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Five-Year Results by Intensive High Voltage Therapy of Inoperable Bronchial Carcinoma

HANS-JÜRGEN EICHHORN

Central Institute of Cancer Research of the Academy of Sciences of the GDR, Department of Experimental and Clinical Radiotherapy, Lindenberger Weg 80, 1115 *Berlin-Buch, German Democratic Republic*

Abstract—*The influence of intensive radiotherapy on cure and survival rates in the case of inoperable bronchial carcinoma is investigated in* 1046 *cases with histologically confirmed tumours limited to one thorax side. Thirty-seven per cent* 1-yr, *and* 2.5% 5-yr *cures were achieved by telecobalt therapy with* >50 Gy (5000 rad) *tumour-dose. For highly differentiated carcinomas we obtained* 6.5% *and for small-cell carcinomas* 2.5% 5-yr *survival rates. The increase in survival rates as compared with our control group of untreated but prognostically more favourable cases* (105 *thoractomized patients*) *as well as with our patients treated with* 200 kV *therapy can be regarded as convincing* (*double the rate of* 1-yr *and more than three times of* 2-yr *survival*). *Nevertheless, the total result for more than half of the cases is so unfavourable that trials with systemic therapy, though of an invasive kind, must be regarded as justified. Up to this time chemotherapy does not influence the survival times* (*with the exception of small-cell tumour types*). *Therefore randomized trials with highly dosed, prophylactic irradiation of the whole body* [2 × 8 Gy (800 rad) *midline-dose*] *are recommended. My own experiences with this method confirm the unexpectedly high subjective tolerance.*

INTRODUCTION

IN ALL highly civilized countries lung cancer is the first or second in frequency among malignant tumours. For the GDR, which already decades ago laid down by law that every case of cancer has to be registered in a national cancer registry, it can be shown that the number of people who fall ill each year with lung cancer is 4–5 times higher than the total number of adults and children falling ill with any form of leukemia or lymphogranulomatosis [1]. It seems necessary to continually point out these social hygienic proportions, because at present the emphasis in therapy as well as the efforts in clinical research contrast with these facts.

As surgical tumour removal is possible in only 15% of all cases [2], radiotherapy should play an important role in the treatment of lung cancer. However, only 20–25% of all diagnosed inoperable cases of bronchial carcinoma are actually referred to the radiotherapist [2, 3]. Apart from capacity problems of our radiotherapy departments, this is due to the sceptical attitude among physicians towards the palliative and curative effect of radiotherapy when applied to this type of tumour. The effect of this therapy on life prolongation and cure has also been repeatedly discussed in international literature. Since 1950 we have contributed to this interpretation by a number of prospective studies, the results of which are summed up in the present paper [4–6].

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MATERIALS AND METHODS

Selection of patients

Since 1950 the patients for intensive radiotherapy have invariably been selected according to the following criteria:

(1) The tumour has been proved histologically (cytological proof is insufficient).
(2) The tumour is radiologically and clinically limited to one side of the thorax (including mediastinum and supraclavicular fossa). Involvement of thorax wall, paresis

of the diaphragm and/or of the N. recurrens are admissible.

(3) There is no large pleural effusion with tumour cells. (A small effusion without tumour cells is admissible.)

(4) Metastases distant from the primary tumour cannot be established clinically (by physical examination only) or radiologically (skeletal radiographs if indicated by pain, no prophylactic radiographs, cerebral or skeletal scintigrams).

(5) The operation was considered impossible because of the local extension of the tumour or a medical contraindication, or it was refused by the patient.

Based on these criteria we admitted patients for an intensive 200 kV therapy between 1950 and midyear 1958, and since then for an intensive telecobalt therapy. The large majority of these cases had locally far advanced tumours. A distinctly smaller proportion consisted of those locally limited cases which were inoperable due to age or condition of their heart or cardiovascular system. The number of those patients who were operable but refused an operation was negligible. A subdivision of these groups was not made because the criteria of differentiation (E.C.G., functional tests of the respiratory and the cardiovascular system, mediastinoscopy) had not been employed in a uniform manner, so that the final decision was often based on the subjective judgement of the surgeon.

The composition of the total group of our patients was analysed twice with regard to the various prognostically relevant histological tumour types. For the years 1950 until 1960 inclusive and 1958 until 1974 inclusive, almost identical distributions were observed. In addition, the average age was the same for the two periods (62 and 63 yr, respectively). In view of the fact that there are constant parameters for identical criteria of selection, which coincides with the observation made in our daily work, we can draw the conclusion that the composition of our group of intensively irradiated patients has not changed since 1950 (Table 1).

Table 1. Comparison of histological tumour types during two (overlapping) periods

Tumour type (histological)	1950–1960*	1958–1974†
Squamous cell carcinoma	49	55
Adenocarcinoma	2	3
Small-(oat) cell carcinoma	25	23
Other types	24	19

*Values given are percentages of 288 patients treated with 200 kV and Co-60.

†Values given are percentages of 1046 patients treated with Co-60 only.

The composition of patients regarding the histological tumour types (as the most important prognosis factor) did not change.

Methods

The following irradiation techniques were employed successively as elaborated (no selection of patients) [4, 6]. (1) Two parallel opposing fixed fields. (2) A fixed field in front and an oblique fixed field with wedge filter at the back. (3) Wedge-filter pendulum irradiation (Fig. 1). Up to 1965 use was made predominantly of the fixed field techniques, after that time almost exclusively of wedge-filter pendulum irradiation. We intended the tumour dose (80% isodose enclosing the tumour area) to amount to 55 Gy (5500 rad) for telecobalt therapy and to 40 Gy (4000 rad) for 200 kV therapy, respectively. In every case the mediastinum outside the tumour region (from jugulum to diaphragm) was irradiated with 25 Gy (2500 rad). The supraclavicular fossa was irradiated only if nodes were palpable with the full tumour dose. Most patients ($\simeq$75%) were treated five times weekly with 1.8–2.5 Gy (180–250 rad), 130 patients received 5.0 Gy (500 rad) every 5th day and 120 patients started with grid-therapy (see below).

Out of our total material of symptomatically, palliatively and intensively irradiated cases, 123 patients tolerated a minimum tumour dose of 35 Gy (3500 rad) during the 200 kV area (1950–1958); later on (1958–1974) a further 1046 patients received a minimum tumour dose of 50 Gy (5000 rad) given

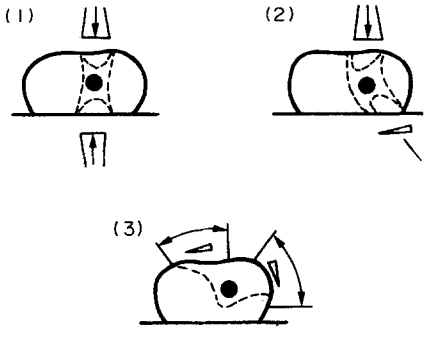

Fig. 1. The three methods of irradiation used during 24 yr one after another.

with telecobalt therapy. The former group was included in this paper *in toto* for comparison of survival rates, the latter group represents our analyzed material. A certain number of other patients did not receive the primarily intended intensive tumour-dose; mostly due to distant metastases appearing during the course of treatment, exceptionally because of refusal by the patient (they are not included in this material). However, the size of that group was tested regarding the years 1965, 1970 and 1974. Out of 210 patients scheduled for intensive therapy during these three years, irradiation was cut short in 18 cases (9%). On the other hand we have 120 cases (11%) within our 1046 full-dose patients, which were primarily started mostly because of the tumour-size with palliative intention only [200 kV-grid-therapy, twice within 3 days, 10 Gy (1000 rad) total tumour dose]. But approximately 3–6 weeks later it was possible to increase the total dose to 55 Gy (5500 rad) with a second series of 5 × weekly irradiations and they are therefore included in this material. Consequently the numbers of patients overestimated and underestimated regarding full irradiability before starting treatment are equal (10%).

A special analysis was made of four subgroups with possibly special prognosis:

Subgroup I comprised all women (only 77 cases equalling 8% of the total number of patients). Their average age (62 yr) was identical with that of the total group. Apart from a lower proportion of squamous cell carcinoma (35%) and a higher proportion of adenocarcinoma (11.6%) the subgroup showed a very similar composition to that of the total group.

Subgroup II consisted of those patients who had been irradiated as planned, that is, of all those cases, regardless of the histological type, who had received their full dose without a delay which might have become necessary because of fever, a marked deterioration of their general condition, etc. The number of these cases was 438 (42% of the total number of patients.

Subgroup III consisted of all cases of fully differentiated squamous cell carcinoma (with and without ceratinisation), who received their full dose within 42 days. These were 153 cases (14.3% of the total number of patients). Their average age was 63 yr.

Subgroup IV comprised all purely small-cell or oat-cell carcinomas representing 240 cases (23% of the total number of patients), whose average age was 59.7 yr.

RESULTS

The analysis of the survival rates is presented in Tables 2–4, showing the total result for the 200 kV-period and that for the patients treated with telecobalt therapy in the subsequent period up to 1974 (Table 2).

Table 2. Comparison of survival rates for 200 kV- *and* Co-60-*irradiation*

No. of patients irradiated	Survivors (%) 1	2	3	5 yr
200 kv (1950–1958) 123	22	3.5	1	0
Co-60 (1958–1974) 1046	37	10.6	5	2.5

The strongly increased survival rates for 1–3 yr (2–3 times) by the advent of high-voltage therapy are demonstrated.

Furthermore, the survival rates for the subgroups are given (Table 3); 19–43% of the patients survived for 1 yr, 4–9% for 3 yr and 2.5–6.5% for 5 yr. For the prognostically most unfavourable group, that of small-cell carcinomas, the mean survival time was 10.55 months, 6 of 240 patients living longer than 5 yr following treatment. Altogether, 28 patients or 2.5% (25 men, 3 women, average age 63.5 yr) survived by at least 5 yr.

Table 3. Survival rates of special groups, Co-60-*irradiation*

Special group (No. of patients irradiated)	Survivors (%) 1	2	3	5 yr
I All female patients (77)	34	10.3	5.1	3.8
II 'In time' (438)	39	14	7.5	4.5
III Fully differentiated (153)	43	15	9	6.5
IV Small-(oat cell (240)	19	6	4	2.5

Analysis made for patients with possibly different prognosis. No different results with women (I). Best results, as expected, with highly differentiated tumours (III). Irradiation without unprovided interruption gave better survival rates than in the total material (II). 2.5% 5-yr survivors with small-cell tumours seem to be remarkable (IV).

Autopsy was performed on 17 of the 24 patients who had died meanwhile after more than 5 yr. Autopsy revealed that 6 of them still

had tumours (after 5–7 yr), two in the form of local recidivation, four in the form of distant metastases. For the remaining 11 patients, cardiac insufficiency or pneumonia was given as cause of their death without a clear or direct relation to the previous treatment.

DISCUSSION

The most important question is whether, and to what extent, prolongation of lifespan or permanent cure can be achieved in lung cancer by radiotherapy. A general answer cannot be given because all reports are based on patient groups selected by different methods. Our 1046 cases can be regarded as representative for patients having regionally enlarged tumours, clinically–but not really–free from distant metastases. We compared with a control group consisting of patients without specific tumour treatment, namely, 105 patients who had been thoracotomised in our hospital, but were not resectable (deducting those who died postoperatively in the hospital. Prognostically, this control group can be regarded as a more favourable selection (certainly not as a less favourable one) because the patients were originally considered to be operable, their average age was 57.7 yr and the proportion of small-cell tumours was lower (15%) [4]. Nevertheless, the survival rate of the primarily inoperable but irradiated patients was three times as high after 1 yr and five times as high after 2 yr (Table 4).

Table 4 shows another untreated control group of an American randomized trial on 200 kV-irradiation [7]. The selection of patients was based on roughly the same criteria as we had used, and gave the same distribution of the histological tumour types. The survival rates obtained for the untreated control group and the 200 kV-therapy group of that trial resembled our results, thus confirming our findings with regard to the prolongation of survival times by radiotherapy.

Table 4. Survival rates of control groups

Control group (No. of patients)	Survivors (%) 1	2	3	5 yr
Thoracotomy only[4] (105)	13	2	0	0
Placebo[7] (246)	16	—	—	—
200 kV[7] (308)	22	0		

Control groups without therapy and with 200 kV therapy correspond to our results (see Table 2).

The 1- and 5-yr survival rates obtained by Schumacher [8] were even higher. His extensive pre-examination program, however, suggests that his selection criteria were rigid. For special groups, such as persons who refused an operation and for thoracotomised patients, the 5-yr results after radiotherapy given in the literature [5, 9, 10] range from 8.7 to 22%.

These and many other reports in the literature on curative results [5] do not agree with an investigation carried out in Oxford [11, 12], which was based on a random distribution of 148 patients into three groups for high-voltage therapy, for monochemotherapy and for multichemotherapy. With 1-yr survival rates of 12–20% and a mean survival time of 4 months, there was no difference between the three ways of treatment. The low mean survival time and the high proportion of pretherapeutically established distant metastases indicate that these patients represented advanced generalised cases. Hence, an effect of local radiation treatment on survival time could not be expected. Furthermore, no effect was achieved by means of systemic chemotherapy. Compared with our patients the 48 irradiated cases of this trial represent a negative selection. They cannot, however, be regarded as representative for most cases of bronchial carcinoma.

Tables 2 and 3 clearly demonstrate the gain on survival time obtained in patients with inoperable lung cancer by supervolt-therapy. The 2- and 3-yr rates increase three times and but now we got 5-yr survivors. This gain comparing to 200 kV-therapy is based on the much better dose distribution and therefore a higher applicable tumour-dose and smaller volume-dose. We also consider it remarkable that 6 cases of small-cell carcinoma (2.5%) survived more than 5 yr and that the average survival time is 10.5 months in all patients of this tumour type.

Our 28 patients who lived longer than 5 yr differed from the total number of cases by a little higher proportion of fully differentiated tumours (16 = 57% squamous cell carcinoma, 1 = 3.5% adenocarcinoma, 6 = 25% small-cell carcinoma, 5 = 14% others), whereas their average age of 63.5 yr did not differ from that of the total group of patients. For 7 of these patients an operation was not possible because they refused and for 9 patients because of cardiovascular insufficiency. (No mention is made whether there were also local contraindications.) The volume of their tumours was examined by means of X-ray photography as we had done this for a sample of

223 autopsy patients of our total material [6]. The average tumour volume (154 cm^3) of these 16 out of 28 5-yr survivors (not having a contraindication to operation by local tumour spread) was 24% smaller than of the total group checked (223 patients). That means our permanently cured patients were distinguished by a little smaller but not by very small tumours.

For 58% of the total number of patients only the low 5-yr survival rate of <2.5% was achieved. It must be assumed that there were subclinical metastases distant from the primary tumour when therapy was started. Therefore, the combination with systemic therapy, including invasive treatment, appears to be necessary. In this connection reference should be made to the—already half forgotten—large randomized trial carried out by Brunner [13] with prophylactic monochemotherapy after radical operation, which led to significantly worse results for the group under treatment. The two new randomized trials at Oxford [11, 12] with mono- and multichemotherapy of advanced inoperable tumours in comparison with no therapy or local irradiation seems to have led to better results for the untreated group. A number of treatments combining local irradiation with various anti-tumour drugs did not result in a prolongation of life [5], which is accounted for by a suppression of immunity resistance. Only for small-cell (and possibly other very undifferentiated) tumour types a combination of radio-and chemotherapy seems to be promising [14, 15]. Further records are expected in this field. A method which is still largely unknown and not yet tested as a prophylactic therapy is the highly dosed irradiation of the whole body (800 rad for each half of the body, with a 6 weeks interval) which in Toronto has been applied to clinically generalized tumours with great success for years [16]. For radiobiological reasons we consider total body irradiation as promising in the case of subclinical micrometastases. In view of economic considerations and because of only small subjective side-effects and low strain on the patients we regard this method as particularly suitable when used for a systemic treatment of inoperable bronchial carcinoma. For 6 months we have now been irradiating more than 30 patients in this way and we have satisfied ourselves as to the excellent tolerance. Serious cases of bone marrow complications (leucocyte values under 1600, thrombocyte values under 50,000) have not yet occurred. A randomized trial for comparison with multichemotherapy on small-cell carcinoma is being prepared.

Finally, it should be mentioned that in a sample of 223 autopsies from our cases neither a local tumour-rest nor distant metastases could be detected in 27 patients (16.5%). From this we draw the conclusion that more efficient local treatment (e.g., by neutron therapy) could also improve somewhat the rate of permanent 5-yr survivors.

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