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# RADICAL RADIOTHERAPY OF INOPERABLE NON-SMALL CELL LUNG CANCER

## Irradiation techniques and tumor characteristics in relation to local control and survival

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**The relation between tumor characteristics, irradiation technique, local tumor control and survival was retrospectively studied in 323 patients with non-small cell lung cancer who started radical radiotherapy in 1974–1981. At that time three non-randomized different fractionation schedules were used: 16 × 3.25 Gy, total dose 52 Gy, 3 fractions/week (schedule 1), 11 × 4 Gy, total dose 44 Gy, 2 fractions/week (schedule 2) and 25 × 2 Gy, total dose 50 Gy, 5 fractions/week (schedule 3). The highest survival rates were observed in the patient group treated according to schedule 2. The 2-year survival rate was 30% compared with 18% and 6% in the patients treated according to schedule 1 and 3 respectively. However, this can at least partly be explained by patient selection. A correlation between size of the tumor, target volume and survival was observed: the larger the tumor, the poorer the survival. Pleural effusion showed to be an unfavorable prognostic factor. The prognosis of inoperable lung cancer on the whole remained poor: the 1-year survival rate was 43% and 2-year survival rate 16%. Only 3% of the patients lived at least five years.**

In non-small cell lung cancer (NSCLC) surgery is the treatment of choice. However, for a great part (70–80%) of the patients either wide extension of the disease or poor general condition exclude surgery and radiotherapy remains as the only method that may achieve curative result. Chemotherapy has shown to be ineffective in NSCLC (1, 2). Combined with chemotherapy, radiotherapy plays also a role in limited stage small cell lung cancer (SCLC) for obtaining better local control (3).

There are many different opinions on patient selection, optimal total radiation dose, fractionation and target volume. In spite of the technical development within radiotherapy, the results of radiotherapy for NSCLC have hardly improved at all: the 5-year survival rates for inoperable patients are still under 10% (4–7). Radical radiotherapy can, however, give curative results. Smart (8) has published a 5-year survival rate as high as 22.5% for carefully selected patients. More efforts should be made to find, amongst the heterogeneous group of lung cancer patients, those most likely to benefit from radical radiotherapy. If such a selection is possible the remaining patients could be spared the burden of long and tiring radiotherapy.

In the present retrospective investigation an attempt was made to evaluate factors connected with treatment technique and tumor characteristics, and which possibly affect tumor control and survival.

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### Material and Methods

The study material consisted of 323 inoperable NSCLC patients treated at the Department of Oncology of Tampere University Hospital during the years 1974–1981. Patients who received cytostatics in addition to radiotherapy

as part of the primary treatment or those treated with purely palliative intent were excluded from the analysis. Data have been gathered retrospectively from medical records and radiographs, and survival data from the national death register. Chest x-rays were available for 289 patients (89%) while for the remainder radiographs taken immediately before radiotherapy were lacking. In addition chest x-rays performed at the end of the radiotherapy existed for 84% of the patients. Most patients (88%) had their first control including chest x-rays within three months after cessation of treatment and thereafter according to individual schedules depending on symptoms, but usually at least every three months. The follow-up period ended on December 31, 1987. For evaluation of treatment response and local control the follow-up covered 79% of the patients. For the remainder only survival data were available, since the follow-up visits were transferred to other departments (9%) or since the patients did not arrive to any control visit (12%).

The average age was 65 years (range 36–84 years) and 297 (92%) of the patients were men. The diagnosis of lung cancer was established by histology in 54%, by cytology in 41%, and by purely clinical and radiological signs in 5% of the patients. Microscopically, 61% of the tumors represented squamous cell carcinoma, 8% adenocarcinoma, and 26% undifferentiated or unclassified carcinoma. In the majority of the patients (n = 297, 92%) surgical treatment was regarded as unsuitable and for the remainder explorative thoractomy had been performed before radiotherapy. Over half the patients (53%) belonged to clinical stage III, while 28% were classified as stage II and 19% as stage I (UICC, 1973). The tumors were divided into central (72%) and peripheral (28%) on the basis of bronchoscopy and radiographic findings. Tumors at bronchoscopy situated distally from the segmental bronchus and radiologically separate from the hilum were classified as peripheral.

For most patients (94%) an individual treatment plan was made with two or three treatment fields of which one or two had oblique beam direction in order to reduce the dose in the spinal cord (Figure). The remainder were treated from two anteroposterior opposing fields. Of the patients 66% were treated by 25 MV x-rays from a betatron, 29% by $^{60}$Co-beam and 2% by 14 MV x-rays from a microtron. The remaining 3% received treatment from two different supervoltage equipments. The minimum target dose was used for registration of the radiation dose. At the beginning of the study period the following fractionation schedule was commonly used: 16 × 3.25 Gy = 52 Gy, 3 fractions/week (fr/wk) (schedule 1). Some long journey out-patients with relatively good general condition were also treated with hypofractionation: 11 × 4 Gy = 44 Gy 2 fr/wk (schedule 2). For the final years there was a change to 5 fractions per week: 25 × 2 Gy = 50 Gy (schedule 3). In the middle of the treatment period there was usually a 2–3 weeks' pause. The mentioned therapy schemes were, however, only guide-lines and in individual patients there were divergences from the total dosage (see Results). Since CT was not available in our department at that time, the tumor size was measured from the patients' chest x-ray images; for assessing response to treatment its greatest diameter and, when possible, also the corresponding perpendicular diameter were measured. The site of the tumor and tumor-associated changes, such as atelectasis and pleural effusion, were also recorded.

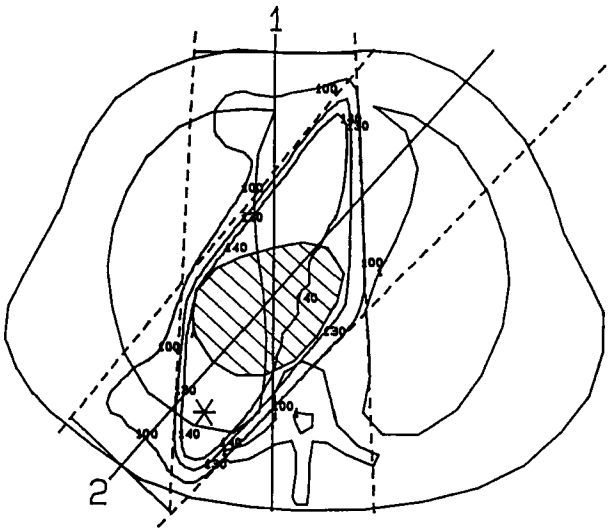


*Figure.* A typical treatment plan for central lung cancer (25 MV x-rays from betatron)

Data from the follow-up period were gathered regarding response to treatment, tumor recurrence and survival. If chest x-rays were available, the treatment response was assessed up to 9 months from the beginning of therapy using WHO criteria (9). The state of the tumor was also defined by a radiologist and this statement in medical records was also used in evaluation of local control. If no regression at all was observed, or if the tumor began to regrow after a positive response to treatment, local failure was recorded. In responding patients the duration of local control was calculated from the beginning of the treatment to the detection of local failure. Survival time was also calculated from the beginning of treatment.

The statistical significance of the results was tested by the $\chi^2$-test.

Survival analyses were made using the BMDP statistical software (10). Cox's proportional hazards model (BMDP2L program) was used in multivariate regression analyses of the survival data. All variables used were treated as contiguous and summarized in Table 1.

## Results

After one year from the start of treatment, 43% of the patients were still alive and after two years 16%. Only 9

**Table 1**

*Independent predictors of survival time according to a multivariate Cox's regression analysis (n = 289)*

| Prognostic parameter | Related to survival (p-value) |
|---|---|
| Total dose | 0.028 |
| Fraction size | 0.006 |
| Tumour size | 0.037 |
| Pleural effusion | NS |
| Atelectasis | NS |

NS = not significant

patients (3%) lived for 5 years or more. For one-third of the patients (35%) treatment did not produce any response or the disease reappeared locally already within 6 months. For 18% of the cases local control remained at least for one year and for 5% for two years or longer. Exact follow-up data were lacking for 20% of the patients and the time of reappearance of the disease could not be determined (of the 39 patients who did not come to the first control, 70% died within 6 months). Response to therapy was measured only for patients with chest x-rays available for retrospective analysis (n = 289). Good response (75–100% tumor regression) was achieved for 8% of these patients. After one year 67% in this group were alive and after two years 46%. If the response was less pronounced (25–49% or 50–74% regression) its degree was not found to be significantly associated with survival; less than 16% of these patients were alive after two years. The majority of the local recurrences (78%) appeared within the treated volume (infield) while the remainder appeared in the same lung but outside the treated volume.

In only one patient was it necessary to stop the treatment due to poor tolerance. In a further 12 patients (4%) therapy was discontinued due to progression of the disease. In 6% of the patients unplanned interruptions were made because of side-effects of the treatment. During the treatment period symptoms of respiratory infection was registered in 23% of the patients. In the follow-up radiation pneumonitis was radiologically found in 68% of the patients, while in 27% no radiation pneumonitis was observed. In 5% the situation could not be assessed due to tumor recurrence, lack of x-ray images, etc.

*Radiation doses and fractionation.* Most of the patients (71%) were treated according to schedule 1 (3 fr/wk). The mean total dose given in this group was 48.5 Gy in minimum, mean maximum dose was 55.0 Gy and the average fraction size 3.1 Gy. Treatment schedule 2 (2 fr/wk) was used only for 7% of the patients with a mean given total dose of 45.3 Gy/min and 50.9 Gy/max, the average fraction dose was 3.9 Gy. The rest of the patients (22%) received 5 fr/wk (schedule 3) and the doses were 49.7 Gy, 55.0 Gy and 2.0 Gy respectively. The biological effect of different fractionation schedules was compared using Ellis' formula (TDF). It was almost the same in the groups which were treated according to schedules 1 and 2. The average TDF-values were 89.6 and 89.4 respectively. In the daily fractionated group (schedule 3) the biological 'dose' became lower; mean TDF was 77.7. Altogether 18 patients (6%) received less than 40 Gy and only 4 patients (1%) received over 55 Gy minimum tumor dose. The possible correlation between total dose and survival was analysed in the group of patients treated according to the most common schedule (number 1, 3 fr/wk). For those patients who received the prescribed doses, neither survival nor local control was found to be clearly correlated with total dose (Table 2). The survival figures were highest in the patients treated with fractionation schedule 2 (4 Gy/fr), intermediate with 3.25 Gy/fraction schedule and lowest with conventional fractionation. However, there was no correlation between local control of the disease and fractionation (Table 3).

*Target volume.* Mediastinum was included in the target volume in 86% of the patients, while for the remainder

**Table 2**

*Correlation between survival, local control and total dose given in the patient group treated according to schedule 1 (3fr/wk) (n = 229)*

| | Total dose | | | | |
|---|---|---|---|---|---|
| | <40 Gy n = 13 | 40–44.9 Gy n = 13 | 45–49.9 Gy n = 97 | 50–54.9 Gy n = 109 | >55 Gy n = 1 |
| Survival (%) | | | | | (n) |
| >1 year | 8 | 38 | 53 | 42 | – |
| >2 years | 0 | 8 | 24 | 17 | – |
| Local control (%) | | | | | |
| >1 year | 0 | 15 | 25 | 16 | – |
| >2 years | 0 | 0 | 8 | 5 | – |
| Missing follow-up | 38 | 8 | 23 | 16 | – |
| Total | 5% | 5% | 42% | 48% | |

**Table 3**

*Correlation between survival, local control and fractionation (n = 323)*

| | Fractionation | | |
|---|---|---|---|
| | 5 fr/wk n = 71 | 3 fr/wk n = 229 | 2 fr/wk n = 23 |
| Survival (%) | | | |
| >1 year | 44 | 44 | 87 |
| >2 years | 6 | 18 | 30 |
| Local control (%) | | | |
| >1 year | 15 | 18 | 26 |
| >2 years | 3 | 5 | 4 |
| Missing follow-up | 24 | 19 | 35 |
| Total | 22% | 71% | 7% |

only the primary tumor was treated. Of the patients in whom mediastinum was included, 44% were alive after more than a year and 13% after two years. For those receiving treatment only to the primary tumor the corresponding rates were 68% and 34%. The size of the target volume was measured from the treatment plan by multiplying the area of target (shadowed in the Figure) by the height of the treatment fields. For almost half the patients the target volume was 800–1 600 $cm^3$ and for these patients the 1-year survival rate was 47% and the 2-year survival rate 13%. The survival rate increased with decreasing size of the target volume which may be due to an association between target volume and tumour size. The target volume was not found to be significantly associated to local tumor control.

*Treatment pauses.* Treatment interruptions made for different reasons were analyzed together. With the exception of 11 patients a preplanned split pause was inserted half way during treatment. In 19 patients (6%) an additional interruption was made due to side-effects. The group of patients treated without a pause also included patients for whom the treatment had to be discontinued at an early stage which explains the low survival rate for this group (1- and 2-year survival rates 18% and 0% respectively). In 67% of the patients there was a treatment pause of 1–3 weeks and 48% of these patients were alive after one year, 16% after two years. The patients with longer treatment pauses, 3–5 weeks, had similar 1- and 2-year survival rates (47% and 18% respectively). No association could be found between total treatment time and survival.

*Size of the tumor.* For 40% of the patients the size of the tumor could not be measured because of atelectasis, pleural effusion, pneumonia, etc. In patients with measurable tumor, the greatest diameter correlated negatively with both local control time and survival (Table 4).

*Site of tumor, pleural effusion and atelectasis.* Patients with peripheral carcinoma had a better prognosis than patients with central tumors. After one year 60% of the peripheral and 42% of the central carcinoma patients were alive. The corresponding 2-year survival rates were 27% and 11%.

Pleural effusion could be estimated semiquantitatively (none, some, abundant) for 97% of the patients with initial x-rays available and in 16% of those a measurable quantity was found. Pleural effusion in chest x-rays clearly worsened the prognosis for the patient ($p < 0.05$), but patients with small and abundant effusion had similarly poor prognosis (Table 5).

The presence of atelectasis was observed in 38% of the patients. Atelectasis covering the whole lung was found in 4 patients (1%). There was a trend towards poorer prognosis in patients with atelectasis but this was not statistically significant (Table 6).

*Multivariate analysis.* With the aid of a multivariate regression model an attempt was made to assess the prognostic significance of factors associated with tumor and treatment. Variables chosen were the size of the tumor, pleural effusion, atelectasis, total treatment dose and

**Table 4**

*Correlation between survival, local control and tumour size (n = 289)*

| | Greatest diameter | | | | | | |
|---|---|---|---|---|---|---|---|
| | Non-measurable n = 116 | <3 cm n = 19 | 4 cm n = 40 | 5 cm n = 30 | 6 cm n = 25 | 7 cm n = 20 | >8 cm n = 39 |
| Survival (%) | | | | | | | |
| >1 year | 58 | 90 | 68 | 50 | 44 | 45 | 33 |
| >2 years | 16 | 37 | 28 | 20 | 8 | 5 | 8 |
| Local control (%) | | | | | | | |
| >1 year | 22 | 37 | 25 | 7 | 15 | 8 | 13 |
| >2 years | 6 | 5 | 10 | 3 | 4 | 0 | 3 |
| Missing follow-up | 17 | 16 | 13 | 43 | 36 | 5 | 18 |
| Total | 40% | 7% | 14% | 10% | 9% | 7% | 13% |

**Table 5**

*Correlation between survival and pleural effusion (n = 279)*

| | Quantity of pleural effusion | | |
|---|---|---|---|
| | none n = 234 | some n = 26 | abundant n = 19 |
| Survival (%) | | | |
| > 1 year | 54 | 38 | 32 |
| > 2 years | 18 | 8 | 5 |
| Total | 84% | 9% | 7% |

**Table 6**

*Correlation between survival and atelectasis (n = 285)*

| | Extent of atelectasis | | |
|---|---|---|---|
| | none n = 176 | segment n = 40 | lobe n = 69 |
| Survival (%) | | | |
| > 1 year | 53 | 45 | 45 |
| > 2 years | 20 | 11 | 13 |
| Total | 62% | 14% | 24% |

fraction size. The endpoint was survival. According to this analysis tumor size, fraction size and total dose (when also patients receiving <40 Gy included) were the best predictors of survival. No other factors had a significant independent correlation to the prognosis (Table 1).

## Discussion

In spite of the numerous publications and wide clinical experience, treatment of inoperable lung cancer varies greatly between different centres. Optimal total doses or fractionations are not yet known. Perez & Emami (11) regarded 50–75 Gy during 6–7 weeks as a potentially curative dose for patients with disease limited to one side of the thorax. Such a large total dose requires thorough dose planning because of risks of normal tissue damage. With regard to pulmonary radiation toxicity Cox et al. (12), however, considered therapy volume a more important factor than the treatment dose.

In several investigations (13–23) it has been shown that better intrathoracic tumor control is achieved by higher doses. No such clear correlation, however, has been found between treatment dose and survival. In a prospective study of 551 inoperable lung cancer patients, Perez et al. (18) obtained some improvement in the 3-year survival by raising the total dose from 40 Gy to 60 Gy (6% versus 15%). Higher doses gave no improvement of survival in their study (18). Also Salazar et al. (21) made similar observations after doses varying between 45–70 Gy. This poor correlation between radiation dose and survival might be explained by early spread of lung cancer beyond the thorax. However, opposite opinions have been expressed in other reports (19, 20, 23, 24). In these higher total doses have been proposed on the grounds that the few patients who live long have usually had a complete remission, which in turn is clearly shown to be dose-dependent (12, 19, 23). Mantravadi et al. (23) found in a retrospective material of 267 patients a clear correlation between total dose and disease-free survival. The patients were divided into three dose groups, 55–65 Gy, 45–55 Gy and <45 Gy. Complete remission was achieved in 35%, 23% and 13% and 2-year disease-free survival was 21%, 11% and 4% respectively. Complete remission was clearly associated with better 5-year survival (17% for complete responders and 7% for all the patients). This is in agreement with our own study which showed that patients with good response to therapy had a longer survival than those who responded poorly. However, an opposite result was found in another Finnish study, where Holsti & Mattson (4) could not see any difference in survival between responders and non-responders.

In the present investigation, no significant relation was found between total tumor dose and survival in the patients who received >40 Gy, and the rate of local control was only slightly (not statistically significant) correlated to the dose. However, the dose range in this material was rather narrow and various fractionation schedules made the material less suitable for analysis of the effect of the total dose. The local control rate in our material was somewhat lower than usually reported, which may be due to the fact that the total doses were rather low compared with those of other studies (13–18, 20, 21, 23, 25, 26). Even so, the survival rates were comparable with those in earlier publications (27).

Various fractionation schedules have been used in lung cancer radiotherapy, and the most usual at present is probably about 2 Gy daily with five weekly fractions up to a total dose of 40–60 Gy. For treatment with fewer fractions some differing results have been presented. Cox stated that hypofractionation (1–3 fr/wk) reduces the local control rate (28, 29). Eichhorn (30), investigating histological autopsy specimens after differently fractionated radiation therapy, reported that treatment carried out with small daily doses gave markedly better effect. Opposite observations have been presented by Slawson et al. (26) and Salazar et al. (31) from a randomized trial comparing conventional 5 fr/wk fractionation with one fraction per week. Both tumor response and survival were somewhat better in the latter group, even though not statistically significant. Petrowich et al. (32) has published a prospective investigation in which they compared a conventional fractionation 25 × 2 Gy, 5 fr/wk in 5 weeks with a shorter model 15 × 2.8 Gy up to a total dose of 42 Gy in 3 weeks. They reported that the two schedules gave similar results concerning both local control and survival.

In the present patient material, 2 times weekly treatment was associated with longer survival. This might be due to the higher fraction dose since the TDF-value was the same in the two hypofractionation groups. Another, perhaps more probable, explanation may be the fact that treatment according to schedule 2 was given principally to 'long journey' out-patients in rather good general condition. Since the material was non-randomized, no reliable conclusions can thus be drawn from the observed association between hypofractionation and survival in the present study.

Target volume may also be a factor influencing the result of radiotherapy. In the literature it is recommended to include in the irradiation volume the primary tumor and regional lymph nodes comprising mediastinum at a 1–3 cm margin (3, 18), which inevitably leads to large treatment volumes and thus to an increase of treatment-related complications. In our study the highest survival rates were found in the group of patients for whom mediastinum was not included in the target volume which, however, may have been due to a selection of more advanced tumors in the group receiving mediastinal irradiation.

There is no definite opinion in the literature concerning the maximal tumor size for meaningful radiotherapy. However, a linear correlation has been found between tumor size and patient survival (32–35), which is in agreement with our results. Even so, local control was surprisingly good in tumors >8 cm in diameter. This may be explained by the fact that these large tumors metastasized early and the patients died before local progression could be observed.

Pleural effusion is found in about 10–24% of the lung cancer patients (27, 36). Its appearance generally signifies a bad prognosis whether the cytology is positive or negative (37–40). Our own observations supported the findings in the literature and, furthermore, we could not find any difference in survival between patients with some and abundant effusion. In many prognostic investigations, atelectasis due to the tumor has shown a slight negative association with the prognosis (40) and this was also the case in our own material. However, these results may have been confounded by the fact that atelectasis is often associated with a large central tumor.

In conclusion, our study illustrated the difficulty of reliably analysing the influence of treatment-related factors in a heterogenous retrospective material. The study confirmed the generally poor outcome of patients treated with radiotherapy for NSCLC. The study also confirmed that large tumor, central site and pleural effusion are negative factors concerning length of survival.

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