Long-term survival following chemoradiation for inoperable non-small cell lung cancer

Nikki M Plumridge, Michael J Millward, Danny Rischin, Michael P MacManus, Andrew Wirth, Michael Michael, Kally Yuen and David L Ball

ABSTRACT

Objective: To measure long-term survival following combined chemotherapy and radiotherapy for inoperable non-small cell lung cancer.

Design and setting: Two prospective Phase I/II studies in the multidisciplinary Lung Service of a dedicated cancer hospital in Victoria, commencing in 1996 and 1997–1998.

Patients: 33 patients referred for treatment of histologically or cytologically proven inoperable non-small cell lung cancer, who had no evidence of distant metastases, Karnofsky performance status > 70%, weight loss < 10%, and no prior treatment for lung cancer. Patients were followed until death or for a minimum of 9 years.

Interventions: Patients in both studies were treated concomitantly with chemotherapy and radiotherapy 60 Gy in 30 fractions over 6 weeks. Chemotherapy in the first study (LURTCE) consisted of cisplatin and etoposide; in the second study (LURTCF), chemotherapy consisted of escalating doses of carboplatin and fluorouracil.

Main outcome measure: Overall survival.

Results: Six of 33 patients were still alive 9 years after commencement of treatment. Median survival for the whole group was 2.1 years (95% CI, 1.3–3.1 years), with 18% (95% CI, 8%–35%) of patients still alive at 5 years (plateau).

Conclusion: Long-term survival can be achieved in some patients with inoperable non-small cell lung cancer treated by radical chemoradiation alone, suggesting the possibility of cure.

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Although lung cancer is not Australia's most common cancer, it is the commonest cause of cancer death, with 7264 deaths recorded in 2004.[1] The survival time of patients with lung cancer is among the poorest of any cancer, and it has only marginally improved in the past 15 years. In Victoria, 5-year relative survival increased slightly from 8% in 1990 to 11% in 2004.[2] These grim statistics create a sense that treatment is ineffective, engendering a sense of nihilism among patients and their doctors, especially if the cancer cannot be surgically removed. As an example, a recently published book on interpreting cancer imaging includes the statement that "surgery offers the only chance of cure in non-small cell lung cancer".[3]

Patients with locoregional non-small cell lung cancer (NSCLC) whose disease is inoperable are usually treated primarily with radiotherapy. For these patients, recent meta-analyses indicate that the combination of chemotherapy given concomitantly with radiotherapy is superior not only to radiotherapy alone[4] but also to the combination of radiotherapy and chemotherapy administered sequentially.[5] These studies demonstrated a statistically significant survival benefit at 3 years of 3.2% comparing concomitant chemoradiation with radiotherapy alone (16.6% v 13.4%), and 6.6% comparing concomitant chemoradiation with sequential radiotherapy and chemotherapy (24.8% v 18.2%).

While these survival benefits are important, longer-term benefits of treatment are also of interest to patients when making a decision about choice of treatment. In a survey of patients with a variety of advanced cancers, 85% wanted to know the longest possible survival time with treatment.[6]

At our dedicated cancer hospital in Victoria, studies of various concomitant chemoradiation strategies for inoperable NSCLC have been conducted by the multidisciplinary Lung Service since the early 1990s. Two groups of patients enrolled in prospective studies in the late 1990s have now been followed for a minimum of 9 years; here, we report their survival.

METHODS

Source of patients

Patients were selected from two single-centre, single-arm clinical trials, coded as LURTCE and LURTCF.

LURTCE was a Phase I/II study to test the feasibility of administering concomitant full-dose cisplatin and etoposide chemotherapy with radiation therapy for patients with locally advanced NSCLC (15 patients accrued between 22 January and 26 August 1996). LURTCF was a Phase I/II study of concomitant carboplatin and fluorouracil chemotherapy with radiation therapy for patients with unresectable NSCLC. It was designed to establish the maximum tolerated dose (MTD) and activity of carboplatin and fluorouracil in conjunction with full-dose radiotherapy (24 patients accrued between 18 March 1997 and 13 August 1998).

Both studies were approved by the institutional ethics committee. Each participating patient provided written informed consent. Data analysis for both trials was completed prior to this study.

Eligibility criteria

All patients had to have histologically or cytologically proven NSCLC, confined to the primary site and regional nodes (hilum and mediastinum); a Karnofsky performance status of > 70%; weight loss of < 10% within the past 3 months; and no previous radiotherapy or chemotherapy. Eligible patients also had a 24 h creatinine clearance or glomerular filtration rate > 60 mL/min, haemoglobin level > 10 g/L, neutrophils $> 2.0 \times 10^9$/L and platelets $> 100 \times 10^9$/L.

Disease staging was based on a computed tomography scan of the thorax and upper abdomen. Fluorine-18 deoxyglucose positron emission tomography scanning was not a required part of the staging protocol.

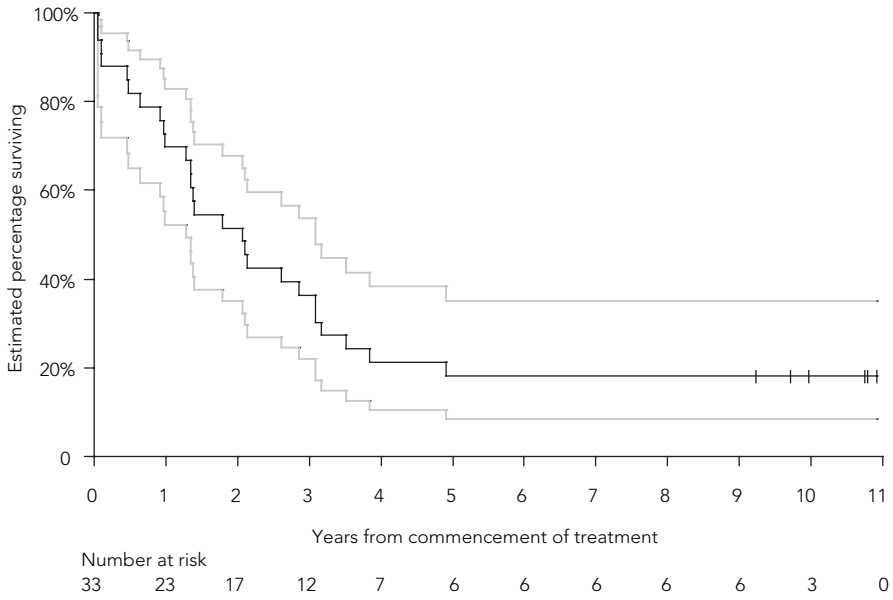
Since the purpose of this study was to assess long-term survival following chemoradiation, six patients (two in LURTCE, four in LURTCF) who had previously had surgical resection of their NSCLC were excluded. Data for the remaining 33 previously untreated patients were analysed.

1 Patient characteristics in each trial

	LURTCE	LURTCF	Total
No. of patients	13	20	33
Sex			
Male	10	11	21
Female	3	9	12
Age at last birthday			
Median (years)	58	62	60
Range (years)	45–71	32–77	32–77
⩽ 39 years	0	1	1
40–49 years	1	1	2
50–59 years	7	4	11
60–69 years	2	10	12
⩾ 70 years	3	4	7
Histological type			
Squamous	8	13	21
Non-squamous	5	7	12
ECOG performance status			
0	8	4	12
1	5	16	21
Weight loss in past 3 months			
None	11	13	24
⩽ 10%	2	7	9
Disease stage (UICC)			
IA	1	0	1
IB	1	4	5
IIB	2	1	3
IIIA	6	9	15
IIIB	3	6	9

ECOG = Eastern Cooperative Oncology Group.
UICC = International Union Against Cancer. ◆

2 Overall survival of patients from both studies combined



Grey lines indicate 95% confidence intervals. ◆

Treatment

In both trials, the planned dose of radiation was 60 Gy in 30 fractions delivered using daily fractions, 5 days per week for 6 weeks.

In the LURTCE trial, the planned chemotherapy doses were cisplatin 20 mg/m^2/day and etoposide 60 mg/m^2/day for 5 days in Week 1 and Week 6 of radiotherapy. In the LURTCF trial, escalating doses of carboplatin and continuous-infusion fluorouracil were given until the MTD was reached:

- Dose level 1: carboplatin area under the curve [AUC] 4, fluorouracil 750 mg/m^2/day × 4
- Dose level 2: carboplatin AUC 5, fluorouracil 750 mg/m^2/day × 4
- Dose level 3: carboplatin AUC 5, fluorouracil 1000 mg/m^2/day × 4

As in LURTCE, chemotherapy was given during Weeks 1 and 6 of radiotherapy. The total dose of carboplatin was divided over 5 days.

Statistical analysis

The endpoint was overall survival, measured from commencement of treatment to death from all causes. All patients were followed until death or the close-out date of 24 May 2007. No patients were lost to follow-up.

Overall survival was estimated using the Kaplan–Meier method. Survival curves were compared between trials using both unstratified and stratified (for Eastern Cooperative Oncology Group [ECOG] performance status) log-rank tests. The Karnofsky performance status scores used in the LURTCE trial were converted to ECOG values. The association between disease stage (according to International Union Against Cancer [UICC] staging criteria) and overall survival was examined using Cox regression.

Two-sample t test, Fisher exact test and test for trend were used to compare the two trials with respect to patient characteristics. All tests were two-sided, and P values less than 0.05 were deemed statistically significant. Analyses were performed using the S-PLUS 2000 (Release 3; MathSoft Inc, Boston, Mass, USA) statistical package.

RESULTS

Patient characteristics

Patient characteristics are shown in Box 1. There was no significant difference between the two studies in patient characteristics, except in ECOG performance status, with a greater proportion of asymptomatic patients (ECOG score = 0) enrolled in LURTCE than in LURTCF (62% v 20%, $P = 0.027$).

Survival

Twenty-seven patients died within the first 5 years of starting treatment. The remaining six patients were still alive at the close-out date (median follow-up, 10.3 years; range, 9.2–10.9 years).

The overall survival of patients from both studies combined is shown in Box 2. The estimated median survival was 2.1 years (95% CI, 1.3–3.1 years). For the whole group, 2-year and 5-year survival rates were 52% (95% CI, 35%–68%) and 18% (95% CI, 8%–35%), respectively. There was no significant difference in overall survival between the two trials ($P = 0.57$). This conclusion remained the same after stratifying for ECOG performance status ($P = 0.49$).

There was no evidence that overall survival was associated with disease stage ($P = 0.65$; hazard ratio, 0.9 [95% CI, 0.6–1.4]). This did not change after adjusting for trial ($P = 0.61$). Noting that most of the patients (73%) had Stage III disease, a further analysis restricted to Stage III patients was performed to compare those with Stage IIIA and Stage IIIB disease. The result of this statistical test was not significant. Of the six long-term survivors, one had Stage I and five had Stage III disease.

DISCUSSION

Although 27 of 33 patients treated in the two trials reported here died within the first 5 years, the remaining six surviving patients have been followed for a minimum of 9 years. Thus, the proportion of patients still alive after 9 years is 18%. While falling well short of the success rates reported with the treatment of other common cancers, these survival data challenge some widely held beliefs about the incurability of inoperable NSCLC, and represent important information to have on hand when discussing treatment options with patients who have inoperable NSCLC.

A recently completed larger study (but with shorter follow-up) has reported similar survival rates. This was a trial in which 191 patients in one arm were randomly assigned to receive chemoradiation without surgery; estimated survival at 5 years for these patients was 20.3%.[7]

The term "cure" is a contentious one in oncology, and this is particularly true for NSCLC, where competing causes of death from other smoking-related comorbidities can confound the interpretation of survival data. Five-year survival probability is often used as a surrogate for "cure", as relapse following radiotherapy-based treatment is unusual after this time, although it can occur.[8] Informing patients of the longest observed survival time is an alternative way of presenting them with prognostic information. In a study of patient preferences in the setting of metastatic disease from a variety of cancers, patients more often wanted to know the longest survival time with treatment than the 5-year survival rate.[6]

The strengths of our study are that it is based on two prospectively conducted trials using contemporary treatment techniques, and the survival analysis is based on intention-to-treat. Its weaknesses include the small sample size and the absence of a no-treatment control arm.

It might be argued that in the absence of a control arm of untreated patients, the survival reported here may reflect the natural history of a carefully selected group of patients, rather than being a consequence of treatment. This seems unlikely, given that the 5-year relative survival of untreated patients with locally advanced NSCLC recorded in a large United States database ranged from 1% to 4%, depending on stage and histology.[9] This is similar to the 5-year survival rate of 1% observed in patients treated with palliative radiotherapy.[10]

The outcomes for good performance-status patients with NSCLC who have locoregional disease that cannot be resected are poor, but not hopeless. Treatment with a combination of chemotherapy and radical radiotherapy may offer the prospect of long-term survival for almost one in five patients.

COMPETING INTERESTS

None identified.

AUTHOR DETAILS

Nikki M Plumridge, FRANZCR, Radiation Oncologist[1]
Michael J Millward, MBioethics, FRACP, Cancer Council Professor of Clinical Cancer Research[2]
Danny Rischin, MD, FRACP, Head[3]
Michael P MacManus, MD, FRCR, FRANZCR, Associate Director (Research)[1]
Andrew Wirth, FRACP, FRANZCR, Radiation Oncologist[1]
Michael Michael, FRACP, Medical Oncologist[3]
Kally Yuen, MSc, AStat, Statistician[4]
David L Ball, MB BS, MD, FRANZCR, Deputy Director[1]

1 Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC.
2 Sir Charles Gairdner Hospital, Perth, WA.
3 Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC.
4 Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre, Melbourne, VIC.

Correspondence: david.ball@petermac.org

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