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Inoperable Non-small Cell Lung Cancer: Radiation With or Without Chemotherapy*

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Abstract—*We report a randomized multicentre study of split-course radiotherapy (RT), with or without combination chemotherapy (CT), in* 238 *patients with inoperable non-small cell lung cancer (NSCLC), previously untreated, confined to one hemithorax and the mediastinal nodes. In both treatment groups RT consisted of* 55 Gy *in* 20 F *given over* 7 *weeks with a* 3*-week rest interval. CT consisted of the* 3*-drug regimen CAP: C = cyclophosphamide* 400 mg/m^2, *A = adriamycin* 40 mg/m^2, *P = cisplatin* 40 mg/m^2; 2 *cycles of CAP given before RT, one during the rest interval and six after RT. Seventy per cent in the RT arm and* 67% *in the RT–CT arm had epidermoid carcinoma. No significant difference was apparent between the RT and the RT–CT arms with respect to objective response rates (CR + PR) (*44 *and* 49%, *respectively), median duration of response (*278 *and* 320 *days), local failure (*31 *and* 20%), *distant progression (*23 *and* 20%) *or median survival (*311 *and* 322 *days). The survival figures showed an almost significant (*P = 0.05) *therapeutic advantage of the combined regimen with stage IIIM$_0$ disease. Progressive disease was the cause of death in* 92% *and* 88%.

We conclude that chemotherapy did not contribute significantly to either local control or survival as compared to radiotherapy alone.

INTRODUCTION

DURING the past decade, increased knowledge of the biology of non-small cell lung cancer (NSCLC) [1] has led to improved understanding of the role played by different treatment modalities in the management of this disease. In the treatment of NSCLC there remain the problems raised by a high rate of unresectable tumours, of distant metastases at the time of diagnosis, and of locally recurrent or distant spread of the disease following initial local treatment with surgery or radiation therapy (RT). Consequently, every effort should be made to improve local control on the one hand, and to develop effective systemic therapy on the other. In the early seventies this led to a multitude of clinical trials of combined treatment programmes, despite the lack of available drugs with response rate above 15% when used as single agents [2] or 25% when used in combination [3]. The majority of published trials of NSCLC up to 1980 using combination chemotherapy (CT) alone were not randomized. The results of the combined use of RT and CT suggested that the addition of CT did not affect the survival of lung cancer patients treated with RT [4–7]. Subsequently, with the more effective cisplatin-containing regimens [8–10] for disseminated NSCLC, however, the response rates rose to 40–60%, a finding which indicated the need to re-evaluate the efficacy of combined CT–RT treatment.

In 1982 the Finnish Lung Cancer Study Group (five treatment centres) activated a randomized study of radiation therapy with or without cisplatin-containing CT for NSCLC. The study was aimed at determining whether such a potentially more effective regimen, namely cyclophosphamide, adriamycin and cisplatin (CAP), added to split-course RT improved the median survival and cure rates as against those achieved with split-course RT alone in patients with localized NSCLC, along with documentation of the morbidity of treatments and failure patterns. Our approach was the so-termed 'sandwich technique', with the CT being given

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before, during and after the split-course RT regimen.

MATERIALS AND METHODS

Patients from five treatment centres were randomized to one of two treatment arms by sealed envelopes by means of permuted random blocks and stratification by treatment centres.

Those eligible for incorporation in the study were previously untreated patients with a cytologically (several specimens) (37%) or histologically (63%) proven diagnosis of NSCLC. The tumour had to be inoperable and confined to one hemithorax and the mediastinal nodes. The pretreatment investigations included the following: medical history (weight loss), physical examination, chest X-ray, bronchoscopy, blood count, urine analysis, liver and renal function tests, and radiological studies including liver and bone scans. CT scans of the thorax or of the brain, or mediastinoscopy were performed only in individual cases. The evaluation of pretreatment cardiorespiratory function was made by ECG, spirometry and determination of diffusing capacity for carbon monoxide (D_L). Patients were required to have measurable or evaluable lesions, a Karnofsky performance status of $\geq$60%, to be aged 70 years or less, and to have normal bone marrow, renal and hepatic function. Patients with markedly diminished vital capacity, FEV_1, or diffusing capacity ($\leq$45% of predicted), or with severe cardiovascular or CNS disease were excluded from the study.

The treatment schedule comprised either split-course RT alone, or the same split-course therapy combined with nine cycles of CT. The split course therapy applied in four of the five treatment centres was given from two opposed fields and consisted of 30 Gy given as 3 Gy/fraction for 10 fractions in 2 weeks. After a 3-week rest, there was administered a second course of 25 Gy, 2.5 Gy/fraction for 10 fractions in 2 weeks (NSD 1750 ret). In the remaining treatment centre the fractionation scheme differed from the above, but the biological RT dose administered was similar (NSD 1748 ret): 27 Gy given as 4.5 Gy/fraction for 6 fractions in 3 weeks, followed after a 3-week rest by a second course of 22.5 Gy, 4.5 Gy/fraction for 5 fractions in 2.5 weeks [11]. The primary tumour, the mediastinum and the ipsilateral hilar nodes were included in the radiation volume. The energy was 8 MeV photons delivered from a linear accelerator. A shrinking-field technique was used and a posterior spinal cord block was applied during the second half of treatment to protect the spinal cord. Chemotherapy consisted of the CAP regimen: cyclophosphamide (400 mg/m^2), doxorubicin (40 mg/m^2) and cisplatin (40 mg/m^2) given intravenously every 4 weeks. Two cycles of CAP were given before radiotherapy, 1 during the rest interval, and 6 after radiotherapy. Chemotherapy was mostly administered on an outpatient basis.

Assessments were made from serial PA and lateral radiographs, first after completion of the initial two cycles of CAP, then after the completion of radiation therapy ('maximum response'), and again after every 2 cycles of CAP or every 2nd month during a 1-year period following radiotherapy. CT scans and/or bronchoscopy were used only exceptionally as methods of assessment of tumor response.

Definition of the response and grades of toxicities was as specified by WHO [12]: complete response (CR): the disappearance of all evidence of disease (confirmatory bronchoscopy was not required) for at least 1 month; partial response (PR) $\geq$50% reduction in the product of the two greatest perpendicular diameters of one lesion lasting 1 month, and not accompanied by increasing lesions elsewhere. Response was assessed by a team in each treatment centre but was not blind. Patients in both groups were considered evaluable for maximum response if they had undergone the entire radiotherapy programme which in the RT + CT arm included 3 cycles of CAP in addition to RT.

Survival time was measured from the day of randomization until death. Statistical comparisons of survival were made by application of the log-rank (Mantel–Haenszel) test [13] and survival curves were derived by the method of Kaplan and Meier [14]. The Cox proportional hazards regression analysis (programme 2L of BMDP-81) was used in a forward stepwise mode for assessment of the simultaneous effects of several factors on survival. For differences in frequencies the chi-square test was applied.

RESULTS

Two hundred and fifty-two patients were incorporated in the study between January 1982 and February 1985.

Fourteen patients were excluded from the trial before any study treatment had started (9 RT arm; 5 RT + CT arm). The causes for such exclusion were: rapid clinical deterioration (six patients), discovery of M_1 lesions (three patients), erroneous treatment (two patients), haemoptysis (one patient), second cancer (one patient) and kidney disease (one patient). The survival of the excluded patients was similar for both treatment arms.

The remaining 238 patients (119 RT arm; 119 RT + CT arm) comprise the basis of this report. The analysis is presented for the total patient sample (238 patients) as well as separately for those patients evaluable for maximum response in accordance with the evaluability criteria defined above (176 patients; 72 RT+CT, 104 RT).

The clinical characteristics of the total patient

Table 1. Clinical characteristics of the 238 randomized patients

	RT arm	RT + CT arm
n	119	119
Mean age, years	62	62
Epidermoid cell type (%)	70	67
Stage I (%)	17	21
III (%)	66	64
T1/T2 (%)	8/58	8/58
N1/N2 (%)	26/50	25/47
Asymptomatic(%)	11	7
Symptoms <6 months (%)	46	43
Performance status		
Karnofsky (%) 80–100	70	68
60–70	5	8
Mean weight loss (kg)	1.8	1.7

Table 2. Response rates of 238 randomized patients and of 176 patients evaluable for maximum response, as analysed by cell type

	RT arm	RT + CT arm
All patients (*n*)	119	119
CR + PR (%)	44	49
Evaluable for maximum response (*n*)	104	72
CR (%)	11	15
CR + PR (%)	50	64
Evaluable for maximum response		
Epidermoid (*n*)	78	51
CR (%)	11	22
CR + PR (%)	57	71
Large cell (*n*)	10	11
CR (%)	10	0
CR + PR (%)	50	55
Adeno (*n*)	16	10
CR (%)	6	0
CR + PR (%)	19	40

sample randomized are indicated in Table 1. Epidermoid carcinoma was the dominating cell type. In both treatment arms the majority of patients had a good performance status.

Response

Of the 238 randomized patients, there were 52/119 (44%) with objective response (CR + PR) to RT alone and 58/119 (49%) to combined RT + CT. Of the 176 patients evaluable for maximum response, there were 11/104 (11%) with CR and 41/104 (39%) with PR in the RT arm compared to 11/72 (15%) with CR and 35/72 (49%) with PR in the RT + CT arm (NS). In the two treatment arms (Table 2), the CR + PR rates of the different cell types varied from 19% (adenocarcinoma) to 71% (epidermoid carcinoma). On comparison by treatment, these rates were not statistically significantly different. Comparison by clinical stage, performance status and the duration of symptoms did not indicate any statistically significant difference in response rates. Table 3 illustrates the detailed response pattern of the patients in the RT + CT arm. The 11 patients who achieved a complete response received a total of 3, 3, 3, 4, 5, 5, 6, 6, 9, 9, 9 cycles of CAP, respectively.

Table 3. Tumour response after chemotherapy alone and after additional radiotherapy of 72 patients evaluable for maximum response in the combined treatment arm

Response	Number of patients: After 2 cycles of CAP	After 3 cycles of CAP and additional radiotherapy*
CR	1	11
PR	17	35
MR	4	4
NR	50	22
Total	72	72

CR = complete response; PR = partial response; MR = minor response; NR = no response.
*'Maximum response'.

*Table 4. Relapse pattern in responders**

	Percentage of patients: RT arm *n* = 52	RT + CT arm *n* = 46
Local recurrences†	31	20
Distant metastases	23	20
Both	4	11
Death without progression of disease	35	41
No progression	7	8

*Minimum length of follow-up 337 days, median 1038 days.
†Within the radiation field.

The overall median duration of response for the 52 responders in the RT arm was 278 days, and that for the 46 responders in the RT + CT arm 320 days (NS). Table 4 illustrates the relapse pattern of responders. Thirty-one patients in the RT arm and 20 in the RT + CT arm relapsed locally. Due to the small patient sample, no detailed analysis of inside or outside radiation field relapses will be presented, since it would not allow any conclusions to be drawn on the effect of radiation dose and/or technique utilized.

Survival

Survival by treatment of all the patients randomized and treated is indicated in Fig. 1.

The curves for RT and RT + CT are similar. At the time of analysis 84% of the patients in both

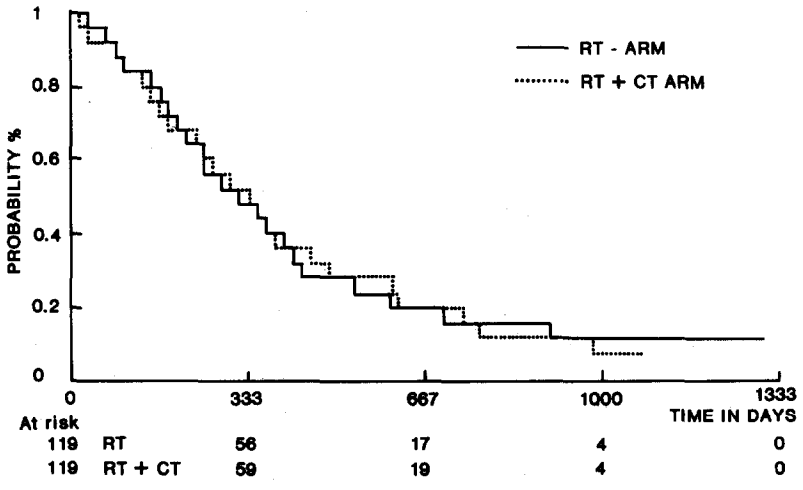

Fig. 1. Survival by treatment of all randomized patients.

treatment arms had died. Median survival of all randomized patients from the day of randomization was 311 days in the RT arm and 332 days in the RT + CT arm. The corresponding 1- and 2-year survival figures were 41% and 17%, and 42% and 19%, respectively.

Survival according to histological subtype did not show any statistically significant difference. When the regression analysis was restricted to stage III, the combined therapy (CR + RT) almost significantly ($P = 0.05$) favourably effected survival. When all the stages were analysed together the type of treatment did not emerge as a factor with a significant influence upon survival. Among the multifactorial analyses, factors with an unfavourable influence upon survival were the short duration of symptoms ($P = 0.005$), mediastinal nodes at diagnosis ($P = 0.016$) and loss of weight ($P = 0.023$). Survival analysis was also performed on all randomized patients, i.e. including the 14 patients who never started any treatment. Also after inclusion of these patients, there was no significant difference between treatment arms with respect to survival.

The treatment centre was the only pretreatment stratification variable; it had no significant influence upon survival.

Toxicity

Patients displayed few side-effects during the course of radiotherapy. About 20% developed oesophagitis after the first course of the split-course regimen. This lasted for 7–10 days and only occasionally delayed initiation of the second course of radiotherapy in the RT arm, or the third cycle of CAP to be given during the rest interval in the RT + CT arm. Almost all patients developed some degree of radiographic pulmonary fibrosis. Pulmonary function tests were repeated only as clinically indicated, and did not reveal major deterioration secondary to radiation fibrosis. CAP chemotherapy did not add significantly to pulmonary toxicity or oesophagitis based upon clinical and radiographic evaluation.

Myelosuppression was clinically insignificant in both treatment arms. Nausea and vomiting secondary to CAP chemotherapy was a common occurrence. Only 31% of all randomized patients received 6 cycles of CAP, and 12% the entire protocol treatment of 9 cycles. The reasons for discontinuation varied in the different treatment centres: patient refusal, mainly related to nausea and vomiting, 16–25%, weakness and anorexia 11–42%, disease-related death 10–33%.

Cardiac side-effects were reported in 5% of patients in the RT + CT arm. Accordingly, the combination of CAP and split-course irradiation did not cause an unacceptable degree of cardiomyopathy, as might be anticipated in the combination of a doxorubicin-containing regimen with radiation therapy.

DISCUSSION

The usefulness of combined radiation and chemotherapy in the treatment of NSCLC has not been established. In our study, the 11% CR and 50% CR + PR rates for radiation alone were similar to results reported in several other studies [15–17]. However, studies published by RTOG [18] as well as others [7] showed a dose–response relationship with greater CR being achieved by higher doses of radiation.

The impact of the radiation technique upon tumour control, survival and normal tissue reactions has been discussed by many authors [18–19]. The split-course schedule employed in this study with fraction sizes of 3–2.5 was selected because it appears to be better tolerated by patients, and is

nevertheless just as effective for tumour control as a conventionally fractionated continuous course [19]. The use of a posterior block to shield the spinal cord in the second portion of the treatment decreases the dose delivered to the central mediastinum by 10% according to our isodose curves. When oblique fields are used, more lung tissue is irradiated.

As local therapy alone is of limited efficacy for NSCLC, the development of an effective systemic therapy represents an important goal. Published studies of chemotherapy trials in NSCLC have reported a wide variation of treatment results, tumour shrinkage in 5–57%, and median survival of 2–9 months, dependent upon the selection of patients with varying prognostic factors and the selection of drugs of varying activity, the most active single agents have resulted in objective response rates of less than 20%.

When this study was initiated, significant objective response rates of 39–42% in patients with advanced NSCLC had been reported with the CAP combination chemotherapy regimen [8]. This regimen could safely be introduced on an out-patient basis as well. The use of CAP concurrently with radiation therapy was associated with an improvement in survival as compared to other chemotherapy regimens applied in combination with radiotherapy [20]. In the present study, the response rate of 20% to 2 cycles of CAP chemotherapy prior to the addition of radiotherapy was similar to the 22% response rate reported for patients with extensive disease [16, 21] and considerably less than the 39% response rate initially reported by Davis *et al.* [8] or Eagan *et al.* [20] or 36% by Gralla *et al.* [10], who combined cisplatin with vindesine. The low response rate in our study may be attributable to the short duration of chemotherapy, 2 cycles, at the time of response evaluation to chemotherapy alone. When the radiotherapy was added to CAP, a response rate of 64% was subsequently achieved, a figure only marginally above the overall response of 50% achieved in the present study subsequent to radiation therapy alone. In addition, the low dose (40 mg/m^2) of cisplatin administered in our study may have contributed to the low initial response rate to CAP. The study by Gralla *et al.* [10] showed a median duration of response of 12 months after 120 mg/m^2 cisplatin, compared to only 5.5 months after 60 mg/m^2.

Patients with CR or PR in the CT + RT arm had a median survival of 439 days, whereas the median survival of those patients with MR or NR was 345 days. This indicates that the responders had a more favourable prognosis than the non-responders, but does not necessarily imply that prolonged survival was attributable to CAP CT *per se* [22].

In our study, maximal response was achieved after 3 cycles of CAP and radiotherapy in the RT + CT arm. Only in occasional patients did further chemotherapy increase the response. Ten per cent of our patients stopped chemotherapy after 3 cycles, that is after the completion of radiotherapy.

Even if the quality of life was not systematically assessed in the present study, the high percentage of discontinuation of CAP chemotherapy after the third cycle because of nausea, vomiting, weakness and anorexia (14%) and patient refusal (26%) indicates substantial impairment of the quality of life following treatment.

Our patient population differed from most studies published in the American literature with respect to the high percentage of patients with epidermoid carcinoma, a good prognostic feature. A median survival of 11 months in the RT + CT arm in this instance exceeds that of 9 months observed by Fram *et al.* [21] and Hande and Malcolm [16] in similar studies, and 10 months previously reported by Bleehen [23] after radiation therapy alone; both of the last mentioned studies had a majority of patients with adenocarcinoma. However, the 'long-term' survival figures (1, 2, 3 years) did not display any significant differences between studies or treatments. The only study to date where CAP chemotherapy in a randomized study prolonged the disease-free survival in non-small cell lung cancer was published by Holmes and Gail [24] in 1986 and concerned completely resected lung cancer of adenomatous and large cell type. The number of patients in our study would have made possible the detection of a difference in survival of about 15% with a power of 90% at a significance level of 0.05.

We conclude that chemotherapy as employed in our study did not contribute significantly to either local control or survival of patients with inoperable locoregional NSCLC, as compared to similar patients treated by radiation therapy alone.

REFERENCES

1. Gazdar AF, Carney DN, Minna JD. The biology of non-small cell lung cancer. *Semin Oncol* 1983, **10**, 3–19.
2. Selawry OS. The role of chemotherapy in the treatment of lung cancer. *Semin Oncol* 1974, **1**, 259–272.
3. Aisner J, Hansen HH. Commentary: current status of chemotherpy for non-small cell lung cancer. *Cancer Treat Rep* 1981, **65**, 979–986.

4. Hosley HF, Marangoudakis S, Ross CA, Murphy WT, Holland JF. Combined radiation–chemotherapy for bronchogenic carcinoma. *Cancer Chemother Rep* 1962, **16**, 467–471.
5. Samuels ML, Barkley HT, Holoye PY, Rosenberg PJ, Smith TL. Combination chemotherapy with bleomycin (NSC-125066), vincristine (NSC-67574) and methotrexate (NSC-740) plus split-course radiotherapy in the treatment of non-oat cell bronchogenic carcinoma. *Cancer Chemother Rep* 1975, **59**, 377–383.
6. Sealy R. Preliminary results in combined radiotherapy and chemotherapy in non-small cell carcinoma of the lung. In: Muggia F, Rozencweig M, eds. *Progress in Therapeutic Research*. New York, Raven Press, 1979, 315–323.
7. Van Houtte P, Salazar OM, Henry J. Radiotherapy in non-small cell lung cancer: present progress and future perspectives. *Eur J Cancer Clin Oncol* 1984, **20**, 997–1006.
8. Davis S, Rambotti P, Park YK. Combination cyclophosphamide, doxorubicin and cisplatin (CAP) chemotherapy for extensive non-small cell carcinoma of the lung. *Cancer Treat Rep* 1981, **65**, 955–958.
9. Eagan RT, Frytak S, Nichols WC *et al.* Cyclophosphamide and VP16-213 with or without cisplatin in squamous cell and small cell lung cancers. *Cancer Treat Rep* 1981, **65**, 453–458.
10. Gralla RJ, Casper EJ, Kelsen DP *et al.* Phase II studies in non-small cell lung cancer. The Memorial Hospital experience, 1977–80. In: Cortes Funes H, Rozencweig M, eds. *New Approaches in Cancer Therapy*. New York, Raven Press, 1982, 139–145.
11. Taskinen PJ. Large dose fractions in telecobolt radiotherapy. A report on the treatment of inoperable lung cancer. *Strahlentherapie* 1969, **137**, 522–529.
12. *WHO Handbook for Reporting Results of Cancer Treatment*. Geneva, World Health Organization, 1979.
13. Peto R, Pike MC, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *Br J Cancer* 1977, **35**, 1–39.
14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
15. Rissanen PM, Tikka U, Holsti LR. Autopsy findings in lung cancer treated with megavoltage radiotherapy. *Acta Radiol* 1968, **7**, 433–442.
16. Hande KR, Malcolm AW. Chemotherapy and radiation therapy of non-small cell lung cancer. In: Greco FA, ed. *Biology and Management of Lung Cancer*. Boston, Martinus Nijhoff, 1983, 191–217.
17. Holsti LR. Combined chemotherapy and radiotherapy in lung cancer. *Cancer Treat Symposia* 1985, **2**, 63–67.
18. Perez CA, Stanley K, Grundy G. Impact of irradiation technique and tumor extent in tumor control and survival of patients unresectable non-oat cell carcinoma of the lung: report by the Radiation Therapy Oncology Group. *Cancer* 1982, **50**, 1091–1099.
19. Holsti LR, Mattson K. A randomized study of split-course radiotherapy of lung cancer: long term results. *Int J Radiat Oncol Biol Phys* 1980, **6**, 977–981.
20. Eagan RT, Lee RE, Frytak S *et al.* Randomized trial of thoracic irradiation plus combination chemotherapy for unresectable adenocarcinoma and large cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 1979, **5**, 1401–1405.
21. Fram R, Skarin A, Balikian J *et al.* Combination chemotherapy followed by radiation therapy in patients with regional stage III unresectable non-small cell lung cancer. *Cancer Treat Rep* 1985, **69**, 587–590.
22. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. *Clin Oncol* 1983, **1**, 710–719.
23. Bleehen NM. The treatment of inoperable lung cancer radiotherapy and chemotherapy. *Int J Radiat Oncol Biol Phys* 1980, **6**, 1007–1012.
24. Holmes EC, Gail M. Surgical adjuvant therapy for stage II and stage III adenocarcinoma and large-cell undifferentiated carcinoma. *J Clin Oncol* 1986, **4**, 710–715.