Cancer Care Ontario Practice Guidelines Initiative

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

Altered Fractionation of Radical Radiation Therapy in the Management of Unresectable Non-Small Cell Lung Cancer

Practice Guideline Report #7-12

ORIGINAL GUIDELINE: October 8, 1999
MOST RECENT LITERATURE SEARCH: September 2002
NEW EVIDENCE ADDED TO GUIDELINE REPORT: October 2000
APPENDIX UPDATED: January 2003

New evidence found between completion of the original guideline and October 2000 is consistent with the original recommendations. No new evidence has been found by update searches since October 2000.

SUMMARY

Guideline Question
Do any altered fractionation radiation schemes prolong survival in the treatment of locally advanced, unresectable stage III non-small cell lung cancer (NSCLC) compared with the North American standard of 60 Gy in 30 fractions?

Target Population
These recommendations apply to patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC).

> ***Note:*** *The current standard treatment for unresected stage III NSCLC is combined modality therapy (Practice Guideline Report #7-3: Unresected Stage III Non-Small Cell Lung Cancer – see Appendix 1 in Full Report).*

Recommendations
Key Recommendations

- There is evidence from one randomized controlled trial demonstrating that Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) improves survival over standard radiotherapy of 60 Gy in 30 fractions, in patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC). Selected patients (with ECOG performance status ≥ 1 who do not fit the criteria for induction chemotherapy and radiotherapy or patients who prefer radiotherapy only) may be considered for CHART.
- Evidence from a comparative cohort study suggests that Hyperfractionated Accelerated Radiation Therapy (HART) also improves survival over standard radiotherapy.

- Of those trials designed to improve therapeutic ratios in patients with locally advanced, unresectable stage III NSCLC there is insufficient data of high quality to recommend hyperfractionation over standard radiotherapy of 60 Gy in 30 fractions. Further randomized controlled trials are necessary to confirm the benefits, if any, of hyperfractionation radiotherapy.
- Trials examining therapies providing greater convenience to patients with locally advanced, unresectable stage III NSCLC did not show evidence of a survival benefit for either hypofractionation or split-course radiotherapy. If symptom palliation is the main concern, patients may consider participating in clinical trials examining the role of hypofractionation or split-course radiotherapy.
- The effect of treatment on quality of life or health care costs was not reviewed in most of these trials. Therefore, if quality of life and health care costs are issues of concern, there is insufficient evidence at this time to draw any conclusions on the value of altered fractionation.

Qualifying Statements

- The main adverse effect associated with these altered fractionation treatments is acute esophagitis.

Methods

Entries to MEDLINE (through September 2002), CANCERLIT (through September 2002) and Cochrane Library (through Issue 4, 2002) databases have been searched for evidence relevant to this practice guideline. The most recent literature search was performed in October 2002.

Evidence was selected and reviewed by three members of the Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI) Lung Cancer Disease Site Group (Lung DSG) and methodologists. This practice guideline has been reviewed and approved by the Lung DSG, which comprises medical and radiation oncologists, pathologists, surgeons, a psychologist, a medical sociologist and two community representatives.

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 (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.

Key Evidence

- One published meta-analysis, eight randomized controlled trials, one comparative cohort study and two randomized phase I/II trials evaluating altered fractionation (including continuous hyperfractionated, accelerated, CHART, HART, Continuous Hyperfractionated Accelerated Radiation Therapy Weekendless (CHARTWEL), or hypofractionated and split-course radiotherapy) were reviewed.
- The published meta-analysis demonstrated a significant survival benefit for hyperfractionated over standard radiotherapy (odds ratio, 0.69; 95% confidence interval, 0.51 to 0.95; p=0.02). The CCOPGI's Resource Group conducted an (unpublished) meta-analysis of the same trials as the published meta-analysis which did not demonstrate a significant survival benefit for hyperfractionated over standard radiotherapy (odds ratio, 0.67; 95% confidence interval, 0.42 to 1.07; p=0.091).
- Three of four randomized controlled trials demonstrated a survival benefit for hyperfractionation compared with standard radiotherapy, although not all results were statistically significant [data from one of the three trials were not statistically significant; data from the second trial demonstrated a three year survival rate of 22% for hyperfractionated

versus 0% for standard radiotherapy, but no significance level was reported; and the third trial demonstrated a statistically significant two-year survival benefit ($p<0.05$)].

- With respect to hyperfractionated accelerated radiotherapy: one randomized controlled trial which compared CHART with standard radiotherapy demonstrated an advantage with CHART for two-year survival rates (30% versus 21%) and five-year survival rates (20% versus 13%) (hazard ratio, 0.78; 95% confidence interval, 0.65 to 0.94; $p=0.008$). One comparative cohort study demonstrated a three-year survival benefit for HART of 28% versus 6% for standard radiotherapy ($p<0.001$). No survival data were cited in the full report of one phase I/II study of CHARTWEL; the authors state that there was no survival difference between the two groups at 18 months after radiotherapy.
- One randomized controlled trial showed that hypofractionation improved three-year survival (19% versus 9% for standard radiotherapy) but no significance was reported. Acute treatment toxicity was reduced in the hypofractionation patients (30% experienced no esophagitis compared with 70% of standard radiotherapy patients).
- Hyperfractionation, CHART and hypofractionated radiotherapy demonstrated no significant differences in late toxicity compared with standard radiotherapy. Esophagitis was more severe ($p=0.004$) and of longer duration ($p<0.0001$) in patients receiving accelerated radiotherapy compared to the standard radiotherapy group. Esophagitis was experienced by 87% of HART patients versus 44% of standard radiotherapy patients ($p<0.05$). Accelerated radiotherapy was shown to increase acute toxicity over standard radiotherapy. It is unclear whether toxicity was monitored for split-course radiotherapy.

Prepared by the Lung 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 (CCO) 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 multidisciplinary Disease Site Groups of the CCOPGI using the methodology of the Practice Guidelines Development Cycle.[1] The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic review, evidence synthesis and input from a broad community of practitioners. They are intended to promote 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.

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 the most current versions of the guideline reports and information about the CCOPGI and the Program, please visit our Internet site at:
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FULL REPORT

I. QUESTION

Do any altered fractionation radiation schemes prolong survival in the treatment of locally advanced, unresectable stage III non-small cell lung cancer (NSCLC) compared with the North American standard of 60 Gy in 30 fractions?

II. CHOICE OF TOPIC AND RATIONALE

Altered fractionation radiation is a type of radiation therapy designed either to increase control of the primary tumour and decrease the toxicity to normal tissues, thereby improving the therapeutic ratio, or to permit greater convenience for patients without compromising primary tumour control and normal tissue effects. There are at least five altered fractionation schemes of radiation therapy: a) hyperfractionated radiation therapy; b) accelerated radiation therapy; c) hyperfractionated accelerated radiation therapy; d) hypofractionated radiation therapy, and e) split-course radiation therapy.

III. DEFINITIONS

Hyperfractionated Radiation Therapy (Non-Accelerated)

Hyperfractionation is defined as the use of two or more fractions daily of smaller than conventional fraction size. This results in an increased total nominal tumour dose compared with standard radiation. The rationale is to exploit the enhanced repair capacity of dose-limiting, late-reacting, normal tissues compared with rapidly proliferating tumours.

Accelerated Radiation Therapy

Accelerated radiation therapy is defined as the use of two or more fractions of standard fraction size daily to the same conventional total dose as standard radiotherapy, but increasing the number of fractions per week and shortening the overall treatment time. The intent of accelerated radiation therapy is to reduce re-population in rapidly proliferating tumours. Acute normal tissue toxicity is usually increased.

Hyperfractionated Accelerated Radiation Therapy

Hyperfractionated accelerated radiation therapy combines the features of an accelerated and hyperfractionated regimen as outlined above (i.e., the use of two to three fractions of smaller fraction size daily, delivered over a shorter period of time than conventional therapy). The rationale is to reduce long-term normal tissue toxicity by smaller fraction size and to reduce the risk of re-population in rapidly proliferating tumours. Variants of hyperfractionated accelerated radiation therapy include Continuous Hyperfractionated Accelerated Radiation Therapy (CHART), Continuous Hyperfractionated Accelerated Radiation Therapy Weekendless (CHARTWEL), and Hyperfractionated Accelerated Radiation Therapy (HART).

Hypofractionated Radiation Therapy

Hypofractionation is an altered fractionation scheme in which radiation is given at least once weekly instead of daily. The fraction size is larger than the conventional 1.8 to 2.0 Gy fraction and the total overall treatment time is usually shorter than that of the conventional treatment. In the past, hypofractionation has been used primarily to accommodate radiation modifiers, e.g., hyperbaric oxygen (1) and radiosensitizers (2,3), both of which require fewer weekly treatments to achieve best results or are limited to a reduced frequency of treatments by potential toxicity. Hypofractionation schedules have been used to accommodate relative equipment shortages and the convenience of patients who must travel long distances (4).

Split-Course Radiation Therapy

Split-course radiation therapy is an altered fractionation regimen originally designed to diminish radiation morbidity by splitting the total dose into at least two separate courses with an interruption of 10 to 14 days (5). Most radiation oncologists consider split-course radiotherapy to be disadvantageous compared with continuous treatment because the decreased radiation morbidity of normal tissues will also result in lower anti-tumour efficiency and reduced local control rates. There is also concern about repopulation during the rest period (6). There are at least three regimens of split-course radiotherapy:

1. Standard total treatment dose at 1.8 to 2.0 Gy fraction size, but with different total treatment time and an interruption interval of one to two weeks (7).
2. Standard total treatment dose but different fraction size to maintain the same overall treatment time including the interruption interval of one to two weeks (8).
3. Different total treatment dose, fraction size, overall treatment time and interruption interval (9).

Members of the Cancer Care Ontario Provincial Lung Cancer Disease Site Group (Lung DSG) decided to examine the altered fractionation schemes and determine whether there was evidence that any of these regimens improve the survival of patients with locally advanced, unresectable stage III NSCLC.

IV. METHODS

Guideline Development

This guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle (1u). Evidence was selected and reviewed by three members of the CCOPGI's Lung DSG and methodologists. The guideline is a convenient and up-to-date source of the best available evidence on altered fractionation of radical radiation therapy in the management of unresectable NSCLC, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. It is intended to promote evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

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

The MEDLINE (Ovid) database was searched from January 1987 to July 1999 and the CANCERLIT (Ovid) database from January 1987 to April 1999 using these terms: carcinoma, non small cell lung; radiotherapy; hyperfractionation; accelerated fractionation; hypofractionation; altered fractionated; randomized controlled trial; meta-analysis; and guidelines. The Physician Data Query file (PDQ) and the Cochrane Library (1999, Issue 2) were also searched to identify clinical trials.

Update

The original literature search has been updated using the MEDLINE and CANCERLIT (through September 2002) and Cochrane Library (through Issue 4, 2002) databases and the

2002 proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society for Therapeutic Radiology and Oncology.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomized controlled trials comparing altered fractionation (including continuous hyperfractionated, accelerated, CHART, HART, CHARTWEL, or hypofractionated and split-course radiotherapy) with conventional fractionation in the treatment of stage III NSCLC.
2. Comparative cohort studies and phase I/II studies were eligible where data from randomized controlled trials were not available.
3. Survival was the primary outcome of interest. Toxicity was also considered.

Synthesizing the Evidence

A published meta-analysis (fixed effects Peto model) of three randomized controlled trials comparing standard fractionation radiotherapy to hyperfractionated radiotherapy was identified (10). The CCOPGI's Resource Group conducted an (unpublished) meta-analysis of two-year survival data from the same three randomized controlled trials (fixed effects Peto model) using the software application Meta-analyst[0.988] provided by Dr. Joseph Lau, Tufts New England Medical Centre, Boston, MA. Results were expressed as an odds ratio for deaths, with a 95% confidence interval. Pooling of data could not be performed for any other altered fractionation strategy due to lack of published randomized controlled trials.

V. RESULTS

Literature Search Results

Eight randomized controlled trials, one comparative cohort study and two randomized phase I/II trials were reviewed. Results are summarized in Table 1a and details of the radiotherapy regimens are summarized in Table 2a; the phase I/II trial on hyperfractionation was excluded from the tables, since randomized controlled trial data were available, but is discussed in the text.

Update

Reviewing and updating activities identified three reports, each of which provided updated or final data for a trial already included in the practice guideline report. Results provided in the new reports are summarized in Table 1b and details of the radiotherapy regimens in the new reports are provided in Table 2b.

Table 1a. Trials in the original practice guideline report that examined altered fractionated radiotherapy: Results.

First Author, Date (Reference)		Tumour Stage	No. Patients	Survival (%)			Median Survival (mo)	Significance
				1-yr	2-yr	3-yr		
Hyperfractionation								
Sause 1995 (11)	Standard	95% III + II	149	46	19	6	11.4	p=0.08 logrank
	Hfx		152	51	24	13	12.3	
Fu 1994 (12)	Standard	90% III + I, II	51	32	9	NR	NR	p<0.05 2 year survival
	Hfx		54	53	13	NR	NR	
Kagami 1992 (13)	Standard	100% III	18	NR	31	0	NR	NR
	Hfx		18	NR	50	22	NR	
Wang 1996 (14)	*Standard	68% III + II	33	64	15	3	NR	NR
	*Hfx		30	80	23	10	NR	
Hyperfractionated Accelerated								
CHART								
Saunders 1996, 1997 (15,16)	Standard	61% III + I, II	338	55	20	NR	NR	HR=0.76 95% CI 0.63 to 0.92, p=0.004
	CHART		225	63	29	NR	NR	
CHARTWEL								
Saunders 1998 (17) Phase I/II	54 Gy	82% III+ I	17	NR	NR	NR	NR	not significant
	60 Gy	70% III + I, II	30	NR	NR	NR	NR	
HART								
Fu 1997 (18) Comparative Cohort Study	Standard	85% III + I, II	50**	60	18	6	14	‡p<0.001 §p<0.05
	HART		60**	72	47	28	22.6	
Accelerated								
Ball 1995 (19) (preliminary results)		72% III + I, II	100 (whole group)	NR	33***	NR	17.1***	NR
Hypofractionation								
Slawson 1988 (20)	Standard	94% III + IV	63	49	23	9	NR	NR
	Hypo		57	59	29	19	NR	NR
Split-Course								
Routh 1995 (7)	Standard	69% III + I, II	159	NR	NR	NR	10.9	p=0.8298
	Split		114	NR	NR	NR	11.6	

NOTE: CI = confidence interval; Hfx = hyperfractionation; HR = hazard ratio; Hypo = hypofractionation; mo = months; No. = number; NR = not reported; yr = year.

* plus chemotherapy (adriamycin, etoposide, cisplatin)

** both groups treated during the same time period

*** whole group

‡ 3-year survival

§ median survival

Table 1b. Trials found during review and updating activities which examined altered fractionated radiotherapy: Results.

First Author, Date (Reference)		Tumour Stage	No. Patients	Survival (%)			Median Survival (mo)	Significance
				1-yr	2-yr	3-yr		
Hyperfractionation								
Sause 2000 (4u) * RTOG 8808	Standard	99% III +II	152	47	21	*5-yr:* 5	11.4	p=NS
	Hfx	96% III +II	154	52	24	*5-yr:* 6	12	
Hyperfractionated Accelerated								
CHART								
Saunders 1999 (2u) †	Standard	61% III+ I, II	338	NR	21	13	13	HR=0.78 95% CI 0.65 to 0.94, p=0.008 logrank
	CHART	61% III+ I, II	225	NR	30	20	16.5	
Accelerated								
Ball 1999 (3u) ‡§	Standard	78% III+ I, II	53	60	26	*5-yr:* 10	13.8	NR
	Accelerated	78% III+ I, II	46	61	28	*5-yr:* 13	14.4	

NOTE: CI = confidence interval; Hfx = hyperfractionation; HR = hazard ratio; mo = months; No. = number; NR = not reported; NS = not statistically significant; RTOG = Radiation Therapy Oncology Group; yr = year.

* This is the final report of the trial included in the original practice guideline as Sause 1995 (11) and Sause 1998 (21) (abstract).
† This report provides mature data from the trial included in the original practice guideline as Saunders 1996, 1997 (15,16).
‡ This is the final report of the trial included in the original practice guideline as Ball 1995 (19).
§ Survival data cited are for patients with stage III disease only. There were 42 stage III patients in the standard radiotherapy arm and 36 stage III patients in the accelerated arm.

Table 2a. Trials in the original practice guideline report examining altered fractionated radiotherapy: Radiotherapy schedules.

First Author, Year (Reference)	Total Dose and Radiotherapy Schedules	
Hyperfractionation		
Sause 1995 (11)	Standard	60 Gy; 2 Gy/fraction, 5 days/week over 6 weeks
	Hyperfractionated	69.6 Gy; 1.2 Gy/fraction twice per day, consecutive days until total dose achieved
Fu 1994 (12)	Standard	63.9 Gy; 1.8 to 2.0 Gy/fraction daily
	Hyperfractionated	69.6 Gy; 1.15 to 1.25 Gy/fraction twice per day, 52 fractions
Kagami 1992 (13)	Standard	65 Gy; 2.5 Gy/fraction daily, 26 fractions
	Hyperfractionated	71.5 Gy; 1.37 Gy/fraction twice per day
Wang 1996 (14)	*Standard	60 Gy; 2 Gy/fraction, 5 days/week over 7 weeks
	* Hyperfractionated	72 Gy; 1.2 Gy/fraction twice per day, 5 days/week over 3 weeks; second course given after 2 weeks rest
Hyperfractionated Accelerated		
CHART		
Saunders 1996, 1997 (15,16)	Standard	60 Gy; 2 Gy/fraction, 30 fractions over 6 weeks
	CHART	54 Gy; 1.5 Gy three times per day over 12 days
CHARTWEL		
Saunders 1998 (17) Phase I/II	54 Gy	54 Gy; 1.5 Gy/fraction, 3 fractions/day, Monday to Friday over 16 days
	60 Gy	60 Gy; 1.5 Gy/fraction, 3 fractions/day, Monday to Friday over 18 days
HART		
Fu 1997 (18) Comparative Cohort Study	Standard	63.9 Gy; 34 fractions over 48 days
	HART	74.3 Gy; 1.1 Gy/fraction, 3 fractions/day, 5 days/week, 33 days
Accelerated		
Ball 1995 (19) (preliminary results)	† Standard	60 Gy in 30 fractions, 5 fractions/week over 6 weeks
	† Accelerated	60 Gy in 30 fractions, 10 fractions/week over 3 weeks
Hypofractionation		
Slawson 1988 (20)	Standard	60 Gy; 2 Gy/fraction, 5 fractions/week over 6 weeks
	Hypofractionated	60 Gy; 5 Gy/fraction, 1 fraction/week over 12 weeks
Split-Course		
Routh 1995 (7)	Standard	55 to 59.4 Gy in 33 fractions
	Split	60 to 53 Gy in 35 fractions; treatment interrupted for 10 to 14 days after first 18 fractions

* plus chemotherapy (mitomycin, etoposide, cisplatin)
† with/without chemotherapy

Table 2b. Trials found during review and updating activities which examine altered fractionated radiotherapy: Radiotherapy schedules

First Author, Year (Reference)	Total Dose and Radiotherapy Schedules	
Hyperfractionation		
Sause 2000 (4u)	Standard	60 Gy; 2 Gy/fraction, 5 days/week over 6 weeks
	Hyperfractionated	69.6 Gy; 1.2 Gy/fraction twice per day, consecutive days 5 days/week until total dose achieved
Hyperfractionated Accelerated		
CHART		
Saunders 1999 (2u) *	Standard	60 Gy; 2 Gy/fraction, 30 fractions over 6 weeks
	CHART	54 Gy; 1.5 Gy three times per day over 12 days
	HART	74.3 Gy; 1.1 Gy/fraction, 3 fractions/day, 5 days/week, 33 days
Accelerated		
Ball 1999 (3u) †	‡ Standard	60 Gy in 30 fractions, 5 fractions/week over 6 weeks
	‡ Accelerated	60 Gy in 30 fractions, 10 fractions/week over 3 weeks

* This report provides mature data from the trial included in the original practice guideline as Saunders 1996, 1997 (15,16).
† This is the final report of the trial included in the original practice guideline as Ball 1995 (19).
‡ with/without chemotherapy

Outcomes

Hyperfractionated Radiotherapy

One meta-analysis, four randomized controlled trials and one randomized phase I/II trial have been published comparing hyperfractionated radiotherapy to standard radiotherapy in patients with locally advanced, unresectable stage III NSCLC.

Sause et al (11) conducted a three-arm randomized controlled trial in which patients received standard fractionation radiotherapy, combined modality therapy (standard fractionation preceded by two cycles of cisplatin and vinblastine) or hyperfractionated radiotherapy. Ninety-five percent of patients had stage IIIA or IIIB NSCLC. One-year survival rates were 46% for standard radiotherapy, 60% for combined modality therapy, and 51% for hyperfractionated radiotherapy. Median survival rates were 11.4 months, 13.8 months, and 12.3 months, respectively. A comparison of the overall survival curves demonstrated that combined modality therapy was superior to either standard or hyperfractionated radiotherapy (p=0.03 logrank), with no statistically significant benefit observed for hyperfractionated over standard radiotherapy (p=0.08 logrank, p=0.03 Wilcoxon). There were six cases of acute toxicity (grade 4) related to radiotherapy; four occurred in the hyperfractionated group, one in the standard radiotherapy group and one in the combined modality group.

Sause et al published five-year results, in abstract form (21). With minimum follow-up of five years, five-year survival rates were 5% for standard radiotherapy, 8% for combined modality therapy, and 6% for hyperfractionated radiotherapy; median survival rates were 11.4 months, 13.7 months, and 12.2 months respectively. The survival differences were statistically significant, favouring the combined modality arm (p=0.04). Treatment-related deaths were highest in the combined modality arm; four patients died in the combined modality arm, one patient in the hyperfractionated arm, and no patients in the standard therapy arm.

Fu et al (12) randomized patients to receive hyperfractionated radiotherapy or standard radiotherapy. Ninety percent of patients had stage III NSCLC. Hyperfractionation improved one- and two-year survival rates, as well as local control rates. One-year survival rates were 64% for hyperfractionated radiotherapy and 18% for standard radiotherapy, while two-year survival rates were 32% and 6%, respectively (p<0.05). One-year local control rates were 47.3% and 29.1%, respectively (p<0.05).

Kagami et al (13) randomized 18 patients to receive hyperfractionated radiotherapy and 18 patients to receive standard radiotherapy. All patients had stage IIIA or IIIB NSCLC. The

overall two-year survival rates were 50% for hyperfractionated radiotherapy and 31.1% for standard radiotherapy; three-year survival rates were 21.8% and 0%, respectively. This trial suggests that hyperfractionated radiotherapy may improve survival but significance was not reported. Fever due to radiation pneumonitis occurred in seven hyperfractionated patients and four standard radiotherapy patients. No severe late toxicity was observed in either group.

Wang et al (14) randomized patients to four different groups: hyperfractionated radiotherapy plus chemotherapy, standard radiotherapy plus chemotherapy, split-course radiotherapy plus chemotherapy, and standard radiotherapy-alone. Sixty-eight percent of patients had stage III NSCLC and they were evenly distributed across all four groups. The one-year survival rate was 80% for hyperfractionated radiotherapy plus chemotherapy and 63.6% for standard radiotherapy plus chemotherapy. Two-year survival rates were 23.3% and 15.15%, respectively, and three-year survival rates were 10% and 3.3%, respectively. The observed differences in survival rates were not statistically significant, likely due to the small number of patients.

Stuschke and Thames (10) conducted a meta-analysis on survival data from the trials by Sause et al (11), Fu et al (12), and Kagami et al (13). They reported improved survival for hyperfractionated radiotherapy over standard radiotherapy (odds ratio, 0.69; 95% confidence interval, 0.51 to 0.95; p=0.02).

Data from published reports of the trials by Sause et al (11), Fu et al (12), and Kagami et al (13) were pooled and examined by the CCOPGI's Resource Group, using Meta-analyst[0.988] (Figure 1). Based on two-year survival rates and a fixed effects model (Peto), this meta-analysis did not demonstrate a significant survival benefit for hyperfractionated radiotherapy over standard radiotherapy (odds ratio, 0.67; 95% confidence interval, 0.42 to 1.07; p=0.091). This meta-analysis has not been published.

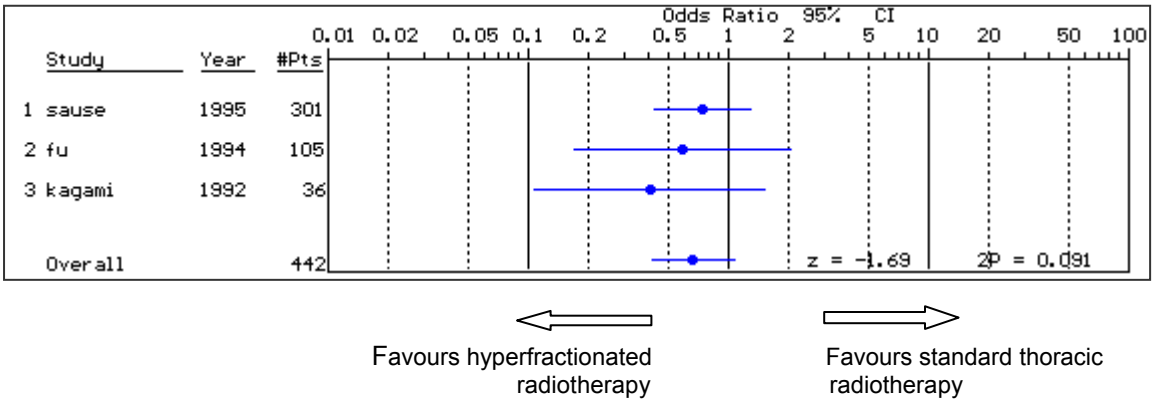
Cox et al (22,23) randomized 848 patients with stage II to III NSCLC to either standard radiotherapy (60 Gy total) or various hyperfractionated doses (64.8 Gy, 69.6 Gy, 74.4 Gy, and 79.2 Gy total doses) in a phase I/II randomized dose-escalation study. Patients were initially randomized to the three lowest doses (60 Gy, 64.8 Gy, 69.6 Gy). After assessment of acute and late risks, the fourth dose arm (74.4 Gy) was opened and the 60 Gy arm closed, after which the 79.2 Gy arm was opened and the 64.8 Gy arm closed. Because Cox et al (16, 17) is a phase I/II randomized trial that entered patients into the various arms at different times, it is not comparable to, and was not analyzed with, the data from Sause (11), Fu (12), Kagami (13) and Wang (14).

Update

Sause et al published the final results of their three-arm randomized controlled trial in which patients received standard fractionation radiotherapy, combined modality therapy (standard fractionation preceded by two cycles of cisplatin and vinblastine) or hyperfractionated radiotherapy. (4u). Final results indicated median survival rates of 11.4 months, 13.2 months, and 12 months, respectively, with five-year survival rates of 5%, 8% and 6% respectively. Comparison of the overall survival curves demonstrated that combined modality therapy was superior to either standard or hyperfractionated radiotherapy (p=0.04 logrank), with no statistically significant benefit observed for hyperfractionated over standard radiotherapy. There were six cases of acute toxicity (grade 4 or higher) related to radiotherapy; four occurred on the hyperfractionated arm and one each in the standard radiotherapy and combined modality arms. Late toxicity (90 days or longer after treatment, grade 4 or higher) occurred in three patients on the standard radiotherapy arm and five patients on each of the combined modality and hyperfractionated arms. Treatment-related deaths were highest in the combined modality arm; three patients died on the combined modality arm, one patient in the hyperfractionated arm, and no patients in the standard therapy arm.

Figure 1. Meta-analysis Examining Standard versus Hyperfractionated Thoracic Radiotherapy

Study	Hyperfractionated radiotherapy		Standard thoracic radiotherapy		Odds Ratio for Death	95% Confidence Interval	
	Deaths	Total	Deaths	Total		Low	High
Sause 1995 (11)	116	152	121	149	0.75	0.43	1.30
Fu 1994 (12)	47	54	47	51	0.58	0.17	2.02
Kagami 1992 (13)	9	18	13	18	0.40	0.11	1.51
TOTAL	172	224	181	218	0.67	0.42	1.07



Accelerated Radiation Therapy

Preliminary results from one randomized controlled trial of accelerated radiotherapy have been published by Ball et al (19). One hundred patients were randomized to four groups: standard radiotherapy, accelerated radiotherapy, standard radiotherapy plus carboplatin in weeks one and five, or accelerated radiotherapy plus carboplatin in week one. Seventy-two percent of patients had stage III NSCLC. The estimated median survival for the whole group was 17.1 months (95% confidence interval, 13.2 to 22.0 months); no comparative survival data are available yet.

Update

Ball et al published the final report of four-arm randomized controlled trial of accelerated radiotherapy versus standard radiotherapy with or without chemotherapy (3u). Two hundred and four patients were randomized to four groups: standard radiotherapy only, accelerated radiotherapy only, standard radiotherapy plus chemotherapy (carboplatin for five days during weeks 1 and 5), or accelerated radiotherapy plus chemotherapy (carboplatin for five days during week 1). Seventy-eight percent of patients in the two radiotherapy-only arms had stage III NSCLC. Median survival for patients with stage III disease in the standard radiotherapy arm was 13.8 months, for stage III patients in the accelerated radiotherapy arm, 14.4 months. One- and two-year survival rates for the stage III patients who received standard radiotherapy were 60% and 26%, for accelerated radiotherapy were 61% and 28%. No statistical comparisons between these two groups were reported.

Hyperfractionated Accelerated Radiation Therapy

Continuous Hyperfractionated Accelerated Radiation Therapy (CHART)

One randomized controlled trial examining the effect of CHART has been published by Saunders et al (15,16). Patients were randomized to receive either standard radiotherapy or CHART. Each group consisted predominantly (61%) of patients with stage IIIA or IIIB NSCLC. All analyses were by intention-to-treat. Both survival and local control were improved for CHART. One-year survival was 63% for CHART versus 55% for standard radiotherapy, while

two-year survival rates were 29% and 20%, respectively. The Kaplan-Meier hazard ratio was 0.76 (95% confidence interval, 0.63 to 0.92; p=0.004 logrank), indicating a 24% reduction in the relative risk of death with CHART at two years. The hazard ratio for local control was 0.77 (95% confidence interval, 0.61 to 0.97; p=0.027), indicating a 23% reduction in relative risk of progression with CHART. The two-year progression-free rate was 23% for CHART and 15% for standard radiotherapy. Acute esophagitis was more severe in patients receiving CHART but at three months was similar to that of patients receiving standard radiotherapy. There was no difference in late morbidity.

These data were updated by direct communication with the author. Median survival for CHART was 15.6 months compared with 12.9 months for standard radiotherapy. This corresponds to a decrease in the relative risk of death of 22%. Four year survival for CHART was 13% compared with 6% for standard radiotherapy. This corresponds to a hazard ratio of 0.78 (95% confidence interval, 0.65 to 0.94; p=0.008).

Additional data were collected to assess the long- and short-term side effects of CHART versus conventional radiotherapy, using the Rotterdam Symptom Checklist and the Hospital Anxiety and Depression Scale (24). Results confirm the previous finding of few differences in side effects between CHART and conventional radiotherapy.

Update

Saunders et al published mature data from the randomized controlled trial examining the effect of CHART (2u). Patients were randomized to receive either standard radiotherapy or CHART. Mature data confirmed that both survival and local control were improved for CHART. Two-year survival was 30% for CHART versus 21% for standard radiotherapy, while three-year survival rates were 20% and 13%, respectively. The Kaplan-Meier hazard ratio for death was 0.78 (95% confidence interval, 0.65 to 0.94; p=0.008 logrank), indicating a 22% reduction in the relative risk of death with CHART at three years. Median survival was 16.5 months for CHART versus 13 months for standard therapy. The hazard ratio for local control was 0.79 (95% confidence interval, 0.63 to 0.98; p=0.033), indicating a 21% reduction in relative risk of progression with CHART. Acute esophagitis was confirmed to be more severe in patients receiving CHART but at three months was similar to that of patients receiving standard radiotherapy. There was no difference in late morbidity.

Continuous Hyperfractionated Accelerated Radiation Therapy Weekendless (CHARTWEL)

Saunders et al (17) have published a report of a phase I/II dose escalation study of CHARTWEL. Sixty-four patients were entered into the study and assigned to one of four CHARTWEL regimens: 54 Gy over 16 days (n=17), 57 Gy over 17 days (n=7), 58.5 Gy over 17 days (n=10) or 60 Gy over 18 days (n=30). Data cited in the paper are comparisons of 54 Gy versus 60 Gy. Acute and late reactions in the 57 and 58.5 Gy arms were no higher than with 54 Gy. The authors state that there was no difference in overall survival between 54 Gy and 60 Gy in the first 18 months after radiotherapy; no survival data are cited in the report.

Dysphagia and analgesia use were measured on scales developed by the authors. Acute dysphasia was more severe, required more analgesia and lasted longer in the 60 Gy group, but by 12 weeks 54 and 60 Gy groups showed similar levels of esophagitis. No differences between the groups were seen in early radiation pneumonitis; after 6 months, the 60 Gy group showed a higher incidence of mild pulmonary complications.

Hyperfractionated Accelerated Radiation Therapy (HART)

One comparative cohort study has been published by Fu et al with regard to HART (18). There were 60 patients in the HART group; 50 patients were selected from the control group of another trial of hyperfractionated radiation for NSCLC in order to compare the outcome of HART with conventional radiotherapy. Eighty-five percent of patients receiving HART and 86% of those receiving standard radiotherapy had stage IIIA or IIIB NSCLC. Patients with stage III

disease also received adjuvant chemotherapy, before and/or after radiotherapy (cisplatin 25-30mg/m^2/day and etoposide 50-60mg/m^2/day for three days each month). Both survival and local control were improved in the HART group; three-year survival was 28% versus 6%, $p<0.001$ and three-year local control was 29% versus 5%, $p=0.008$. Median survival for HART was 22.6 months compared with 14.0 months for standard radiotherapy patients ($p<0.05$). Radiation esophagitis was the predominant acute side effect; 87% of HART patients experienced grade 1-3 esophagitis compared with 44% of standard radiotherapy patients ($p<0.05$).

Hypofractionated Radiation Therapy

One randomized controlled trial examining hypofractionated radiotherapy has been published by Slawson et al (20). Sixty-three patients received standard radiotherapy of 60 Gy (2 Gy/fraction, 5 fractions/wk, 6 wks) and 57 patients received hypofractionated radiotherapy of 60 Gy (5 Gy/fraction, 1 fraction/wk, 12 wks). All patients had stage III NSCLC except for five stage IV NSCLC patients in the control group and two in the hypofractionated radiotherapy group. Both survival and local control rates were improved with hypofractionated radiotherapy. One-, two-, and three-year survival rates for hypofractionated radiotherapy were 59%, 29% and 19%, respectively, compared with 49%, 23%, and 9%, for standard radiotherapy. No significance values were provided. Seventy percent of hypofractionated radiotherapy patients experienced no esophagitis compared with 30% for standard radiotherapy.

Split-course Radiation Therapy

One randomized controlled trial examining split-course radiotherapy was identified, in which total dose and fraction size were similar in both arms of the study. Routh et al (7) randomized 159 patients to receive standard radiotherapy and 114 patients to receive split-course radiotherapy where treatment was interrupted for 10 to 14 days after the first 18 fractions, followed by 17 further treatments. Sixty-nine percent of patients had stage IIIA or IIIB NSCLC. There was no significant difference in survival between the two groups ($p=0.83$ logrank). Median survival for the standard radiotherapy group was 11.6 months compared with 10.9 months for split-course radiotherapy. A detailed analysis of morbidity was not reported.

VI. INTERPRETIVE SUMMARY

Altered fractionation can be divided into regimens that are designed to improve the therapeutic ratio (hyperfractionation; accelerated radiation therapy; and hyperfractionated, accelerated radiation therapy) and those which are designed to permit greater convenience for the patient (hypofractionation and split-course radiation therapy).

Altered Fractionation Designed to Improve Therapeutic Ratios

Hyperfractionation

Three of four randomized controlled trials (12,13,14) and one randomized phase I/II trial (22,23) demonstrated improved survival for hyperfractionated over standard radiotherapy. This was found to be statistically significant in one randomized controlled trial (12). A fourth randomized controlled trial did not demonstrate a survival benefit or detriment for hyperfractionated radiotherapy over either standard radiotherapy or standard radio-chemotherapy (11). A published pooled analysis of data from three of these randomized controlled trials (10) found that hyperfractionated radiotherapy significantly improved survival compared with standard radiotherapy (odds ratio, 0.69; 95% confidence interval, 0.51 to 0.95; $p=0.02$). An unpublished meta-analysis of the same three trials (conducted by the CCOPGI's Resource Group using the Peto method) failed to demonstrate a significant survival benefit for hyperfractionated over standard radiotherapy (odds ratio, 0.67; 95% confidence interval, 0.42 to 1.07; $p=0.091$). We cannot account for the discrepancy other than that contributed by different

algorithms used by each group to conduct the meta-analyses. It is possible that the published meta-analysis used the number at risk from the published reports of the three trials as their denominator. This would result in precision estimates (confidence intervals) at each time point that are wider than those found by the CCOPGI's Resource Group.

While the majority of patients included in these hyperfractionation trials had stage III NSCLC (90% to 100%), only 68% of patients had stage III NSCLC in one trial (14). This study was not included in either pooled analysis. There was no significant difference in toxicity between the hyperfractionated and control groups, except for an increase in acute esophagitis that was found to be significant in the phase I/II trial (22,23).

Meta-analyses provide an estimate of the overall magnitude of a treatment effect for the total body of available evidence. However meta-analyses should be carefully assessed before applying them as the basis of a treatment recommendation in the absence of a large, definitive trial. Many studies are available which provide guidelines for conducting and appraising meta-analyses. Large meta-analyses (greater than 200 outcome events) using individual patient data or fully published data, free from selection bias and with p values ≤ 0.01 are likely to be clinically relevant (25-29). Due to the discrepancy of results between the published and unpublished meta-analyses, a concern regarding the sensitivity of meta-analysis, the absence of individual patient data in either meta-analysis, and the modest p value in the published meta-analysis ($p=0.02$), the Lung Cancer Disease Site Group concluded that there is insufficient data of high quality at this time to recommend hyperfractionated radiotherapy. Further trials are necessary to confirm the findings and, if possible, further collaborative study using individual patient data for a meta-analysis.

Accelerated Radiation Therapy

Preliminary results from one randomized controlled trial indicate that esophagitis was more severe ($p=0.0041$) and experienced for a longer duration ($p<0.0001$) in patients receiving accelerated radiotherapy compared with standard radiotherapy (19). Data comparing survival in both trial groups is not yet available. Therefore, accelerated radiation is not recommended outside the context of a clinical trial.

Hyperfractionated Accelerated Radiotherapy

One randomized controlled trial comparing CHART to standard radiotherapy showed a 24% reduction in the relative risk of death in patients receiving CHART ($p=0.004$) (15,16). Of note, 61% of patients in each arm of the trial had stage III NSCLC. Since survival is known to be superior for patients with stage I and II disease, disease stage of patients in this study should be taken into account when overall survival rates are considered. While acute esophagitis was initially more severe in the CHART group, levels were equal to the control group at three months. This information was updated by communication with the author. The median survival was greater for CHART (15.6 months versus 12.9 months; relative risk of death, 22% less for CHART). Four-year survival for CHART was 13% compared with 6% for standard radiotherapy. This corresponds to a hazard ratio of 0.78 (95% confidence interval, 0.65 to 0.94; $p=0.008$). One phase I/II CHARTWEL study (17) does not indicate whether there is a survival benefit for this type of radiotherapy compared with standard radiotherapy, or whether it results in toxicity. One comparative cohort study comparing HART to standard radiotherapy (18) demonstrated significant survival benefit for the HART group ($p<0.001$ for three-year survival and $p<0.05$ for median survival) with esophagitis as a side effect of HART; however, randomized controlled trials are required before recommendation of HART.

Therefore, of these three modes of hyperfractionated accelerated radiotherapy, only CHART can be recommended over standard radiotherapy for selected patients. These selected patients might include those patients who for various reasons are not candidates for induction chemotherapy (e.g., serious renal disease, neuropathy) or who refuse to receive chemotherapy.

Altered Fractionation Designed to Promote Greater Convenience for Patient

Hypofractionated Radiotherapy

One randomized controlled trial comparing hypofractionated to standard radiotherapy resulted in improved survival rates at one, two and three years for hypofractionation, although it is unclear whether these results were statistically significant (20). Esophagitis, nausea and vomiting were found to be greater in the control group. More studies are necessary before hypofractionated radiotherapy can be recommended over standard radiotherapy in suitable patients.

Split-Course Radiation Therapy

One randomized controlled trial showed similar median survival rates for split-course radiotherapy and standard radiotherapy, with no clear evaluation of treatment-related toxicity (7). Therefore, split-course radiotherapy cannot be recommended over standard radiotherapy until further evidence is available.

Conclusion to Interpretive Summary

Of those strategies designed to improve therapeutic ratios, hyperfractionation cannot be recommended due to insufficient and conflicting data. Evidence from one randomized controlled trial indicates that CHART significantly improves survival over standard radiotherapy, with esophagitis as a side effect. CHART is a reasonable treatment option in selected patients as described above. While HART also appears to improve survival over standard radiotherapy, evidence thus far is from a comparative cohort study only; therefore, phase III trials are required before this treatment may be recommended. Accelerated radiotherapy has not been shown to improve survival. The trials designed to promote greater convenience for the patient (hypofractionated or split-course radiotherapy) did not demonstrate a significant survival benefit over standard radiotherapy.

VII. ONGOING TRIALS

Protocol IDs	Title and details of trial
E-2597	**Accelerated Hyperfractionation** Phase III randomized study of induction paclitaxel and carboplatin followed by standard radiotherapy vs. hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA or IIIB NSCLC. Outcomes of interest: response rate, duration of response, survival. Projected accrual: 294 patients within 3.5 years. Status: closed as of November 2002. Summary last updated: 08/2001.
ARO 97-1:	**CHARTWEL** A randomized multicentre trial of conventional fractionated radiotherapy versus CHARTWEL radiotherapy in patients with locally advanced, inoperable NSCLC. The main endpoint is survival. Projected accrual: 665 patients. The trial was activated in 1997. As of 2001, 230 patients have been accrued (5u).

VIII. DISEASE SITE GROUP CONSENSUS PROCESS

The Lung DSG recognized that the acceptance of CHART as a new standard of treatment in patients with locally advanced NSCLC would have a major impact on radiotherapy resources in Ontario. The scheduling of radiotherapy three times per day for 12 consecutive days would be logistically difficult and require treatment centres to open, for at least some patients, seven days per week. The incremental operating cost to radiotherapy treatment centres from the change in hours of operation is likely to be significant but potentially offset by

decreased length of stay in hospital or lodges for out of town patients. For all patients, treatment is completed more quickly which reduces out of pocket expenses and inconvenience. Further studies are necessary to evaluate the economic issues associated with CHART in the Canadian health care environment.

Studies are also required comparing CHART to the current standard of combined modality therapy (induction chemotherapy followed by radical radiotherapy) in good performance-status patients with locally advanced NSCLC. At present, in the absence of any evidence of superiority of CHART over combined modality therapy, its use should be limited to selected patients who either cannot take induction chemotherapy or who refuse it. These limited indications for the use of CHART should not have a major impact on resources.

The Lung DSG's concerns about the meta-analysis published by Stuschke and Thames (10) were addressed through consultation with Dr. G. DeBoer (biostatistician from the University of Toronto), and suggestions from Dr. G. Browman. The Lung DSG recognized that there were insufficient data (or data of uncertain quality) for the acceptance of hyperfractionated radiation as the new standard of treatment in patients with locally advanced NSCLC. The odds ratios determined by the two meta-analyses were very similar (0.69 and 0.67). Although the significance levels were similar, one did not quite reach the conventional level of statistical significance ($p=0.09$), while the other did ($p=0.02$). Because these results were not very robust to minor differences in method, and given the major implications to treatment centres of switching from conventional to hyperfractionation schedules, the DSG did not feel that the strength of the evidence was sufficient to support a recommendation away from conventional practice towards hyperfractionated therapy.

Combined modality therapy consisting of easily-administered and inexpensive chemotherapy plus conventional radical radiotherapy has been shown to be superior to hyperfractionated radiotherapy and is therefore an accessible and affordable option for locally advanced, unresected, medically fit NSCLC patients. Whether hyperfractionated accelerated radiotherapy (CHART or HART) is equivalent or superior to combined modality therapy has not been tested. The Provincial Lung Cancer DSG recognizes the need for such a trial to be conducted, but felt that the current limitations in radiotherapy resources in Canada would make this a difficult trial to conduct. It is still a high priority to do such a trial in order to evaluate issues of survival, quality of life and economic impact. Several trials are currently evaluating whether the addition of concurrent chemotherapy to hyperfractionated radiotherapy is superior to concurrent chemotherapy and standard thoracic radiotherapy. If these trials are positive, the pressure to adopt hyperfractionated treatment approaches in lung, and potentially other cancers, will increase and necessitate an examination of the resource implications for radiotherapy treatment centres.

IX. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report.

Draft Recommendations

Based on the evidence described in the original guideline report above, the Lung DSG drafted the following recommendations:

Draft Recommendations

- There is evidence from one randomized controlled trial demonstrating that Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) improves survival over standard radiotherapy of 60 Gy in 30 fractions, in patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC). Selected patients (with ECOG performance status ≥

1 who do not fit the criteria for induction chemotherapy and radiotherapy or patients who prefer radiotherapy only) may be considered for CHART.

- Evidence from a comparative cohort study suggests that Hyperfractionated Accelerated Radiation Therapy (HART) also improves survival over standard radiotherapy.
- Of those trials designed to improve therapeutic ratios in patients with locally advanced, unresectable stage III NSCLC there is insufficient data of high quality to recommend *hyperfractionation* over standard radiotherapy of 60 Gy in 30 fractions. Further randomized controlled trials are necessary to confirm the benefits, if any, of *hyperfractionation* radiotherapy.
- The main adverse effect associated with these altered fractionation treatments is acute esophagitis.
- Trials examining therapies providing greater convenience to patients with locally advanced, unresectable stage III NSCLC did not show evidence of a survival benefit for either hypofractionation or split-course radiotherapy. If symptom palliation is the main concern, patients may consider participating in clinical trials examining the role of hypofractionation or split-course radiotherapy.
- The effect of treatment on quality of life or health care costs was not reviewed in most of these trials. Therefore, if quality of life and health care costs are issues of concern, there is insufficient evidence at this time to draw any conclusions on the value of altered fractionation.

Practitioner Feedback

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

Methods

Practitioner feedback was obtained through a mailed survey of 98 practitioners in Ontario (46 medical oncologists, 26 radiation oncologists and 17 surgeons and the heads of radiation oncology programs at the eight regional cancer centres and the Princess Margaret Hospital). The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations 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 were reviewed by the Lung Cancer Disease Site Group.

Results

Key results of the practitioner feedback survey of the original draft guideline report are summarized in Table 3. Sixty-four (69.6%) surveys were returned. Thirty-nine (61%) respondents indicated that the evidence-based recommendation was relevant to their clinical practice and they completed the survey.

Summary of Main Findings and Actions

Twelve (19%) respondents provided written comments. The main points were:

Only a small number of the respondents felt able to comment on this guideline due to its technical and specialized nature. Of those who did have specific comments, there was concern that the recommendations were confusing and did not guide practice. The Lung DSG, therefore, rewrote the guidelines to explicitly state that the standard of practice is combined modality therapy (induction chemotherapy followed by radical radiotherapy for patients with good performance status, unresected stage III NSCLC.) The Lung DSG also provided clearer

direction in the Interpretive Summary as to which patients might be treated with CHART radiotherapy by exception.

Respondents were divided as to whether there was sufficient evidence to change practice to CHART or HART radiotherapy now. The DSG discussed this and concluded that a trial comparing combined modality therapy to CHART/HART would be necessary before a recommendation for a major change in practice could be made. On the other hand, selected good performance status patients who could not receive the current standard therapy could reasonably be offered CHART. Because these patients would be few in number, the resource implications would be modest.

Table 3. Practitioner responses to seven items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing this evidence-based recommendation, as stated in the "*Choice of Topic*" section of the report, is clear.	39 (100)	0	0
A practice guideline on this topic will be useful to clinicians.	29 (74)	8 (21)	2 (5)
The literature search is relevant and complete.	35 (90)	3 (8)	0
The summary of the evidence is acceptable to me.	35 (90)	4 (10)	0
I agree with this evidence-based recommendation as stated.	31 (80)	4 (10)	4 (10)
This recommendation should serve as a practice guideline.	25 (64)	8 (21)	6 (15)
Would you use this practice guideline in your own practice?	**Yes**	**Unsure**	**No**
	26 (67)	5 (13)	6 (15)

NOTE: Some percentages do not add to 100 because of missing data.

Approved Practice Guideline Recommendations

This practice guideline reflects the integration of the draft recommendations in the External Review process and has been approved by the Lung DSG and the Practice Guideline Coordinating Committee.

This practice guideline applies to patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC).

- The current standard treatment for unresected stage III NSCLC is combined modality therapy (*Practice Guideline Report #7-3: Unresected Stage III Non-Small Cell Lung Cancer* – see Appendix 1)
- There is evidence from one randomized controlled trial demonstrating that Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) improves survival over standard radiotherapy of 60 Gy in 30 fractions, in patients with locally advanced, unresectable stage III NSCLC. Therefore, selected patients (with ECOG performance status $\leq$ 1 who do not fit the criteria for induction chemotherapy and radiotherapy or patients who prefer radiotherapy only) may be considered for CHART.
- Evidence from a comparative cohort study suggests that Hyperfractionated Accelerated Radiation Therapy (HART) also improves survival over standard radiotherapy.
- On the other hand, there is insufficient data of high quality to recommend non-accelerated hyperfractionated radiotherapy over standard radiotherapy of 60 Gy in 30 fractions. Further randomized controlled trials are necessary to confirm the benefits, if any, of non-accelerated hyperfractionation radiotherapy.

- The main adverse effect associated with these altered fractionation treatments is acute esophagitis.
- Trials examining therapies providing greater convenience to patients with locally advanced, unresectable stage III NSCLC did not show evidence of a survival benefit for either hypofractionation or split-course radiotherapy. If symptom palliation is the main concern, patients may consider participating in clinical trials examining the role of hypofractionation or split-course radiotherapy.
- The effect of treatment on quality of life was not reviewed in most of these trials. Therefore, if quality of life is the main issue of concern, there is insufficient evidence at this time to draw any conclusions on the value of altered fractionation.

X. POLICY IMPLICATIONS

If CHART radiotherapy were to become the standard of care for patients with unresected stage III NSCLC, there would be a major impact on an already strained provincial radiotherapy system. The requirement to operate cancer centres seven days a week and to provide treatment fractions two to three times per day would create substantial operating challenges in cancer centres. There would also be incremental costs associated with the operation of centres on weekends. On the other hand, only a few selected patients would justify the use of CHART-type radiotherapy now. If randomized trials were to demonstrate a superiority of CHART over combined modality therapy, or if CHART plus chemotherapy were to become a new treatment standard, the impact on the provincial treatment system could be profound. Health system planners and policy makers need to be aware of this potential development.

XI. PRACTICE GUIDELINE

This practice guideline reflects the most current information reviewed by the Lung DSG.

Target Population

These recommendations apply to patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC).

> ***Note:*** *The current standard treatment for unresected stage III NSCLC is combined modality therapy (Practice Guideline Report #7-3: Unresected Stage III Non-Small Cell Lung Cancer – see Appendix 1).*

Recommendations

Key Recommendations

- There is evidence from one randomized controlled trial demonstrating that Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) improves survival over standard radiotherapy of 60 Gy in 30 fractions, in patients with locally advanced, unresectable stage III non-small cell lung cancer (NSCLC). Selected patients (with ECOG performance status $\geq$ 1 who do not fit the criteria for induction chemotherapy and radiotherapy or patients who prefer radiotherapy only) may be considered for CHART.
- Evidence from a comparative cohort study suggests that Hyperfractionated Accelerated Radiation Therapy (HART) also improves survival over standard radiotherapy.
- Of those trials designed to improve therapeutic ratios in patients with locally advanced, unresectable stage III NSCLC there is insufficient data of high quality to recommend hyperfractionation over standard radiotherapy of 60 Gy in 30 fractions. Further randomized controlled trials are necessary to confirm the benefits, if any, of hyperfractionation radiotherapy.

- Trials examining therapies providing greater convenience to patients with locally advanced, unresectable stage III NSCLC did not show evidence of a survival benefit for either hypofractionation or split-course radiotherapy. If symptom palliation is the main concern, patients may consider participating in clinical trials examining the role of hypofractionation or split-course radiotherapy.
- The effect of treatment on quality of life or health care costs was not reviewed in most of these trials. Therefore, if quality of life and health care costs are issues of concern, there is insufficient evidence at this time to draw any conclusions on the value of altered fractionation.

Qualifying Statements

- The main adverse effect associated with these altered fractionation treatments is acute esophagitis.

XII. JOURNAL REFERENCE

Yu E, Lochrin C, Dixon P, Ung YC, Gagliardi A, Evans WK, and the Lung Cancer Disease Site Group. Altered fractionation of radical radiation therapy in the management of unresectable non-small-cell lung cancer. *Current Oncology* 2000;7(2):98-109.

XIII. ACKNOWLEDGEMENTS

The Lung DSG would like to thank Drs. Edward Yu, Catherine Lochrin, Peter Dixon, Yee Chung Ung, William K Evans, and Ms. Angela Eady and Ms. Anna Gagliardi for taking the lead in drafting and revising this practice guideline report.

The Lung DSG would also like to thank Drs. Edward Yu, Yee Chung Ung, William K. Evans and Ms. Barbara R. Markman and Ms. Jean Mackay for taking the lead in updating this practice guideline report.

For a complete list of Lung DSG members, please visit our web site at: http://www.cancercare.on.ca/ccopgi/.

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Update

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Appendix 1. Summary from practice guideline report #7-3: unresected stage ill non-small cell lung cancer.

SUMMARY

ORIGINAL GUIDELINE: March 14, 1997
MOST RECENT LITERATURE SEARCH: December 2002
NEW EVIDENCE ADDED TO GUIDELINE REPORT: January 2003
RECOMMENDATIONS LAST MODIFIED: The recommendations have not been modified since the original guideline was developed.

The Lung Disease Site Group is rewriting this practice guideline report and may revise the recommendations. The rewritten guideline report will include new evidence on the use of palliative radiotherapy, hyperfractionated radiotherapy, and accelerated radiotherapy in the treatment of unresected stage III disease, as well as evidence on the sequencing of chemotherapy relative to radiotherapy in combined modality regimens. The new evidence has not been incorporated into the current guideline report but is listed in the Reference section. When completed, the new practice guideline report will replace the current report.

SUMMARY

Guideline Questions

1. What is the role of different schedules or doses of radiotherapy in patients with unresected, clinical or pathological stage III NSCLC? (Note: unresected stage III NSCLC is defined as: tumours that, for either technical or medical reasons, cannot be completely resected; either clinical or pathological stage III NSCLC.)
2. Does chemotherapy combined with radiation therapy improve survival compared with radiation therapy alone in patients with unresected NSCLC?

Target Population

These recommendations apply to adult patients with unresected clinical or pathological stage III non-small cell lung cancer. (Note: unresected stage III NSCLC is defined as: tumours that, for either technical or medical reasons, cannot be completely resected; either clinical or pathological stage III NSCLC.)

Recommendations

Key Recommendation

- Patients with good performance status (ECOG 0 to 1) and minimal weight loss (less than 5% in the preceding three months) have been shown to have a survival benefit from treatment with combined chemo-radiotherapy and should be considered for this type of treatment approach. For these selected patients, thoracic irradiation of 60 Gy in 30 fractions over a six-week period in combination with cisplatin-based chemotherapy is recommended as a treatment option. A full discussion should occur between the patient and physician concerning the benefits, limitations, and toxicities of therapy.

Qualifying Statements

- Patients not fitting the above criteria are not candidates for combined modality treatment. Those experiencing symptoms amenable to treatment should receive palliative thoracic irradiation.

- At this time, hyperfractionated radiation is not recommended outside the context of a clinical trial.

Methods

Entries to MEDLINE (through December 2002), CANCERLIT (through October 2002) and Cochrane Library (2002, Issue 4) databases have been searched for evidence relevant to this practice guideline. The most recent literature search was performed in January 2003.

Evidence was selected and reviewed by four members of the Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI) Lung Cancer Disease Site Group (Lung DSG) and methodologists. This practice guideline has been reviewed and approved by the Lung DSG, which comprised medical and radiation oncologists, pathologists, surgeons, epidemiologists, a medical sociologist, and a psychologist at the time the guideline was developed. At that time, patients were not represented. Community representatives participated in the updating of the practice guideline report.

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 (PGCC).

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

Key Evidence

- One meta-analysis detected a statistically significant overall benefit at two years for the use of combined chemo- and radiotherapy compared with radiotherapy alone. A hazard ratio of 0.90 (95% confidence interval, 0.83 to 0.97) or a 10% reduction in the risk of death translated into an absolute benefit of 3% at two years and 2% at five years. Subgroup analysis comparing combined chemo- and radiotherapy with cisplatin-containing regimens versus radiotherapy alone demonstrated a 13% reduction in the risk of death in the combined treatment arm (pooled hazard ratio, 0.87; 95% confidence interval, 0.79 to 0.96). This represents an absolute benefit of 4% at 2 years.
- Toxicity from chemotherapy and/or radiotherapy is largely confined to neutropenic-related infection, weight loss, and vomiting. Serious infections requiring hospitalization and weight loss are more prevalent in combined modality therapy (sequential chemo-radiotherapy) compared to radiation alone. Patients receiving concurrent combined chemo-radiotherapy may also be at risk for radiation pneumonitis and esophagitis.
- A second meta-analysis detected a statistically significant advantage to cisplatin-based combination chemotherapy compared with chemotherapy alone. In the cisplatin-based combination chemotherapy group, the reduction in mortality at one and two years was 24% and 30%, with an odds ratio for death of 0.76 (95% confidence interval, 0.6 to 0.9) at one year and 0.70 (95% confidence interval, 0.5 to 0.9) at two years. A third meta-analysis showed a statistically significant advantage to combined modality therapy over radiotherapy alone. The overall relative risk of death for combined modality therapy was 0.87 (95% confidence interval, 0.81 to 0.94; 13% reduction in relative risk) at two years and 0.83 (95% confidence interval, 0.77 to 0.90; 17% reduction in relative risk) at three years, in favour of combined chemo-radiotherapy.