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Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial☆

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Abstract

Objectives: The non-small cell lung cancer (NSCLC) meta-analysis suggested a survival benefit for cisplatin-based chemotherapy when given in addition to surgery, radical radiotherapy or 'best supportive care'. However, it included many small trials and trials with differing eligibility criteria and chemotherapy regimens. The aim of the Big Lung Trial was therefore to run a large pragmatic trial to confirm the survival benefits seen in the meta-analysis. **Methods**: In the surgery setting, a total of 381 patients were randomised to chemotherapy (C, 192 patients) or no chemotherapy (NoC, 189 patients). C was three 3-weekly cycles of cisplatin/vindesine, mitomycin/ifosfamide/cisplatin, mitomycin/vinblastine/cisplatin or vinorelbine/cisplatin. **Results**: Chemotherapy was given before surgery in 3% of patients whilst 97% received adjuvant chemotherapy. Baseline characteristics were: median age 61 years, 69% male, 48% squamous cell, 93% WHO PS 0-1, 27% stage I, 38% stage II, and 34% stage III. Complete resection was achieved in approximately 95% of patients. In the C group, 13% received no chemotherapy, 21% one or two cycles, and 64% all three cycles of their prescribed chemotherapy (60% of the latter with no delays or modification). 30% had grade 3/4 toxicity, mainly haematological, nausea/vomiting and neutropenic fever, and six patients were reported as having a treatment-related death. 198 (52%) of patients have died, but there is currently no evidence of a benefit in overall survival to the C group: HR 1.02 (95% CI 0.77–1.35), $P = 0.90$). **Conclusions**: This trial has failed to observe a survival benefit with adjuvant chemotherapy following complete resection of stage I–III NSCLC. However, the hazard ratio and 95% confidence intervals are consistent with the previously reported meta-analysis and two large recently reported trials, which suggest a small survival benefit with cisplatin-based chemotherapy.

Keywords: Non-small cell lung cancer; Surgery; Chemotherapy

1. Introduction

In 1995 the Non-Small Cell Lung Cancer Collaborative Group published the results of their meta-analysis investigating the value of chemotherapy in non-small cell lung cancer (NSCLC) [1]. They showed a survival benefit with cisplatin-based chemotherapy in all four settings (patients receiving surgery, surgery and radiotherapy, radical radiotherapy and supportive care). Although the survival benefit was statistically significant in the radical radiotherapy and supportive care settings, the increase in median survival was small. Furthermore the meta-analysis included mainly small trials, and trials with differing eligibility criteria and chemotherapy regimens.

The rationale for setting up the Big Lung Trial was therefore to confirm the survival benefits suggested by the meta-analysis by conducting one large simple pragmatic trial in all the above settings, making it therefore open to all patients with NSCLC. This paper reports the findings from the surgery setting of the Big Lung Trial.

The aim of the current trial was to contribute significantly to the data which will be assembled, along with that from other recent parallel trials, into an update of the meta-analysis.

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2. Methods

2.1. Eligibility

The trial was designed to be as inclusive as possible. At the doctor's discretion patients could be randomised to receive neo-adjuvant chemotherapy (i.e. chemotherapy followed by surgery vs surgery alone) or adjuvant chemotherapy (i.e. surgery followed by chemotherapy vs surgery alone). In addition if radiotherapy was planned as part of the primary treatment, chemotherapy could be given before or after all of the primary treatment. The only eligibility criteria for entry into the surgery setting were that the patient:

1. fulfilled the local criteria for histological or cytological diagnosis of NSCLC
2. was planned to receive (or had recently received) potentially curative surgical resection as part of their primary treatment
3. was considered fit to receive chemotherapy
4. had no concurrent malignancy or history of malignancy other than non-melanomatous skin cancer within the last 3 years.

In addition, both the doctor and the patient had to be uncertain about the value of chemotherapy.

Multi-centre and Local Research Ethical Committee approval was obtained, along with individual patient consent.

It should be noted that patients included in this setting were those for whom surgery was considered to be the treatment of choice, rather than being defined by a particular clinical stage or performance status. Consequently the pragmatic inclusion criteria reflects the diversity of practice in the UK during this time period.

2.2. Trial design

This was a multicentre randomised trial comparing surgery (± radiotherapy) alone with surgery (± radiotherapy) plus cisplatin-based chemotherapy. The choice of chemotherapy regimen (from one of the four cisplatin-based regimens) could be made on a patient-by-patient basis but had to be stated prior to randomisation. Randomisation was performed by telephoning either the London Lung Cancer Group trials office or the Cancer Division of the Medical Research Council Clinical Trials Unit. Patients were stratified by centre, choice of chemotherapy regimen, timing of chemotherapy (neo-adjuvant/adjuvant), gender, histology, and performance status. The allocation was to:

(a) Surgery (± radiotherapy) alone (NoC)
(b) Surgery (± radiotherapy) plus three cycles of 3-weekly chemotherapy (C).

2.3. Surgery alone

Patients could receive whatever other treatments were considered appropriate by their clinician, excluding chemotherapy.

2.4. Surgery plus chemotherapy

In addition to surgery (± radiotherapy), patients were prescribed three cycles of 3-weekly cisplatin-based chemotherapy. At the start of the trial (in November 1995) three chemotherapy regimens, all widely used in the UK, were permitted. However, as new drugs became available, a further regimen, vinorelbine (navelbine) plus cisplatin was added in October 1997.

The regimens were:

- MIC—Day 1: cisplatin 50 mg/m^2, mitomycin 6 mg/m^2, ifosfamide 3 g/m^2
- MVP—Day 1: cisplatin 50 mg/m^2, mitomycin 6 mg/m^2, vinblastine 6 mg/m^2
- CV—Day 1: cisplatin 80 mg/m^2, vindesine 3 mg/m^2; day 8: vindesine 3 mg/m^2
- NP—Day 1: cisplatin 80 mg/m^2, vinorelbine 30 mg/m^2; day 8: vinorelbine 30 mg/m^2.

2.5. Reports and investigations

This was a large pragmatic trial and only essential data were collected. At randomisation all the baseline clinical data (age, sex, TNM stage, histology, WHO performance status and choice of chemotherapy regimen) were collected over the telephone. Data on primary and protocol treatment were collected for all patients 3 months after randomisation and included details of chemotherapy (if received), surgery, radiotherapy and any grade 3/4 toxicities experienced. Subsequent follow-up forms, requesting details of date and site of progression and survival were required at 6 months from randomisation, at 1 year and annually thereafter.

3. Statistical design and methods

3.1. Endpoint

The primary endpoint was survival.

3.2. Analysis plan

All analyses were performed on an intention-to-treat basis. Survival was measured from date of randomisation to date of death (from all causes), or the date last seen for surviving patients. Progression-free survival was taken as the time from randomisation to the time of first progression or death, disease-free survivors being censored on the last date seen. The Kaplan–Meier method was used to calculate

the survival curves, and the Mantel–Cox version of the log-rank test to make treatment comparisons. Forest plots were constructed to compare the hazard ratios (HRs) and 95% confidence intervals (CIs) for survival in subgroups of patients.

3.3. Statistical considerations

The meta-analysis [1] suggested that the survival benefit with adjuvant chemotherapy was likely to be about 5% at 5 years (increasing from 50% with surgery alone to 55% with the addition of cisplatin-based chemotherapy). To detect such a difference reliably requires a total of about 4000 patients. It was not felt possible to accrue such a number of patients in one trial, but in view of the other ongoing adjuvant trials, the aim of the BLT was to make a significant contribution to the total numbers, which could be added into an update of the meta-analysis. The aim was therefore to accrue a sample of 500 patients in the UK. On its own this sample was calculated to have only about a 20% power to detect a 5% difference in survival.

3.4. Independent data monitoring and ethics committee

An independent data monitoring and ethics committee, consisting of two clinicians not entering patients into the trial, an independent statistician, and a quality of life expert was set up (quality of life was assessed in the supportive care setting). They met at approximately yearly intervals to review the interim data, advise on the safety of the regimens, consider whether adjustments to the protocol were required, and recommend the continuation or closure of the trial.

4. Results

4.1. Accrual

Between November 1995 and November 2001 a total of 381 patients were entered into the surgical setting of the Big Lung Trial from 52 UK and 4 non-UK centres. This represented 27% of the total of 1394 patients entered into the Big Lung Trial as a whole. The decision to close the trial on the planned closure date but before the target of 500 surgery patients had been reached was taken as funding ceased in November 2001 and accrual to the whole Big Lung Trial had slowed. The independent data monitoring and ethics committee considered that the additional information obtained by keeping the trial open would be offset by the opportunity to report the results earlier.

192 patients were randomised to receive chemotherapy (C), and 189 to no chemotherapy (NoC).

4.2. Patient characteristics

The main baseline patient characteristics are listed in Table 1. The median age was 61 years, 69% were male, 48% had squamous histology and 58% WHO performance status 1. There were 27% stage I, 38% stage II, and 26% stage IIIa. All the characteristics were well balanced between the two groups.

4.3. Primary treatment

The majority, 368 (97%), were randomised in the adjuvant setting, and only a small proportion, 52 (14%), received radiotherapy as part of their planned primary treatment. Of these 25 were in the surgery alone arm while 27 received surgery and chemotherapy.

4.4. Choice of chemotherapy regimen

Only a few centres used the CV regimen in the first 2 years of the trial. Over the course of the trial, NP (which was only introduced 2 years into the trial) and MVP were increasingly used at the expense of MIC, which was given to 61% of patients in the first 2 years of the trial, but only 19% in the last 2 years. Overall MVP was given to 80 (42%) patients; MIC to 63 (33%) patients; NP to 43 (22%) patients and CV to 6 (3%) patients.

Table 1
Baseline patient characteristics

	Chemotherapy, $n = 192$ (%)	No chemotherapy, $n = 189$ (%)
Age (years)		
Median	61.0	61.9
<55	48 (25)	41 (22)
55–64	77 (40)	76 (40)
65–74	55 (29)	61 (32)
75 +	12 (6)	11 (6)
Sex		
Male	125 (65)	136 (72)
Female	67 (35)	53 (28)
Clinical stage		
I	55 (29)	48 (26)
II	71 (37)	74 (40)
IIIa	52 (27)	47 (25)
IIIb/IV	12 (6)	18 (10)
Uncertain	2	2
Histology		
Squamous	92 (48)	92 (49)
Adenocarcinoma	71 (37)	70 (37)
Other NSCLC	29 (15)	27 (14)
WHO PS		
0	67 (35)	66 (35)
1	109 (57)	111 (59)
2	16 (8)	12 (6)

4.5. Immediate treatment

Information on protocol chemotherapy given in the first 3 months after randomisation was collected on the treatment forms. Information on subsequent treatment was not collected systematically.

4.6. Chemotherapy

Of the 192 patients allocated to chemotherapy, 123 (64%) received their prescribed three cycles of the regimen chosen pre-randomisation. A further 14 (7%) patients received two cycles, 27 (14%) received one cycle, 25 (13%) received no chemotherapy and the remaining 3 patients (2%) received a different regimen to that chosen.

Of the 123 patients who received all the three cycles of chemotherapy, 77 (60%) did so without any modifications (a reduction in the dose of any drug of $>10\%$) or delays (of more than 7 days), 12 (10%) patients with modification, 26 (21%) with delay, and 8 (7%) with both.

The reasons for stopping after 1 or 2 cycles were: died mid chemotherapy cycle (5 patients), toxicity (14 patients), patients' request (18 patients), progressive disease (2 patients), and clinical decision (2 patients). The reasons for receiving no chemotherapy were: deterioration or death in the period between randomisation and starting chemotherapy (3 patients), patient refused chemotherapy (12 patients), considered to have become unsuitable for chemotherapy (7 patients), and for the remaining 3 patients no details are available.

Table 2 shows the differences in the number of cycles received in terms of the patients performance status and chosen chemotherapy regimen. In terms of WHO performance status there was very little difference in the proportion of patients receiving all three cycles of chemotherapy, but a greater proportion of patients receiving MIC or MVP received all three cycles compared to those receiving NP, although this is not a randomised comparison.

Table 2
Cycles of chemotherapy received by baseline WHO performance status and by chosen chemotherapy regimen

WHO performance status	PS0 (%)	PS1 (%)	PS2 (%)	
Patients	67	106	16	
Cycles received				
None	5 (7)	19 (18)	1 (6)	
1	12 (18)	15 (14)	0 (0)	
2	6 (9)	5 (5)	3 (19)	
3	44 (66)	67 (63)	12 (75)	
Chosen regimen	CV (%)	MIC (%)	MVP (%)	NP (%)
Patients	6	62	78	43
Cycles received				
0	2 (33)	7 (11)	11 (14)	5 (12)
1	0 (0)	7 (11)	5 (6)	15 (35)
2	1 (17)	3 (5)	6 (8)	4 (9)
3	3 (50)	45 (73)	56 (72)	19 (44)

Table 3
Surgery

	C (%)	NoC (%)
No surgery	2 (1)	0 (0)
Complete resection	157 (84)	158 (84)
Incomplete resection	29 (15)	30 (16)
No details	4	1

Patients were randomised a median of 42 days after surgery, and those that were allocated to chemotherapy started their first cycle a median of 7 days after randomisation.

Five of the 189 patients who were allocated no chemotherapy actually received chemotherapy, as a result of clinical decision, patient's request or administrative error.

4.7. Surgery

Table 3 shows that surgery was not attempted in only two patients. In addition 59 patients were reported as having had only an incomplete resection. As this figure seemed unexpectedly high, further information was sought and obtained on 48 of these patients. This extra information suggested that of these patients 15 had an R0, 21 an R1, and 8 an R2 resection (where R1 represented microscopic and R2 macroscopic residual disease after surgery). Only four patients had an open and close thoracotomy. Therefore the true complete resection rate was probably closer to 95%.

4.8. Toxicity

For the patients who were allocated, and received, chemotherapy, toxicity was much as expected for cisplatin-based regimens. 30% of patients were reported as experiencing grade 3/4 toxicity, mainly haematological (40%), nausea/vomiting (25%), neurological (2%) and renal toxicity (6%). There was no evidence that toxicity was related to baseline WHO performance status, but 55% of patients receiving NP were reported as having grade 3 or 4 toxicity compared to 27% of the MIC and 17% of the MVP patients.

4.9. Survival

At the time of analysis 198 (52%) patients had died, 99 in each group. The median follow-up for the 183 survivors is 34.6 months. The overall survival plot is shown in Fig. 1. The overall hazard ratio (in favour of no chemotherapy) was 1.02 (95% CI 0.77–1.35), $P = 0.90$. The median survival was 33.9 months for C patients, and 32.6 months for NoC patients. 1- and 2-year survival figures were 74 and 58%, and 74 and 60% for C and NoC groups, respectively.

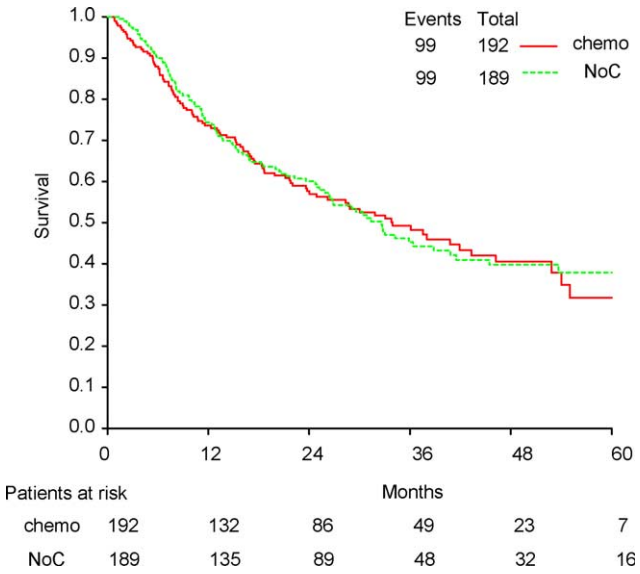


Fig. 1. Overall survival.

Survival was strongly related to stage ($P = 0.0001$) and although there was a suggestion that females and those who received the CV regimen did worse, these differences were not statistically significant ($P = 0.7$ in both cases). There was no evidence that survival was related to WHO performance status ($P = 0.72$), histology ($P = 0.37$), age ($P = 0.54$), timing of chemotherapy ($P = 0.12$), or whether primary treatment was surgery alone or surgery plus radiotherapy ($P = 0.82$).

4.10. Causes of death

In the C group 69 patients were reported as dying of lung cancer, 6 of a treatment-related death, 18 patients of other causes, and for the remaining 6 patients the cause was not available. In the NoC group, the figures are 83, 1, 12 and 3, respectively. There were no deaths within 30 days of surgery in the analysis. Most patients were randomised after surgery.

4.11. Progression-free survival

A total of 168 patients (79 C, 89 NoC) were reported as having progressed. Table 4 shows that there was no difference in the pattern of sites of first relapse between the two groups. The progression-free survival plot is shown in Fig. 2. The median survival was 27.0 months for the C group, and 24.7 for the NoC group, and the proportions of patients alive and progression-free at 1 and 2 years were 66% C, 63% NoC, and 53% C and 51% NoC, respectively. The overall hazard ratio (in favour of surgery and chemotherapy) was 0.97 (95% CI 0.74–1.26), $P = 0.81$.

Table 4
Site(s) of first relapse

	C	NoC
Liver	2	8
Brain	19	13
Bone	11	17
Lung (local)	26	27
Lung (distant)	20	25
Other	14	16
Total patients	79	89
Total sites	92	106

4.12. Interactions

Hypothesis generating survival analyses of subgroups of patients, as defined by the baseline characteristics listed in Table 1, were undertaken. Forest plots of the hazard ratios and confidence intervals for age, sex, stage of disease, WHO performance status, histology and chosen chemotherapy regimen are shown in Fig. 3. There was no evidence that any subgroup benefited more or less from chemotherapy. For patients in each disease stage there was no evidence that the addition of chemotherapy improved survival. The proportions of patients alive at 2 years being 80 and 81% for stage I C and NoC groups, respectively, 52 and 60% for stage II C and NoC groups, and 42 and 39% for stage III C and NoC groups (Fig. 4).

5. Discussion

The NSCLC meta-analysis [1] which combined the results of eight trials, involving a total of 1394 patients, suggested that the survival benefit with cisplatin-based chemotherapy would be around 3% at 2 years and 5% at 5 years. However, even with this number of patients the confidence intervals around the hazard ratio were wide,

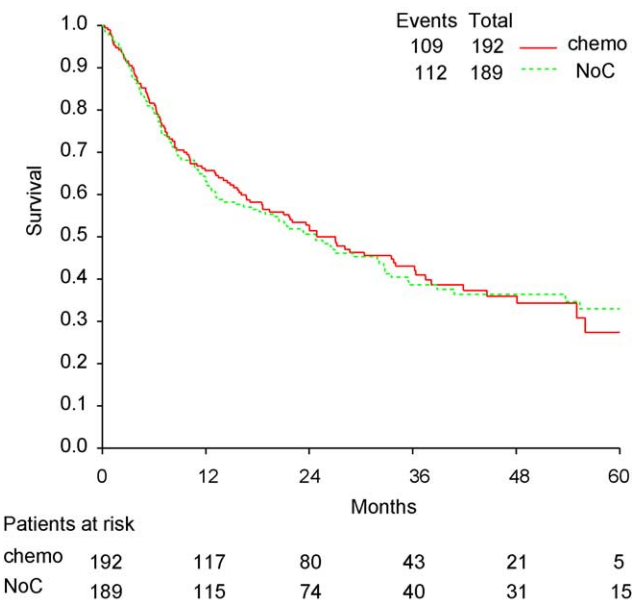
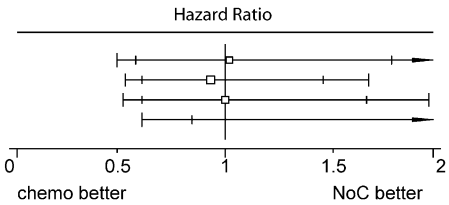


Fig. 2. Progression-free survival.

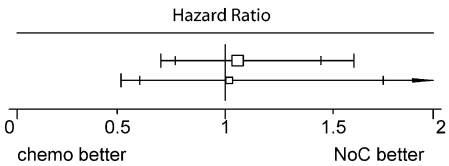
Age

	(no. events/no. entered) chemo	NoC	O-E	Variance
<55	25/48	23/41	0.18	11.65
55-64	37/77	39/76	-1.28	18.96
65-74	28/55	30/61	0.04	14.44
75+	9/12	7/11	3.02	3.45



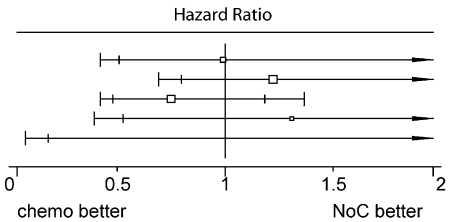
Sex

	(no. events/no. entered) chemo	NoC	O-E	Variance
male	69/125	76/136	1.91	35.70
female	30/67	23/53	0.31	12.98



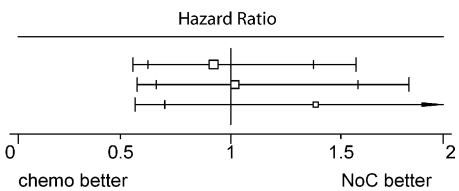
Stage

	(no. events/no. entered) chemo	NoC	O-E	Variance
I	18/55	15/48	-0.06	7.93
II	40/71	37/74	4.01	19.02
IIIa	32/52	37/47	-5.11	17.07
IIIb/IV	8/12	10/18	1.15	4.21
uncertain	1/2	0/2	0.50	0.25



Histology

	(no. events/no. entered) chemo	NoC	O-E	Variance
sqamous	43/92	48/92	-1.81	22.60
adenocarcinoma	39/71	37/70	0.29	18.69
other	17/29	14/27	2.59	7.66



WHO performance status

	(no. events/no. entered) chemo	NoC	O-E	Variance
PS 0	30/67	38/66	-7.53	16.65
PS 1	60/109	54/111	7.65	27.87
PS 2	9/16	7/12	0.02	3.90

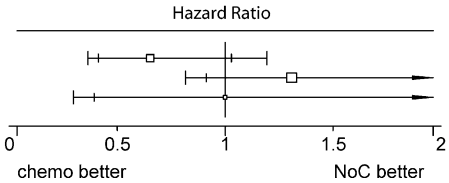


Fig. 3. Forest plots.

and could not rule out the possibility of a 26% benefit or a 2% detriment in survival with the addition of cisplatin-based chemotherapy. To reliably confirm a survival benefit of about 5% requires approximately 4000 patients.

Within the Big Lung Trial a total of 381 patients was accrued from 56 centres over a 6-year period. On average only about one patient was enrolled by each centre per year which could bring into question the clinical validity of the trial. In reality there were 6–10 centres who recruited the majority of patients to this trial. But even in these centres this only represented a minority of those undergoing surgery. Although clinicians could choose, on a patient-by-patient basis, whether to give adjuvant or neo-adjuvant chemotherapy, the vast majority of patients received adjuvant chemotherapy, in common with the meta-analysis. Two trials that both closed early [2,3] suggested a large survival benefit with the use of neo-adjuvant chemotherapy, but this will only be clarified

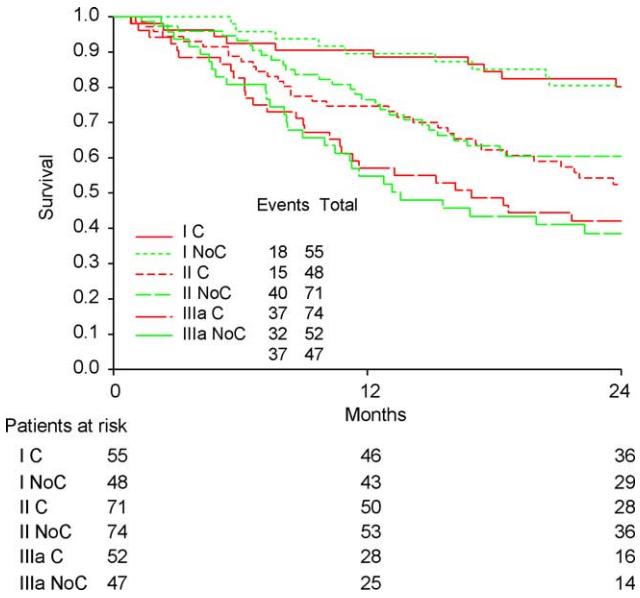


Fig. 4. Survival by tumour stage.

when the results of at least four large ongoing trials are known.

The reason why so few patients in this trial received neoadjuvant chemotherapy is not clear. The fact that a separate Medical Research Council trial (LU22) of neoadjuvant chemotherapy in resectable NSCLC ran concurrently during the latter years of the Big Lung Trial must be taken into account.

Adjuvant chemotherapy is certainly feasible, as indicated by the fact that nearly two-thirds of patients received all three prescribed cycles, and toxicity was much as expected with cisplatin-based chemotherapy, although there were a small number of treatment-related deaths. However, the case for assessing neoadjuvant chemotherapy is strengthened by this relatively low compliance with full treatment. It should be noted that 12 patients declined chemotherapy and a further 18 patients requested termination of the chemotherapy program after 1 or 2 cycles. As noted in the ALPI study [4] this factor may explain why the full benefit of adjuvant therapy has not been demonstrated.

However, there was no evidence that the addition of chemotherapy improved survival, with a hazard ratio of 1.02, although the confidence intervals (0.77–1.35) do not rule out the possibility of about a 25% improvement or about a 35% detriment. Importantly, there was also no evidence from the current trial that any subgroup of patients, defined by age, sex, stage, histology, performance status or chemotherapy regimen, benefited more or less from chemotherapy.

With regards to the surgical aspects of the trial, the relatively low survival of less than 50% at 2 years in stage II patients is of note. This may unfortunately reflect inaccurate or incomplete intraoperative lymph node staging. It has been noted previously [5] that there has been a deficiency in the UK practice of lymph node sampling at operation when 45% of surgeons did not resect or sample macroscopically normal lymph nodes. A recent update of this survey [6] in 2002 found little improvement in the UK practice of intraoperative nodal staging with extreme variability between surgeons. This potential problem may have caused an underestimation of the number of patients with stage IIIa disease in the study. It has been shown previously that adjuvant chemotherapy has little benefit in this stage of disease [7], thus there may be some confounding factors in the interpretation of our results.

The initial reports of incomplete resections in this study prompted re-evaluation of the pathological reports. The majority of cases where R1 resection margins had been described contained positive nodal involvement rather than positive resection margins. This may be partly explained by the completion of proforma by non-surgical personnel. The final complete resection rate of around 95% allows the results of this trial to be compared with other large studies.

Since the meta-analysis (MA) was published, the preliminary results of two large trials have been presented. In the ALPI trial [4] patients with stage I–IIIa NSCLC were randomised to receive three cycles of MVP or no adjuvant treatment. Overall 1209 patients were enrolled and 69% of the 606 patients randomised to chemotherapy completed the prescribed chemotherapy course. With a median follow-up of 64.5 months there was no evidence of a survival benefit from chemotherapy (HR 0.96, $P = 0.585$). Interpretation of the ALPI results is complicated by the non-uniform use of adjuvant radiotherapy which may have contributed to some of the early deaths in the study. It is of note that the proportion of patients receiving planned radiotherapy in this Big Lung Trial was only 14% compared to 43% in ALPI. Furthermore, the proportion of patients with resected stage IA disease was not reported and it has been shown previously that adjuvant chemotherapy is of little benefit in these patients whose underlying prognosis is already excellent [8]. Indeed there appears to be a difference in the effectiveness of adjuvant chemotherapy between those patients with T1 and T2 tumours.

In the IALT trial [9] a total of 1867 patients with stage I–III NSCLC were randomised to receive 3–4 cycles of cisplatin-based chemotherapy after complete surgical resection. At a median follow-up of 56 months there was a 5% increase in 5-year survival in the 935 patients who received chemotherapy (RR 0.86, CI 0.76–0.98, $P < 0.003$). There was also a significant increase in the disease-free survival in the chemotherapy group at both 2 and 5 years after surgery. Of note in the IALT trial is that over half of the patients in the experimental group received etoposide and cisplatin, a regimen not used in this trial or in ALPI and one with potentially less severe toxicity.

In both of the above trials, and in common with the current trial, there was no evidence that any subgroup of patients benefited more or less from chemotherapy.

Many clinicians are concerned about the side effects of chemotherapy. Whilst quality of life was not formally assessed in this surgical group, in the supportive care setting of the Big Lung Trial it was measured by EORTC QLQ-C30 and LC17 questionnaire data. There was no evidence to suggest a detrimental effect on quality of life from the use of chemotherapy.

Although the IALT trial is 'positive' and the ALPI and the current trial are 'negative' it is important to realise that the confidence intervals of all three trials, and of the meta-analysis, overlap and are completely consistent with a hazard ratio between 0.79 and 0.98. Applying this hazard ratio to a median baseline survival of 30 months with stage II disease would represent a survival benefit of between 2 weeks and 8 months.

In the next year the results of two other large trials will be available: the NCI-Canada trial (BR-10), of 482 patients randomised to receive adjuvant cisplatin and vinorelbine, and the ANITA-1 trial in which 831 patients have been randomised to receive a similar regimen. It is therefore essential that an update of the meta-analysis (MA) is performed as soon as possible to define this benefit more accurately.

The updated meta-analysis will clarify whether there is a survival benefit with cisplatin-based chemotherapy, and if so the extent of benefit. However, if there is a clear benefit it will not indicate which particular regimen should be chosen as standard treatment. Although in the current trial, clinicians could choose, on a patient-by-patient basis, which of four regimens to give to the patient, it was not a randomised comparison of regimens. There is now some evidence from randomised trials in advanced NSCLC that indicates that the 3-drug regimens, MVP and MIC, which were received by 77% of patients in the chemotherapy arm of the current trial, are probably inferior in terms of survival and quality of life to 2-drug regimens employing newer agents. For example, in more advanced disease, the combination of gemcitabine and carboplatin has been shown to confer a longer survival than MIC [10] and the combination of cisplatin with either gemcitabine or vinorelbine longer survival than MVP [11]. Thus if no survival benefit is seen with the MA it might be argued that sub-optimal regimens were used, and if a small survival benefit is seen, it could be argued that a greater survival benefit might be expected with newer chemotherapy regimens.

In conclusion, in the current trial there was no evidence of a survival benefit with cisplatin-based chemotherapy. However, the 95%CI for the HR overlap with those of the MA and with the other two recently reported large trials, and are consistent with a small survival benefit. Only when all the data are combined into an updated MA will the survival benefit be reliably defined, and patients and their clinicians will be able to make more informed treatment decisions.

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Appendix A. Conference discussion

Dr W. Weder (*Zurich, Switzerland*): You have to be congratulated for having performed such a large randomised trial. You mentioned that the IALT trial, which has included almost 2000 patients, has shown a clear benefit in survival, and in your data, almost one-third of the patients who in the treatment arm received either no or only one cycle of chemotherapy, which is definitely not enough, do you think this is the explanation, that you have to fail to show a benefit of chemotherapy?

Mr Waller: Yes, and this highlights the problem of adjuvant chemotherapy. Of those in the IALT trial, over 50% of patients received cisplatin and etoposide, which, as we know, is less toxic than some of the mitomycin-based regimens. But of course, this is the real world, and the problem in giving chemotherapy to patients who have had major operations is compliance.

Dr P. Van Schil (*Edegem, Belgium*): I would like to ask you whether you could define any subgroups that do not come out from our anatomical TNM classification but that could probably benefit from adjuvant chemotherapy, as, for example, the patients with R1 resections, extranodal lymph node involvement or patients with lymphovascular permeation?

Mr Waller: No, unfortunately, we haven't been able to demonstrate any subgroup that has benefited from chemotherapy, even the stage IIIa patients, but hopefully it may be possible in the larger meta-analysis to tease out some subgroups, but those specific details may be difficult to pull out from these large trials.

Appendix B. List of participants

The following clinicians, their colleagues and research staff entered patients into this trial:

Addenbrookes and Papworth Hospitals, Cambridge (Dr D. Gilligan, Lavinia Magee),
Airedale General Hospital, Keighley (Dr S.M. Crawford, Aidan Henry, Janet Peace),
Birmingham Heartlands Hospital (Dr P. Sherwood Burge, Dr L.F. Ng, Dr D. Ferry, Linda Brewer, Janet Price, Dawn Richardson),
Bristol Oncology Centre (Dr S. Falk, Dr Gould, Dr Harvey, Dr Whipp, Dr V. Barley, Mr Jeyasingham, Polly Gingell),
Darlington Memorial Hospital (Dr C.K. Connolly, S.M. Alcock),
Derbyshire Royal Infirmary (Dr P. Chakraborti, Dr A. Benghiat, Dr D. Guthrie, Dr D. Otim-Oyet, Sarah Miller, Karen Bishop, Nicola Wilshaw),
Dryburn Hospital, Durham (Dr S. Pearce, Dr N.C. Munro,Jayne McClelland),
Glan Clwyd Hospital (Dr S. Gollins, Dr A.B.W. Nethersell, Dr A.E. Champion, Dr A. Al-Samarraie, Jane Evans),
Hairmyres Hospital, East Kilbride (Mr D. Prakash, Mr A. Jilaihawi, Maureen Canning),
Harefield Hospital, Middlesex (Mr S.W. Fountain, Mr Maiwand, Mr E.R. Townsend, Julia Beeson, Ruth Moxon),
Heatherwood Hospital, Ascot (Dr M. Smith, Ann Archibald),
Hospital for Chest Disease, Athens (Dr A. Rapti),
Ipswich Hospital, Suffolk (Dr J. Morgan, Pam Taylor Neale, Gerda Bailey),
King Edward VII Hopsital, Midhurst (Dr Whitaker, Valerie Hall),
Law Hospital, Lanarkshire (Dr H. Scott),
Leeds NHS Hospitals Trust (Dr M.F. Muers, Dr M. Snee, Dr D. Bottomley, Dr M. Bond, John White, Kate Wren, Kate Hill),
Leicester Royal Infirmary (Dr K. O'Byrne, Dr A. Benghiat, Dr M.D. Peake, Mr D. Waller, Dr I.M. Peat, Catherine Mason, Nathan Rush),
Llandough and Velindre Hospitals, South Glamorgan (Dr A.P. Smith, Dr F.R. Macbeth, Dr S. Gollins, Dr L. Hanna, Barbara Moore, Lynette Lane, Jean Baker, Susan Newton),
Military Hospital, Pakistan (Prof. W. Saeed),
Monklands District General Hospital (Dr L. McAlpine, Janis Dougan),
New Cross Hospital, Wolverhampton (Dr D. Fairlamb, Dr Brammer, Alison Knight, Pauline McCormick, Linda Higgins),
Newport Chest Clinic and Royal Gwent Hospital (Dr I. Williamson, Dr Anderson, Dr Pratheba),
Norfolk and Norwich Hospital (Dr W.M.C. Martin, Dr T. Cotter, Jane Beety, Joan Oldman, Natasha Stevens),
North Devon Hospital (Dr R. Ayres),
North Middlesex Hospital (Dr H. Makkar, Dr T. Eisen, Dr S. Karp, Helen Bridle),
North Staffordshire Royal Infirmary (Dr A. Cook, Dr F. Adab, Marion Evans, Angela Ward, Rowena Smith, Jennifer Walton),
Northampton General Hospital (Dr C. Elwell, Dr A. Jeffrey, Dr Roy Mathew, Nigel Perry, Luisa Josiah),
Northern Ireland Cancer Centre, Belfast (Dr A. Patterson, Dr C. Loughrey, Dr J. Clarke, Dr B. Simms, Dr R. Eakin, Eileen Dillon, Emma Gibson),
Oldchurch Hospital, Romford (Dr A. Gershuny, Dr Alsaffar, Mavis Malcolm),
Plymouth Oncology Centre (Dr C. McGavin, Dr M. Collinson, Dr S.A. Kelly, Dr D. Yiannakis, Lyn Cogley),
Pontefract General Infirmary (Dr A.D.C. Johnson, Dr M. Peake, Tina Greatorex, Claire Swift),
Raigmore Hospital, Inverness (Dr D. Whillis),
Royal Devon and Exeter Hospital (Dr P. Bliss, Mr R.G. Berrisford, Sandra Collinson, Claire Ridler, Dawn Astill),
Royal Free Hospital, London (Dr A. Jones),
Royal Lancaster Infirmary (Prof. M.B. McIllmurray, Josie Bates),
Royal Marsden Hospital (Dr I.E. Smith, Dr T. Eisen, Dr M.E.R. O'Brien, Suzanne Vizor, Alison Norton, Kathy Priest, Dorothy Brett),
Royal Preston Hospital (Dr G. Skailes, Dr A.L. Burton, Dr Tariq Mughal, Tracey Parkinson),
Royal Shrewsbury Hospital (Dr S.T. Awwad, Dr R.K. Agrawal, Helen Moore, Verity Mason),
Royal Sussex County Hospital, Brighton (Dr G. Newman, Dr Wilkins, Dr C.W. Turton, Victoria Rawlings, Emma Richardson),
Royal Victoria Hospital, Belfast (Mr K. McManus, Joy McGrath, Moira Mills),
Scunthorpe General Hospital (Dr T. Sreenivasan, Helen Carolan, Kathy Dent),
Southend General Hospital (Dr C. Trask, Dr Lee, Dr A. Lamont, Dr Koreish, Dr A. Robinson, Dr D. Eraut, Mr K. Kennedy, Gemma Ogden, Marilyn Phillips),
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University College Hospitals (Prof. S. Spiro, Dr J.S. Tobias, Dr S.M. Lee, Denise Blake, Alison Leary),
University Hospital of Crete, Greece (Prof. Bouros, Dr H. Lambrakis),
Walsgrave General Hospital (Dr M. Hocking, Samantha Haggett, Judith Lake, Linda Wimbush),
Western General, Edinburgh (Prof. A. Price, Dr A. Gregor, Dorothy Boyle, Fiona Peet, Fiona Dawson),
Western Infirmary, Glasgow (Dr H.M.A. Yosef, Dr F. McGurk, Dr P. Canney, Dr N. O'Rourke, Dr A. Armour, Dr D. Dunlop, Dr T.B. Habeshaw, Dr R.D. Jones, Claire Lawless),
Whipps Cross Hospital, London (Dr M. Roberts, Dr M. Partridge, Dr R. Taylor),
Whittington Hospital, London (Dr M. Lee, Jill Ireland, Sue Morgan, Alison Leary).