Cancer Care Ontario Practice Guidelines Initiative

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

Unresected Stage III Non-Small Cell Lung Cancer

Practice Guideline Report #7-3

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. 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.

Related Guidelines

Cancer Care Ontario Practice Guidelines Initiative Practice Guideline Report #7-12: *Altered Fractionation of Radical Radiation Therapy in the Management of Unresectable Non-Small Cell Lung Cancer*.

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 reviews, 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. QUESTIONS

1. What is the role of different schedules or doses of radiotherapy in patients with unresected, clinical or pathological stage III non-small cell lung cancer (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?

Survival was selected as the primary outcome of interest, although quality of life was also considered an important outcome. However, as there is a paucity of high quality data pertaining to the impact of treatment on quality of life for patients with unresected, stage III NSCLC, these recommendations do not specifically address quality of life.

II. CHOICE OF TOPIC AND RATIONALE

Until recently, the generally accepted standard therapy for patients with locally advanced, unresectable NSCLC was radiation therapy. Radiotherapy commonly relieves symptoms of locally advanced NSCLC, and there is a small percentage (approximately 5%) of long-term survivors following radical radiotherapy. However, controversy has existed as to whether radiotherapy should be immediate or delayed, and there has been uncertainty as to what the total radiotherapy dose should be. Until 1990, randomized controlled trials had demonstrated no survival benefit for patients who received immediate radiotherapy alone, delivered with modern megavoltage equipment, compared with patients who were followed with a 'wait and see' policy. The use of systemic treatment in combination with radiation has been investigated because of evidence of tumour regression and a small survival benefit in metastatic NSCLC in chemotherapy. Several studies, but not all, have demonstrated a survival benefit for patients treated with combined chemo- and radiotherapy, henceforth referred to as combined modality therapy (1-4). Because of controversies over the most effective therapy, the Lung Cancer Disease Site Group (Lung DSG) chose this topic for development of a treatment practice guideline report.

III. METHODS

Guideline Development

This practice guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle by Browman et al (1u). Evidence was selected and reviewed by four members of the CCOPGI's Lung DSG and methodologists.

The practice guideline report is a convenient and up-to-date source of the best available evidence on unresected, stage III NSCLC, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. The report 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 process 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 and CANCERLIT searches were done for the years 1980 to June 1996. Search terms included: “NSCLC”, “unresectable”, “inoperable”, “drug therapy”, “radiotherapy”, “clinical trials”, “random allocation”, “double-blind method”, “guideline”, and “meta-analysis”. Articles identified by the searches and those cited in relevant papers and recently published reviews were retrieved and reviewed. Feedback on the Evidence-based Recommendation report from practitioners in the province of Ontario and from one external reviewer also yielded information about recent publications relevant to this guideline. These publications were reviewed and where appropriate, incorporated into this practice guideline.

Update

The original literature search has been updated using MEDLINE (through December 2002), CANCERLIT (through October 2002), the Cochrane Library (Issue 4, 2002), and the proceedings of the annual meetings of the American Society of Clinical Oncology (1999 through 2002) and the American Society for Therapeutic Radiology and Oncology (1999 through 2002).

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were full reports or abstracts of randomized controlled trials or meta-analyses that compared either a) different radiotherapy schedules or doses or b) radiotherapy versus combined modality therapy.

Synthesizing the Evidence

There was no discussion of data pooling in the original document, and no data pooling was performed.

IV. RESULTS

Literature Search Results

The following were eligible for inclusion in the systematic review of the evidence: one meta-analysis comprising 52 randomized controlled trials, with an analysis of individual patient data on 3,033 patients from 22 trials comparing combined chemotherapy plus radiotherapy versus radiotherapy alone (10); four randomized controlled trials of radiotherapy alone (6-9); one fully published randomized controlled trial of combined chemo-radiotherapy that was not included in the meta-analysis (11); four randomized controlled trials of hyperfractionated radiotherapy (9,12-14); and four randomized controlled trials published in abstract form of combined chemo-and radiotherapy (15-18) in patients with unresected stage III non-small cell lung cancer.

Survival was selected as the primary outcome of interest, although quality of life was also considered an important outcome. However, as there is a paucity of high quality data pertaining to the impact of treatment on quality of life for patients with unresected, stage III NSCLC, these recommendations do not specifically address quality of life.

Update

The following were found through literature updating activities as of April 2000 and are incorporated into the current version of the guideline: two meta-analyses (2u,3u) and full reports of three randomized controlled trials (4u-6u) that compared radiotherapy alone with combined modality therapy (one of the randomized controlled trials [6u] was the full report of a trial included in the original practice guideline report which had been reported in abstract form only [18]); one randomized controlled trial which compared concurrent versus sequential administration of radiotherapy with chemotherapy (7u); one practice guideline (8u); and one economic analysis (9u).

Additional literature identified during updating activities between May 2000 and December 2002 will be incorporated into the re-written guideline and includes the following: nine randomized controlled trials of radiotherapy alone (10u-18u); six randomized controlled trials which compared radiotherapy alone with combined modality therapy (19u-24u) (including one abstract report [24u], and one report updating a trial included in the meta-analyses [19u]); four randomized controlled trials involving hyperfractionated radiotherapy (18u,25u-27u); one randomized trial involving accelerated radiotherapy (28u); and four trials (reported in abstract form) that compared different sequences of chemotherapy/radiotherapy administration (29u-32u).

Outcomes

Staging of IIIA and IIIB NSCLC

Mountain has demonstrated the prognostic significance of the Tumour Nodes Metastases (TNM) staging system (5). The application of this system to a large database, showed that five-year survival for stage IIIA NSCLC was approximately 15% and 5% for stage IIIB disease. Attempts to improve survival with high dose radiotherapy have been reported in numerous studies. The randomized controlled trials are discussed below.

Meta-Analyses and Randomized Controlled Trials

Role of radiotherapy

Immediate radiotherapy versus 'wait and see'

One early trial, the Oxford study, randomized 249 patients with localized, inoperable NSCLC to either immediate irradiation (40 Gy) or a 'wait and see' arm, offering treatment only with the onset of symptoms (6) (see Table 1 for details of the trial). Survival between these two arms was equivalent. An attempt was made to measure the degree of palliation obtained with immediate, compared to delayed, treatment, and there was no difference between these 2 policies. There was no difference in quality of life, assessed on a four-point functional scale assessing general daily activity.

Variable dosing and schedules of radiotherapy

Perez et al reported the results of a Radiation Therapy Oncology Group trial (RTOG #73-01) in which patients with medically inoperable or unresectable stage III NSCLC were randomly allocated to one of four arms: split course radiotherapy to a total dose of 40 Gy, or continuous course treatments of 40, 50, or 60 Gy (7) (Table 1). A total of 378 patients were evaluated. Two-year survival rates were 10%, 11%, 19%, and 19%, respectively, for each of the treatment arms (not statistically significant [ns]). Median time to infield failure was significantly lengthened with higher doses of radiation suggesting improved local control. Quality of life and its relationship to symptom control, improved local control, and survival were not evaluated.

Hyperfractionated radiation alone

A phase I/II randomized controlled trial was reported by the RTOG (#83-11) in which patients with unresectable NSCLC were allocated to various total doses of radiotherapy delivered in 1.2 Gy fractions administered twice daily with more than four hours between fractions (8) (Table 1). The initial three groups received a total dose of 60.0, 64.8, or 69.6 Gy. With acceptable acute and late toxicities, two additional arms of higher doses (74.4 and 79.2 Gy) were opened and the lower dose arms were closed. A total of 884 patients were entered into the study with 96.4% completing follow-up. No significant survival differences were detected according to the assigned radiotherapy dose. In the subgroup of 350 patients meeting the criteria for the Cancer and Leukemia Group B (CALGB) 84-33 trial, survival was longer for patients receiving higher radiotherapy doses (< 69.6 Gy versus 69.6 Gy, p=0.02); however, the reliability of these results are limited by the fact that randomization would not have been

maintained in this subgroup and different radiotherapy doses were administered during different time periods. No statement about the role of hyperfractionated radiotherapy versus standard radiotherapy is possible, as there was no arm in this trial using standard radiotherapy.

McGinnis et al reported the results of a recently closed randomized controlled trial (9) (Tables 1 & 3). A total of 103 patients were randomized to one of three treatment arms: standard thoracic radiation (n = 35), twice-daily thoracic radiation (n = 34), or twice-daily thoracic radiation plus concomitant chemotherapy (n = 34). With follow-up that ranged from six to 32 months, median survival did not differ significantly between the groups (8.7 versus 12.3 versus 12.9 months, respectively, for standard radiotherapy versus hyperfractionated radiotherapy alone versus combined modality therapy).

Table 1. Randomized controlled trials of radiotherapy/hyperfractionated radiation in stage III NSCLC.

Trial (Reference)	Total n (evaluable pts)	Population (stage of disease)	Treatment Allocation	n/grp (evaluable pts)	Tumour Response (%,CR&PR)	Mean/ Median Survival	Overall survival rate (%)	p-value
Durrant 1971 (6)	249 (249)	No staging reported; inoperable carcinoma	Wait & see RT CT RT + CT	63 (63) 62 (62) 63 (63) 61 (61)	NR	Mean 8.4 mths 8.3 8.7 8.8	NR	ns
Perez 1982 (7)	383 (378)	stage IIIA, IIIB	RT 2000 rads X 2 RT 4000 RT 5000 RT 6000	206 (201)* 92 (92) 85 (85)	46† 51 66 61	Median‡ 42-44 wks	10 (2 yr) 11 19 19	ns
Cox 1990 (8) Randomized phase I/II	884 (848)	RTOG stage II, III, IV	RT 60.0 Gy RT 64.8 RT 69.9 RT 74.4 RT 79.2 All BID	NR (83) (127) (220) (211) (207) Total n, 884	NR	Median 9.2 mths 6.3 10.0 8.7 10.5	16 (2 yr) 14 20 15 20	all pts, ns; sub-grp, 0.02§
McGinnis 1995 (9)	103	stage IIIA/B	Std RT BID RT BID RT + CT	35 34 34	NR	Median 8.7 mths 12.3 12.9	NR	NR

Notes: BID – twice daily, CR – complete response, CT – chemotherapy, grp – group, Gy – gray(s), mths – months, n – number, NR – not reported, ns – not statistically significant, NSCLC – non-small cell lung cancer, PR – partial response, pts – patients, RT – radiotherapy, std – standard, wks – weeks, yr – year.

* Total 206 pts split between groups; RT 2000 X 2 and RT 4000.
† Pts receiving split course RT 2000 X 2 had significantly lower complete response rate compared with other groups, p = 0.02.
‡ For the 316 patients with sufficient data to determine variation in primary irradiation.
§ In a subgroup of 350 pts meeting the selection criteria for CALGB trial 84-33, there was a significant survival advantage for pts receiving a radiotherapy dose of 69.9 Gy or more versus those receiving less than 69.9 Gy.

Role of combined modality therapy

The strongest evidence regarding combined modality therapy is derived from a recent meta-analysis of 52 randomized trials conducted by the Non-small Cell Lung Cancer Collaborative Group (NSCLCCG) (10). The primary intent of the meta-analysis was to examine the role of chemotherapy when added to other therapeutic modalities (i.e., surgery, radiotherapy, best supportive care) in the treatment of NSCLC. The analysis comprises three questions, each derived from three categories of primary treatment targeted to specific stages of disease: early, locally advanced, or advanced disease. Only the analysis of the role of

combined chemotherapy and radiotherapy in the treatment of locally advanced disease is addressed in this recommendation.

Twenty-two randomized clinical trials representing 3,033 patients were included in the analysis examining the role of combined chemo- and radiotherapy versus radiotherapy alone in locally advanced disease. The largest trial randomized 353 patients; the smallest trial randomized 48 patients. All trials selected for inclusion accrued patients between January 1, 1965 and December 31, 1991. Appendix 1 outlines the chemotherapy regimens and doses compared in each trial. The overall pooled hazard ratio was 0.90, demonstrating a 10% reduction in the risk of death and an absolute survival benefit of 3% at two years in the group of patients receiving combined treatment (10) (see Figure 1).

Subgroup analyses were conducted on the basis of the chemotherapeutic agent used in the individual trials. Trials were grouped into four categories based on the chemotherapy regimen employed in the trial: long term alkylating agents, vinca alkaloids or etoposide, cisplatin-based regimens, and 'other' regimens. In these analyses, there were no statistically significant differences between the combined chemo- plus radiotherapy arms versus the radiotherapy alone arms except in the analysis of the 11 trials which used a cisplatin-based regimen. This analysis yielded an overall hazard ratio of 0.87 (95% confidence interval [CI], 0.79 to 0.96), demonstrating a 13% reduction in the risk of death and a 4% absolute benefit at two years for patients treated with combined modality therapy.

One randomized controlled trial was published after the meta-analysis was completed (11). Schaake-Koning et al randomly assigned 331 patients to one of the following therapeutic regimens: radiotherapy alone, radiotherapy combined with cisplatin 30mg/m^2 *weekly*, or radiotherapy combined with cisplatin 6mg/m^2 *daily* (see Table 2). Overall, survival in the *daily* cisplatin group was significantly better than in the radiotherapy alone group; results at one, two, and three years, respectively, were 54% versus 46%; 26% versus 13%; and 16% versus 2% ($p = 0.009$). Survival in the *weekly* cisplatin group was not significantly different than in the radiotherapy alone group ($p = 0.36$). The survival benefit of *daily* chemotherapy plus radiotherapy may have been due to improvement in local control ($p = 0.003$) (11).

An update of one of the randomized controlled trials included in the NSCLCCG's meta-analysis, the CALGB trial, has reported seven-year follow-up (3). This report confirms that five weeks of chemotherapy with vinblastine and cisplatin increases the proportion of long-term survivors. For those receiving chemo- plus radiotherapy, the proportion of patients alive at five, six, and seven years was 17%, 13%, and 13% versus 6%, 6%, and 6% for those receiving only radical radiotherapy ($p=0.012$).

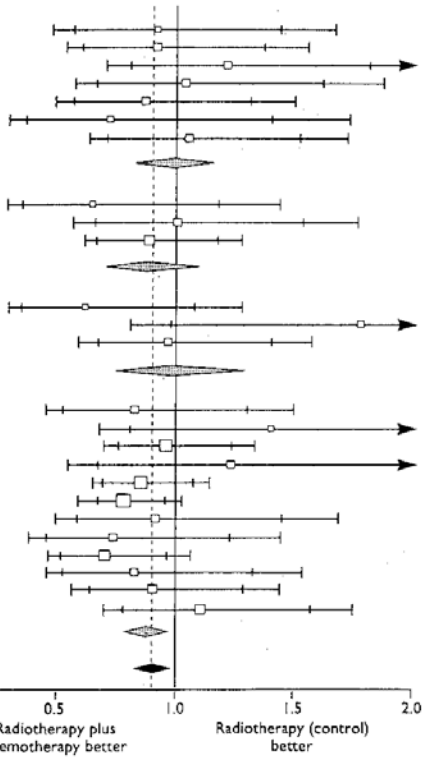
Update

Two additional meta-analyses (2u,3u) and three randomized controlled trials (4u-6u) which compared chemo-radiotherapy with radiotherapy alone were found. One of these trials (6u) is the full report of a trial reported in abstract form in the original guideline (18).

Marino et al reported results of a meta-analysis that compared chemo-radiotherapy with radiotherapy alone for patients with unresectable, stage III NSCLC (2u). The chemo-radiotherapy group was further divided into cisplatin- and non-cisplatin-based regimens. Data were derived from 14 randomized controlled trials involving 1887 patients. An adaptation of the method of Mantel and Haenszel was used to estimate and pool odds ratios of death. In the cisplatin-based group, the reduction in mortality at one and two years was 24% and 30% with an odds ratio for death of 0.76 (95% CI, 0.6 to 0.9) and 0.70 (95% CI, 0.5 to 0.9), respectively. In the non-cisplatin-based group, the odds ratios for death at one and two years were 1.05 (95% CI, 0.7 to 1.5) and 0.82 (95% CI, 0.5 to 1.3) with a respective decrease in mortality of 5% and 18%. There was no significant difference in survival at three and five years between the chemo-radiotherapy and radiotherapy-alone groups. The results favoured combined cisplatin-based chemo-radiotherapy.

Figure 1
Meta-analysis of radiotherapy vs radiotherapy plus chemotherapy

Trial	No of events/ No of patients entered: Radiotherapy plus chemotherapy	Radiotherapy	Observed – expected deaths	Variance
Long term alkylating agents:				
NRH NSC-26271	36/36	38/38	-1.63	17.55
EORTC 08742	45/53	51/64	-1.91	23.36
RTOG 7302a	52/55	48/56	4.58	23.23
RTOG7302b	38/46	43/50	0.84	19.31
RTOG7302c	38/47	53/57	-3.08	22.19
MCL-1	16/25	19/27	-2.79	8.49
Aviano	47/49	61/62	1.15	26.09
Subtotal	272/311	313/354	-2.83	140.23
Vinca alkaloids/etoposide:				
AZ-OC-1-80	22/27	23/25	-4.56	10.35
Gwent 3	40/41	43/44	-0.06	20.25
SECSG 81 LUN375	94/107	97/105	-5.94	47.21
Subtotal	156/175	163/174	-10.55	77.80
Other drugs:				
Gwent 1	23/26	30/30	-6.11	12.47
SWOG 7635	25/30	23/32	6.04	10.44
NCCTG 822451	54/58	59/63	-1.03	28.04
Subtotal	102/114	112/125	-1.10	50.95
Cisplatin based:				
Buenos Aires	43/43	35/38	-3.57	18.26
Brussels	25/31	29/34	4.18	12.31
FLCSG 2	124/125	126/127	-2.49	62.14
Essen	21/22	22/26	2.09	9.80
SLCSG	159/163	161/164	-12.39	77.92
CEBI 138	166/176	173/177	-21.95	82.68
WSLCRG/F1	37/40	35/39	-1.61	17.82
Perugia	32/33	32/33	-4.45	14.84
CALGB 8433	73/89	80/91	-13.39	37.13
EORTC 08842	36/38	37/37	-3.23	17.70
SWOG 8300a	62/64	62/64	-3.07	30.19
SWOG 8300b	63/63	63/63	2.81	30.38
Subtotal	841/887	855/893	-57.08	411.18
Total	1371/1487	1443/1546	-71.56	680.16



Results of trials of radical radiotherapy versus radical radiotherapy plus chemotherapy (test for heterogeneity $\chi^2_{HetT}=22{\cdot}33$, $df=24$, $P=0{\cdot}560$; test for interaction $\chi^2_{HetB}=1{\cdot}91$, $df=3$, $P=0{\cdot}592$

From: Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated individual patient data from 52 randomised clinical trials. Br Med J 1995;311:899-909. Used with permission.

Table 2. Randomized controlled trial of radiotherapy versus combined modality therapy in stage III NSCLC (not included in the meta-analysis [10]).

Trial (Reference)	Total n (evaluable pts)	Population (stage of disease)	Treatment allocation	n/grp (evaluable pts)	Recurrence -free survival (%)	Median survival	p-value	Survival rate (%)	p-value
Schaake-Koning 1992 (11)	331 (246 §)	stage I,II,III	RT RT + CT* RT + CT†	114 (88‡) 110 (79) 107 (79)	19 (2-yr) 30 31	NR	NR	2 (3-yr) 13 16	0.054 (overall) 0.04 (RT vs. any dose of CT)

Notes: CT – chemotherapy, grp – group, n – number, NR – not reported, NSCLC – non-small cell lung cancer, pts – patients, RT – radiotherapy, vs. – versus, yr(s) – year(s).

* Cisplatin 30mg/m^2 IV *weekly* following prehydration with 1 litre of fluid
† Cisplatin 6 mg/m^2 IV *daily* + 2 litres of fluid hydration
‡ Evaluable for response.

Pritchard et al reported results of another meta-analysis that compared chemo-radiotherapy with radiotherapy alone for patients with unresectable stage III NSCLC (3u). Data were derived from 14 randomized controlled trials involving 2589 patients. Two of these trials were also reported in the *'Hyperfractionated radiation versus combined modality therapy'* section of this guideline (12,13). Pooled relative risk for death was calculated using the two-step Grilli method based on the Mantel-Haenszel technique. The overall relative risk of death for combined modality therapy was 0.87 (95% CI, 0.81 to 0.94; 13% reduction in RR) at two years and 0.83 (95% CI, 0.77 to 0.90; 17% reduction in relative risk) at three years. The magnitude of the treatment effect was similar when trials of concurrently and sequentially administered chemotherapy were compared (concurrent: reduction in relative risk, 11% at two years, 14% at three years; sequential: reduction in relative risk 15% at two years, 20% at three years). The data indicated that the addition of chemotherapy to radiotherapy improved survival in patients with locally advanced, unresectable NSCLC.

Morton et al reported the results of a randomized controlled trial that randomized 121 patients with unresectable, stage III NSCLC to thoracic radiation only or combined radiotherapy and chemotherapy arm (radiotherapy: 5000 cGy in 5 weeks starting day 1, 1000 cGy boost in five fractions to a small tumour field; combined modality: two cycles of chemotherapy [methotrexate, doxorubicin, cyclophosphamide, CCNU], then radiotherapy starting four weeks after the second cycle of chemotherapy, then two cycles of chemotherapy starting four weeks after end of radiotherapy) (4u). One hundred and fourteen patients were evaluable (radiotherapy, n = 58; combined modality, n = 56). Median survival times were 313 days for the radiotherapy arm versus 317 days for the combined radiotherapy-chemotherapy arm. Overall survival curves were not statistically significantly different for the two arms ($p > 0.02$); one-, two-, and five-year survival rates for the radiotherapy arm were 45% (CI, 32% to 58%), 16% (CI, 6% to 25%) and 7%, respectively; for the combined modality arm, 46% (CI, 33% to 60%), 21% (CI, 11% to 32%) and 5%, respectively. Results of this trial indicated that the addition of non-cisplatin-based chemotherapy to radiotherapy under the conditions described did not provide a survival advantage to this group of patients with unresectable stage III NSCLC.

Cullen et al reported data from a randomized controlled trial that examined survival and quality of life in 223 patients who received chemo-radiotherapy and 223 patients who received radiotherapy alone (5u). All patients had locally advanced, unresectable NSCLC. The chemotherapy regimen was mitomycin 6 mg/m^2, ifosfamide 3 g/m^2, and cisplatin 50 mg/m^2 every 21 days to a maximum of four cycles. Dose/fractionation schemes varied with site, but patients received a total dose equivalent to not less than 40 Gy in 15 fractions. In the radiotherapy arm, radiotherapy was started after randomization; in the chemo-radiotherapy arm, radiotherapy was started after four cycles of chemotherapy were completed or after chemotherapy failure. The Kaplan-Meier method was used to estimate survival curves, and differences between treatments were assessed using the log-rank test. Mean quality of life score was based on a 12-question adaptation of the European Organization for Research into the Treatment of Cancer (EORTC) questionnaire. There was no statistically significant difference in survival between the two groups ($p=0.14$, chi-square). Median survival was 9.7 months for the radiotherapy-alone arm and 11.7 months for the chemo-radiotherapy arm. One-, two-, and three-year survival rates were 41%, 16%, and 8% for the radiotherapy-alone arm and 49%, 20%, and 12% for the chemo-radiotherapy arm. The mean change in quality of life over six weeks for 50 of the 67 patients participating in the quality of life assessment was found to be significant (radiotherapy, +0.28 versus chemo-radiotherapy, -0.22, where a negative value implies an increase in quality of life; $p = 0.0002$).

Crino et al (6u) published the full report of a trial previously reported in abstract form and included in the original guideline (18). They randomized 66 consecutive patients with regionally advanced (stage III), unresectable NSCLC to either combined modality therapy (cisplatin-based chemotherapy and radiotherapy) or radiotherapy alone. The combined modality group received

cisplatin (100 mg/m^2 on day 1) and etoposide (120 mg/m^2 on days 1,2,3) every three weeks for three courses, then radiotherapy 56 Gy to the pre-treatment tumour volume and 40 Gy on mediastinum and bilateral supraclavicular nodes; the radiotherapy group received the same radiotherapy as was used with the combined modality group. Sixty-one patients were evaluable for survival, 58 for response and toxicity. Median survival for the combined treatment and radiotherapy-only arms were 52 weeks versus 36 weeks respectively (p = 0.11). Survival rates for combined modality therapy compared with radiotherapy alone were 53% versus 45%, 28% versus 14%, and 9% versus 0% for one-, two-, and five years, respectively; all patients had died by the time of the six-year follow-up. Combined modality treatment produced a trend toward improved survival when compared with radiotherapy alone, but a statistically significant survival advantage was not obtained. The authors suggest that the lack of significance may be attributable to the small number of patients enrolled in the trial.

Hyperfractionated radiation versus combined modality therapy

Hyperfractionated radiation has been examined in four randomized controlled trials (9,12-14). One of these four trials has been described elsewhere in this report (9). Sause et al (RTOG #88-08) randomized patients to one of three arms: standard radiation (n = 149), combined modality therapy (using cisplatin-based chemotherapy) (n = 151), or twice-daily hyperfractionated radiation (n = 152) (12) (Table 3). The difference in overall survival between combined modality therapy versus the other two treatment arms was statistically significant in favour of combined modality therapy (p = 0.03). Median survival rates were 11.4 months for standard radiation, 13.8 months for combined modality therapy, and 12.3 months for hyperfractionated radiation. One-year survival rates were 46%, 60%, and 51% for standard radiation, combined modality therapy, and hyperfractionated radiation, respectively.

Jeremic et al examined the role of hyperfractionated radiation compared with combined modality treatment (13). Patients were randomized to one of three arms: hyperfractionated radiation alone (n = 61), combined hyperfractionated radiation and chemotherapy with etoposide and a low dose of carboplatin (100 mg) (n = 52), or combined hyperfractionated radiation and chemotherapy with etoposide and a high dose of carboplatin (200 mg) (n = 56) (Table 3). The two chemotherapy groups received equal doses of etoposide. An overall survival benefit was seen in the patients who received lower dose carboplatin versus those who received radiotherapy alone (p = 0.0027). Statistically significant survival differences were not seen between the patients who received high dose carboplatin versus radiotherapy alone (p = 0.17) or between patients receiving high versus low dose carboplatin (p = 0.14). Survival rates were 7%, 23%, 16% at three years and 5%, 21%, and 16% at five years, for the radiotherapy alone, the low dose carboplatin, and the high dose carboplatin groups, respectively.

In a second randomized controlled trial by Jeremic et al, patients with histologically or cytologically confirmed stage III NSCLC were randomly assigned to receive either hyperfractionated radiotherapy alone (n = 66) or hyperfractionated radiotherapy plus chemotherapy with carboplatin and etoposide (n = 65) (14). Survival was the main outcome of interest. Overall one-, two-, three-, and four-year survival rates were 68%, 26%, 11%, and 9%, respectively, for the hyperfractionated radiotherapy alone group and 74%, 43%, 23%, and 23%, respectively, for the combined modality group (p = 0.21).

Trials of combined modality treatment published in abstract form

Four trials comparing radiotherapy to combined modality therapy using cisplatin-based therapy have been published in abstract form (15-18) (Table 4). Because less data is published in these abstracts, the strength of evidence is weaker than fully published trials; however, they warrant mention since the questions studied are the same questions as those examined in the fully published trials. When the trials are reported in fully published format, the data in this guideline will be updated.

Table 3. Randomized controlled trials of hyperfractionated radiation versus chemotherapy plus radiation in stage III NSCLC.

Trial (Reference)	Total n (evaluable pts)	Population (stage of disease)	Treatment Allocation	n/grp (evaluable pts)	Tumour Response (%, CR&PR)	Median Survival	Overall survival rate (%)	p-value
McGinnis 1995 (9)	103	stage IIIA/B	Std RT BID RT BID RT + CT	35 34 34	NR	8.7 mths 12.3 12.9	NR	NR
Sause 1995 (12)	490 (452)	stage II, IIIA, IIIB	RT CT + RT HFX RT	163 (149) 164 (151) 163 (152)	NR	11.4 mths 13.8 12.3	46 (1 yr) 60 51	0.03
Jeremic 1995 (13)	169 (169)	stage IIIA, IIIB	HFX RT HFX RT + CT* HFX RT + CT†	61 (61) 52 (52) 56 (56)	NR	8 mths 18 13	5 (5 yr) 21 16	0.0027 0.14‡
Jeremic 1996 (14)	135 (131)	stage III	HFX RT HFX RT + CT	68 (66) 67 (65)	85 (p =0.18) 92	14 mths 22	9 (4 yr) 23	0.02

Notes: BID – twice daily, CR – complete response, CT – chemotherapy, grp – group, HFX – hyperfractionated, mths – months, n – number, NR – not reported, NSCLC – non-small cell lung cancer, PR – partial response, pts- patients, RT – radiotherapy, std – standard, yr – year.

* Hyperfractionated radiotherapy + carboplatin (CBDCA) 100mg/m^2 + etoposide (VP-16) 100mg/m^2
† Hyperfractionated radiotherapy + CBDCA 200mg/m^2 + VP-16 100mg/m^2
‡ P-value refers to difference between the low v. the high CBDCA groups

Table 4. Published abstracts of radiotherapy versus combined modality therapy in stage III NSCLC.

Trial (Reference)	Total n (evaluable pts)	Population (stage of disease)	Treatment Allocation	n pts evaluated	Median duration of response	Mean /Median survival	p-value	Survival rate (%)	p-value
Cardiello 1985 (15)	51	NR	RT RT + CT	NR	28.6 wks 52.7 (p<0.05)	Mean 41 wks 60	>0.05	NR	NR
Alberti 1990 (16)	63 (52)	NR	RT RT + CT delayed RT	18 17 17	NR	Median 15 mths 19 11	ns	NR	NR
Brodin 1991 (17)	330	NR	RT RT + CT	NR	NR	NR	NR	NR	NR
Crino 1991 (18)	66 (56)	Stage III	RT RT + CT	NR	NR	Median 9 mths 14	0.056	0 (5 yr) 10	NR

Notes: CT – chemotherapy, mth(s) – month(s), n – number, NR – not reported, ns – not statistically significant, NSCLC – non-small cell lung cancer, pts – patients, RT – radiotherapy, wks – weeks, yr – year.

There was a consistent trend in three of the four trials for improved survival in the combined modality therapy group compared to the radiation alone group (15-18). Cardiello et al (n = 51) demonstrated a statistically nonsignificant trend favouring combined modality treatment when compared with radiation alone (15). Brodin and colleagues randomized 330 patients and found a trend favouring combined modality treatment (17). Crino and colleagues randomized patients with regionally advanced, unresectable NSCLC to either combined modality therapy (cisplatin-based chemotherapy) or radiotherapy alone (18). Median survival was 14 months versus nine months (p = 0.0559) for combined modality therapy compared with radiation alone. Survival rates for combined modality therapy compared with radiotherapy alone were 56% versus 37%, 30% versus 14%, and 10% versus 0% for one, two, and five years, respectively. The fourth trial, by Alberti and colleagues, randomized 63 patients to one of three arms: immediate radiotherapy (group I), combined modality therapy (group II), or delayed radiotherapy

(group III) (16). Median survival was 15, 19, and 11 months for groups I, II, and III, respectively. There was no statistically significant difference in favour of immediate therapy.

Evidence from the abstracts (15,17,18) is consistent with the conclusion that combined modality treatment tends to improve the survival of patients with unresected stage III NSCLC.

Update

Please see above for a description of the Crino et al full report (6u).

Timing of radiotherapy relative to chemotherapy

There was no evidence on this topic when the original guideline report was developed.

Update

Furuse et al (7u) randomized 320 patients with unresectable stage III NSCLC (314 assessable) to receive thoracic radiotherapy either concurrently (n=156) with a chemotherapy regimen of mitomycin (M), vindesine (V), and cisplatin (P) (MVP), or sequentially (n=158) after two cycles of MVP. MVP regimen was P 80 mg/m^2 and M 8 mg/m^2 on day 1, V 3 mg/m^2 on days 1 and 8, repeated every four weeks. Radiotherapy in the concurrent arm was started on day 2 of MVP for three weeks, 2 Gy/fraction to a total of 28 Gy, 10 days of rest, then 28 Gy again over three weeks. Radiotherapy in the sequential arm was started after completion of two cycles of MVP, given in 2 Gy fractions to a total of 56 Gy. Overall survival was significantly improved in the concurrent group relative to the sequential group ($p = 0.04$ logrank). Median survival for the concurrent group was 16.5 months, for the sequential group, 13.3 months. One- two-, three-, four-, and five-year survival rates for the concurrent group were 64.1%, 34.6%, 22.3%, 16.9%, and 15.8%, for the sequential group, 54.8%, 27.4%, 14.7%, 10.1%, and 8.9%. The authors reported that myelosuppression was more frequent in the concurrent arm than in the sequential arm ($p = 0.0001$) and that esophageal toxicity was identical in the two arms.

Practice Guidelines

There were no practice guidelines found when the original guideline report was developed.

Update

The American Society of Clinical Oncology published clinical practice guidelines for the treatment of unresectable NSCLC (8u). The report indicated that, for patients with unresectable stage III NSCLC, two or more cycles of cisplatin-based chemotherapy with, or followed by, radiation enhances survival. Chemotherapy should be administered for no more than eight cycles in stage III or IV NSCLC patients. Radiation should be included as part of the standard treatment for selected patients with unresectable stage III NSCLC whose performance status and pulmonary function are adequate. Definitive-dose thoracic radiotherapy should be no less than 60 Gy in 1.8- to 2-Gy fractions.

V. INTERPRETIVE SUMMARY

The available evidence from one meta-analysis, three subsequent trials, and three of four published abstracts testing various modes of radiotherapy compared to combined modality therapy demonstrated that combined modality therapy, containing cisplatin-based chemotherapy, improves survival in patients with stage IIIA or IIIB NSCLC. These conclusions are limited to patients with good performance status (ECOG 0-1) and minimal weight loss, defined as less than 5% in the preceding three months because these were the characteristics of the patients enrolled in the CALGB and the RTOG studies (2,12). Therefore, if survival is the primary outcome of interest, combined modality therapy using cisplatin-based chemotherapy can be considered.

Although there is a survival benefit for patients receiving combined modality therapy with cisplatin-based regimens compared to patients receiving radiotherapy alone, it is unclear whether the benefit is due to the chemotherapy or to the combination of the chemo- and

radiotherapy. There are currently no randomized controlled trials available for review that adequately address this question.

Neither the trials nor the meta-analysis evaluated the effect of treatment on quality of life or health care costs. Therefore, if quality of life and health care costs are of interest, there is insufficient evidence at this time to make a conclusion on the value of this therapy relative to these outcomes.

For patients who do not meet the performance and weight criteria, and who are experiencing symptoms, standard radiation alone offers the potential of symptomatic relief.

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

Update

One trial, reported by Cullen et al from the United Kingdom (5u), used a trial design very similar to that of the American trials that have shown improved survival with combined modality therapy for unresected stage III NSCLC. Although, this trial did not demonstrate a statistically significant survival advantage for the chemo-radiotherapy-treated patients compared with those treated with radiotherapy alone, the trends favoured the combined approach: a two-month increase in the median survival time and an absolute increase in survival at three years of 4%. Interestingly, a significant difference in overall quality of life favoured the combined modality therapy approach. Differences between this trial and the American trials included different chemotherapy regimens, lower radiotherapy doses, and smaller patient numbers in the U.K. trial.

Another fully published trial reported by Furuse et al (7u) evaluated thoracic radiotherapy (54 Gy in a split course) with concurrently administered chemotherapy (MVP) versus a sequential approach (2 cycles of MVP followed by the same thoracic radiotherapy). Survival was improved with the concurrent approach: median and overall survival were significantly better, and a difference persisted at five years (15.8% versus 8.9% alive). This survival gain was achieved with little difference in treatment-related toxicity. The concurrently treated patients experienced more myelosuppression but not a greater degree of esophagitis.

These two fully published trials support the original recommendation, but for the first time there is evidence that the quality of life of patients receiving combined modality therapy may be improved compared to those who receive radiotherapy alone. The Japanese data also suggest that chemotherapy administered concurrently with radiotherapy may yield higher survival in unresected stage III NSCLC compared with a sequential approach of chemotherapy followed by radiotherapy. Further trials are necessary to clarify the optimal sequencing of these two modalities in the treatment of this group of patients.

VI. ONGOING TRIALS

Protocol ID	Title and details of trial
INRC-PITCAP, EU-20202, INRC-ITA, NCI-V01-1665	Phase III randomized study of paclitaxel and carboplatin or cisplatin followed by radiotherapy with or without concurrent paclitaxel in patients with unresectable stage III non-small cell lung cancer. Outcomes of interest: survival, response rate, tolerability, toxicity. Projected accrual: 300 patients over three years. Status: open. Summary last updated: 2002-06-01.
Cited in Novello et al (32u), page 297.	Randomized trial of radiotherapy alone versus daily carboplatin and radiotherapy, following induction chemotherapy with cisplatin and vinorelbine. Status: open as of November 2002.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

A key issue discussed by the Lung Cancer DSG was the understanding that the available evidence on this topic is generalizable only to patients who have good performance

status and minimal weight loss. It was agreed that the recommendation statement should reflect the fact that the results may not be generalizable to those patients with poor performance status and significant weight loss.

A second issue discussed by the Lung Cancer DSG was the lack of a threshold dose, regimen, or schedule for either chemotherapy or radiation therapy. The optimum method of integrating chemotherapy with radiotherapy is still under investigation. Dosing and scheduling issues are complex when using combined modality treatment, and treatment planning needs careful attention. While evidence can be found to support any one of several schedules for chemotherapy, it is up to individual clinicians to choose which is appropriate on a case-by-case basis.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

This section describes the external review activities undertaken for the original guideline report. For a description of external review activities of the new information presented in the updated sections of this report, please refer to the Update below.

Draft Practice Guideline

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

Draft Recommendations

- For patients with inoperable stage III NSCLC, the combination of cisplatin-based chemotherapy and radical radiotherapy provides a survival benefit compared to radiation alone.
- Patients with good performance status (ECOG 0 to 1) and minimal weight loss (less than 5% in the preceding 3 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 6-week period in combination with cisplatin-based chemotherapy should be recommended as a treatment option. A full discussion should occur between the patient and physician concerning the benefits, limitations, and toxicities of therapy. Patients not fitting the above criteria are not candidates for combined modality treatment. Those experiencing symptoms amenable to treatment should receive immediate palliative thoracic irradiation.
- At this time, hyperfractionated radiation is not recommended outside of the context of a clinical trial.

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 110 practitioners in Ontario (44 medical oncologists/hematologists, 16 radiation oncologists, 18 surgeons, and 32 respirologist/internists). 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 Lung DSG reviewed the results of the survey.

Results

Key results of the practitioner feedback survey of the original draft guideline report are summarized below.

Summary of Main Findings

1. Response rate: 68%.
2. Quality of data synthesis: 90% agreed or strongly agreed with the evidence-based recommendation methods & data synthesis.
3. Endorsed evidence-based recommendation: 81%.
4. Approved of evidence-based recommendation as a guideline: 75%.
5. Would use the practice guideline in practice: 79%.

The main points raised by the practitioner feedback included:

1. Concern about the lack of information on quality-of-life outcomes.
2. Lack of discussion about the cost implications of using combined modality treatment in this patient population.
3. Need for a more precise definition of 'inoperable stage III NSCLC.'

Modifications/Actions

1. While quality of life is recognized as an important outcome in the treatment of patients with unresected, stage III NSCLC, there is very little, if any, data from RCTs that addresses the impact of treatment on quality of life. A statement was added to the 'Methods'[1] section of this guideline indicating that there are no high quality data available addressing the role of combined modality treatment in improving quality of life.
2. Currently, there is no cost benefit analysis available for review. Such an analysis may be available in the near future, and when it is available, the Lung Cancer DSG will review the analysis to determine its applicability to this guideline.
3. The Lung Cancer DSG deliberated extensively over the use of the terms used to describe the patient population for this guideline. Based on feedback from practitioners and an external reviewer, the term 'inoperable' was changed to 'unresected.' The Lung DSG felt the most accurate definition of unresected was one that stated: a patient who has a tumour that, for either technical or medical reasons, cannot be completely resected; either clinical or pathological stage III disease.

Approved Practice Guideline Recommendations

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the external review process. They have been approved by the Lung DSG and the Practice Guideline Coordinating Committee.

- For patients with unresected stage III NSCLC, the combination of cisplatin-based chemotherapy and radical radiotherapy provides a survival benefit compared to radiation alone. This is based on high quality evidence from a meta-analysis and randomized controlled trials.
- Patients with good performance status (ECOG 0 to 1) and minimal weight loss (less than 5% in the preceding 3 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 6-week period in combination with cisplatin-based chemotherapy should be recommended as a treatment option. A full discussion should occur between the patient and physician concerning the

[1] That statement was moved to the 'Results' section of the current document.

benefits, limitations and toxicities of therapy. 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 of the context of a clinical trial. The evidence evaluating the role of hyperfractionated radiotherapy in stage III NSCLC is more fully explored in a separate practice guideline (*Role of Hyperfractionated Radiotherapy in the Treatment of Stage III NSCLC, Practice Guideline Report #7-12*).

Update

The new information from review and updating activities was not subject to external review because it was consistent with the data used to inform the original practice guideline report.

IX. POLICY IMPLICATIONS

This section of the guideline was originally reported under '*Results: Economic Analyses*'.

Evans et al reported the results of an analysis of the costs of combined modality interventions for stage III NSCLC (9u). Their analysis indicated that the cost-effectiveness of combined modality therapy for stage IIIB disease was $3,348 per life year gain (1993, Canadian dollars). For sensitivity analyses, survival gain reported in clinical trials was reduced by 25% and 50% and hospital per diem rates were increased by 10%, 20% and 30%. Even under the most adverse assumptions, the cost-effectiveness estimates were considered acceptable for a new health care technology in Canada. The authors reported that, overall, it appeared that combined modality therapy for stage IIIB NSCLC was cost-effective.

X. PRACTICE GUIDELINE

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

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.

Related Guidelines

Cancer Care Ontario Practice Guidelines Initiative Practice Guideline Report #7-12*: Altered Fractionation of Radical Radiation Therapy in the Management of Unresectable Non-Small Cell Lung Cancer.*

XI. JOURNAL REFERENCE

Okawara G, Rusthoven J, Newman T, Findlay B, Evans WK and the Lung Cancer Disease Site Group. Unresected Stage III Non-Small Cell Lung Cancer. *Cancer Prevention & Control* 1997; 1(3):249-59.

IX. ACKNOWLEDGEMENTS

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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

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

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Appendix 1a

Trials comparing radical radiotherapy with radical radiotherapy plus chemotherapy.

Drugs were given intravenously and doses per cycle were in mg/m^2 unless stated otherwise

Trial	Period of recruitment	Drugs used	Drug dose/ chemotherapy cycle	Cycles (cycles given before radiotherapy	Radiotherapy dose (Gy)/fractions
NRH NSC 26271 (Host[6])	1968-71	Cyclophosphamide			
		followed by	400†	Daily treatment	50/25-31
		Cyclophosphamide*	100	Until tumour progression or toxicity	
EORTC 08742 (Israel *et al*[11])	1973-80	Cyclophosphamide	1000	12	50-60/Not known
		Lomustine*	100		
		Methotrexate	40		
RTOG 7302a (Simpson *et al*[12])	1973-8	Cyclophosphamide	1000	Until tumour progression or toxicity	
RTOG 7302b (Simpson *et al*[12])	1973-8	Cyclophosphamide	1000	Until tumour progression or toxicity	30/10
RTOG 7302c (Simpson *et al*[12])	1973-8	Cyclophosphamide	1000	Until tumour progression or toxicity	40/20
MCL-1 (Sidorowitz[13])	1980-4	Doxorubicin	40	Until tumour progression or toxicity or 34	55/25‡
		Lomustine*	30		
		Cyclophosphamide	400		
		Methotrexate	30		
Aviano (Trovo *et al*[14])	1980-4	Doxorubicin	40	12	45/15
		Cyclophosphamide	600		
		Methotrexate	30		
		Procarbazine*	1000		
AZ-0C-1-80 (Schallier *et al*[15])	1981-5	Vinblastine	6	Until tumour progression or toxicity	55/28
Gwent 3 (unpublished)	1981-5	Etoposide*	1000	7	32/8
SECSG81 LUN 373 (Johnson *et al*[16])	1981-5	Vindesine	3	5	60/33
		followed by Vindesine	6	10	
Gwent 1 (Anderson *et al*[17])	1974-6	Doxorubicin	50	4	32/8
		Fluorouracil	1200§		
SWOG 7635 (White *et al*[18])	1977-9	Doxorubicin	50	8	60/20‡
NCCTG 822451 (Morton *et al*[19])	1983-7	Doxorubicin	40	4 (2)	60/30
		Cyclophosphamide	400		
		Methotrexate	40		
		Lomustine*	30		
Buenos Aires (Cardiello *et al*[20])	1981-5	Cisplatin	40	6	55/22‡
		Doxorubicin	40		
		Cyclophosphamide	400		
Brussels (Van Houtte *et al*[21])	1981-4	Cisplatin	60	3 (3)	55/28
		Etoposide	360		
		Vindesine	3		
FLCSG 2 (Mattson *et al*[22])	1982-4	Cisplatin	40	6 (3)	55/20‡
		Doxorubicin	40		
		Cyclophosphamide	400		
Essen (Alberti *et al*[23])	1983-7	Cisplatin	80	3 (3)	52-56/13-14
		Vindesine	6		
SLCSG (Brodin *et al*[24])	1983-9	Cisplatin	120	3 (3)	56/28
		Etoposide	300		
CEBI 138 (Le Chevalier *et al*[25])	1983-9	Cisplatin	100	6 (3)	65/26
		Cyclophosphamide	600		
		Vindesine	3		
		Lomustine*	75		
WSLCRG/FI (Gregor *et al*[26])	1984-9	Cisplatin	100	8 (2)	50/20
		Vindesine	6		
Perugia (Crino *et al*[27])	1984-8	Cisplatin	100	3 (3)	56/30
		Etoposide	360		
CALGB 8433 (Dillman *et al*[28])	1984-7	Cisplatin	100	2 (2)	60/30
		Vinblastine	5	5 (5)	
EORTC 08842 (unpublished)	1984-9	Cisplatin	100	3 (2)	55/20‡
		Vindesine	6		
SWOG 8300a (unpublished)	1984-8	Fluorouracil	1200	6 (2)	58/29
		Vincristine	2		
		Mitomycin C	10		
		alternating with Cisplatin	40		
		Doxorubicin	40		
		Cyclophosphamide	400		
SWOG 8300b (unpublished)	1984-8	Fluorouracil	1200	6 (2)	58/29
		Vincristine	2		
		Mitomycin C	10		
		alternating with Cisplatin	40		
		Doxorubicin	40		
		Cyclophosphamide	400		

SWOG8300 also randomised to patients receiving (SWOG8300b) or not receiving (SWOG 8300a) prophylactic cranial irradiation.
See appendix 2 for full names of trial groups.
*Given orally. †Daily during radiotherapy. ‡Split course of radiotherapy. §Total dose.

From: Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated individual patient data from 52 randomised clinical trials. Br Med J 1995;311:899-909. Used with permission.

Appendix 2
Administration and Dosage Schedules

Durrant et al 1971 (6)
1. Radiation 4000 rad in 13 or 14 fractions over 28 days
2. Mustine 0.8 mg/kg in 3 IV doses on days 1, 3, 11
3. Radiation 4000 rad in 13 or 14 fractions over 28 days plus Mustine 0.8 mg/kg in 3 IV doses on days 1, 3, 11

Perez et al 1982 (7)
1. Radiation 2000 rad in 5 fractions per week followed by 1-2 weeks rest, then 2000 rad in 5 fractions over week 3
2. Radiation 4000 rad continuously delivered in 4, 5 or 6 weeks
3. Radiation 5000 rad continuously delivered in 4, 5 or 6 weeks
4. Radiation 6000 rad continuously delivered in 4, 5 or 6 weeks

Cox et al 1990 (8)
1. Radiotherapy 60 Gy
2. Radiotherapy 64.8 Gy
3. Radiotherapy 69.6 Gy
4. Radiotherapy 74.4 Gy
5. Radiotherapy 79.2 Gy

McGinnis et al 1995 (9)
1. 60 Gy/30 fractions @200 cGy daily
2. 60 Gy/40 fractions @150cGy BID
3. 60 Gy/40 fractions @150cGy BID plus 2 cycles of concomitant etoposide (100 mg/m^2 days 1-3 + 28-30) plus cisplatin (30mg/m^2 days 1-3 + 28-30)

Sause et al 1995 (12)
1. Radiotherapy 60 Gy at 2 Gy per fraction, 5 days a week over 6 weeks
2. Cisplatin 100 mg/m^2 on days 1 and 29 and vinblastine 5 mg/m ^{2} for 5 weeks starting on day 1 with cisplatin,radiotherapy 60 Gy at 2 Gy per fraction, 5 days a week over 6 weeks beginning on day 50
3. Radiation 69.6 Gy at 1.2 Gy per fraction twice daily

Jeremic et al 1995 (13)
1. Hyperfractionated radiation 1.2 Gy twice daily to a total dose of 64.8 Gy
2. Hyperfractionated radiation 1.2 Gy twice daily to a total dose of 64.8 Gy plus carboplatin (CBDCA) 100mg/m^2 on days 1 and 2 and etoposide (VP-16) 100 mg/m^2 on days 1 to 3 weekly
3. Hyperfractionated radiation 1.2 Gy twice daily to a total dose of 64.8 Gy plus CBDCA 200 mg/m^2 on days 1 and 2 and VP-16 100mg/m^2 on days 1 to 5 of the first, third and fifth weeks

Jeremic et al 1995 (14)
1. Hyperfractionated radiation 1.2 Gy twice daily to a total dose of 69.6 Gy
2. Hyperfractionated radiation 1.2 Gy twice daily to a total dose of 69.6 Gy plus carboplatin (CBDCA) 50 mg/m^2 and etoposide (VP-16) 50 mg/m^2 given on each RT day

Cardiello et al 1985 (15)
1. Radiotherapy 55 Gy
2. Radiotherapy 55 Gy plus cyclophosphamide 400 mg/m^2, doxorubicin 40 mg/m^2, cisplatin 40 mg/m^2 every 4 weeks for 6 courses

Alberti et al1990 (16)

1. Radiotherapy 52-56 Gy weekly
2. Vindesine 3 mg/m^2 on days 1 and 3, cisplatin 80 mg/m^2 on day 2, for 3 courses over 4 weeks plus radiotherapy 52-56 Gy weekly
3. Delayed radiotherapy 52-56 Gy weekly at onset of symptoms

Brodin et al 1997 (17)

1. Radiotherapy 56 Gy delivered in 2 Gy fractions over 7.5 weeks.
2. Cisplatin 120 mg/m^2, on day 1, etoposide 100 mg/m^2 IV on day 1-3 every 4 weeks for 3 courses followed by radiotherapy 56 Gy delivered in 2 Gy fractions over 7.5 weeks.

Crino et al 1991 (18)

1. Cisplatin 100 mg/m^2 on day 1, etoposide 120 mg/m^2 on days 1, 2, and 3 every 3-4 weeks for 3 courses plus radiotherapy 56 Gy
2. Radiotherapy 56 Gy