evidence that is available from randomized trials the effects appear to be clinically acceptable.

Related Guidelines

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

XI. REPORT DATE

November 27, 2000

The Cancer Care Ontario Practice Guidelines Initiative guidelines are reviewed and updated

regularly. The most recent versions of published guidelines and accompanying updates can be found on the Internet at: http://www.cancercare.on.ca/.

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