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AUTOPSY FINDINGS IN LUNG CANCER TREATED WITH MEGAVOLTAGE RADIOTHERAPY

by

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The many advantages of megavoltage therapy have led to its increasing use during the last decade in radiotherapy of inoperable pulmonary carcinoma. The clinical experience obtained so far has not been very favourable, however. For instance, GUTTMANN (1958) achieved a one-year survival rate of 33 per cent and a two-year survival rate of 9 per cent. Many other authors (HAAS et coll. 1957, KUTZ 1958, COCCHI 1961, 1964, BELING & EINHORN 1965, HOLSTI 1965, 1967a, DEELEY 1967) have presented survival rates in roughly the same range. GUTTMANN (1964) reported slightly better results with megavoltage therapy after exploratory thoracotomy although WATSON (1956) was considerably more pessimistic.

There are fairly few studies of the effects of megavoltage therapy on carcinoma of the lung based on autopsy materials. Five of WATSON'S (1956) cases were examined post mortem, and all of them had residual primary malignancy. GUTTMANN (1958) established three complete local cures (16 per cent) in an autopsy material of 19 cases. Four cures were claimed by HAAS et coll. (1957) following autopsies performed in seven cases. BELING & EINHORN (1965) stated that autopsy revealed malignant tissue at the primary site in 48 of their 50 cases.

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The purpose of the present study was to establish from an autopsy material whether megavoltage therapy in the conventional dosage is capable of destroying primary lung carcinoma. In addition, special attention was paid to the cause of death in such cases.

Material and Methods. The material comprised 67 histologically verified cases of inoperable carcinoma of the lung treated during the period 1963—1967 by megavoltage therapy and examined by autopsy 2 months to 4 years and 1 month (average 9 months) later. A total of about 1 400 cases of pulmonary carcinoma were treated at the clinic during the period. The histologic type was verified prior to treatment by biopsy in connection with bronchoscopy, tumour puncture, mediastinoscopy, scalenus biopsy or thoracotomy. Together with roentgenography these methods were used also to determine the size and localization of the growth.

Eight cases had metastases in the lymph nodes of the supraclavicular fossa or the neck, eighteen in the mediastinum, and three elsewhere (brain, liver) at the beginning of therapy. Of those treated, forty-five were regarded as inoperable because of the size, central site, or metastases and five on account of the general condition (poor respiratory function, other lung conditions, cardiac disease). Nine cases were considered to be inoperable after exploratory thoracotomy, and in eight cases partial resection of the tumour was performed.

Forty-six cases were treated with 33 MeV photons and twenty-one with a 3 000 curie ^{60}Co unit. The commonest field size was 6 to 10 cm$\times$10 to 12 cm. Mostly, 2 fields were used in photon therapy and 3 or 4 fields in ^{60}Co therapy.

The tumour dosage ranged from 4 000 to 7 000 rad over 5 to 10 weeks but was usually 4 500 to 5 500 rad over 5 to 8 weeks. Individual treatment planning was the rule, the aim in all treatments being to achieve a homogeneous dose distribution in the treatment volume. Thirty-eight cases were treated with split-course therapy (Holsti 1966, 1967b) and twenty-nine cases continuously. The total tumour dose in the former was roughly 10 per cent higher than in the continuous treatment (Holsti 1967b). The treatment was repeatedly interrupted because of e.g. poor general condition, pyrexia, inflammation and anemia in seven cases; complicating factors in three cases prolonged the treatment time to between 114 and 133 days. Therapy had to be discontinued in seven cases at 2 000 to 3 000 rad on account of the general condition. Sixty cases received the planned therapeutic dose.

The whole material of 67 cases was histologically distributed as follows: squamous cell carcinoma in 29, anaplastic carcinoma in 16, small cell carcinoma in 17, unclassified carcinoma in 3, and adenocarcinoma in 2 cases.

The mean survival time in the series was nine months. Forty-four of the total series died of carcinoma or metastases, and twenty-three from other causes (nine

Table 1

No carcinoma tissue at primary tumour site

Type of tumour	Split-course	Continuous	Total
Squamous cell carcinoma	6	1	7
Anaplastic carcinoma	2	—	2
Small cell carcinoma	4	2	6
Unclassified carcinoma	1	1	2
Adenocarcinoma	1	—	1
Total	14	4	18

Table 2

Islets of carcinoma cells in the fibrotic area at the site of the primary tumour

Type of tumour	Split-course	Continuous	Total
Squamous cell carcinoma	1	3	4
Anaplastic carcinoma	1	4	5
Small cell carcinoma	2	3	5
Unclassified carcinoma	—	—	—
Adenocarcinoma	—	—	—
Total	4	10	14

from pneumonia, eight from cardiac failure and four from a pulmonary embolus; one patient committed suicide and one died in an accident).

Results

The findings have been divided into four groups according to the type of primary growth at autopsy: (1) no carcinomatous tissue evident, (2) no definite malignancy macroscopically, but microscopically fibrosis with obvious islets of carcinoma cells, (3) necrotic areas with malignant infiltration, and (4) viable malignant tissue in the treatment area.

1. *No carcinomatous tissue.* Eighteen cases of the total series (18/60=30 per cent) had no carcinomatous tissue in the treatment area either macro- or microscopically. The distribution of the cases in this group by the histologic appearances appears in Table 1.

Partial resection of the growth was performed in six and exploratory thoracotomy in two of these eighteen cases. The tumour size in this group prior to

Table 3

Necrotic area with carcinomatous tissue (brackets = treatment not completed)

Type of tumour	Split-course	Continuous	Total
Squamous cell carcinoma	3	2 (1)	5
Anaplastic carcinoma	1	2 (1)	3
Small cell carcinoma	1 (1)	—	1
Unclassified carcinoma	—	—	—
Adenocarcinoma	—	—	—
Total	5	4	9

Table 4

Viable tumour tissue in the treatment area (brackets = treatment not completed)

Type of tumour	Split-course	Continuous	Total
Squamous cell carcinoma	7	6 (2)	13
Anaplastic carcinoma	3	3 (1)	6
Small cell carcinoma	3	2 (1)	5
Unclassified carcinoma	1	—	1
Adenocarcinoma	1	—	1
Total	15	11	26

treatment was 3 to 8 cm in diameter, usually 4 to 7 cm; the tumour dose was 4 800 to 6 250 rad. Fourteen (78 per cent) cases of this group were treated by the split-course method and four received the entire course of irradiation as continuous therapy. No cytostatics were used. The pre-planned treatment scheme was fulfilled in all the cases and there were no complications. The condition of these eighteen cases appeared to be distinctly improved at the roentgenologic control performed after the termination of therapy. Eight patients died from distant metastases, and ten of some other cause, such as pneumonia, cardiac failure or pulmonary embolus.

2. *Fibrosis with islets of carcinoma cells.* The fourteen (14/60=23 per cent) cases in this group are recorded histologically in Table 2.

Partial resection of the tumour was performed in one and exploratory thoracotomy in another of these cases. The growth was 4 to 8 cm in diameter and the dosage 4 700 to 7 000 rad. Cytostatics were also administered in three cases. Four of the cases were treated by the split-course method and ten received continuous irradiation. The treatment was completed according to the therapeutic

Table 5

Localization of the metastases established at autopsy of 56 cases

Lymph nodes (including mediastinal and paratracheal lymph nodes)	34
Liver	30
Adrenals	27
Brain	22
Kidneys	20
Pancreas	19
Skeleton	16
Lungs	14
Abdominal cavity	9
Thyroid gland	7
Other	18

scheme in twelve cases, and in the other two was interrupted because of complications (fever, anemia, etc). The condition in twelve cases was improved roentgenologically at the end of therapy, while in two cases no change was observed. The cause of death was distant metastases in eleven cases and other conditions in three cases.

3. *Necrotic areas containing carcinomatous tissue.* The group comprised nine cases. Treatment had to be discontinued in three, leaving only six (6/60=10 per cent) cases that received the planned dosage. The distribution of the cases histologically appears in Table 3.

Three cases were subjected to exploratory thoracotomy. The average diameter of the mass in this group was 6 to 9 cm, the radiation dosage being 4 000 to 5 900 rad. In only three cases was it possible to complete the therapeutic course according to schedule. Six cases had complications (e.g. anemia, fever) necessitating interruption in the therapy. Five cases were managed by the split-course method and four cases received continuous treatment. Four cases were given cytostatics in addition to radiotherapy. Two cases were improved roentgenologically after the termination of the therapy and in the remaining seven cases there was no definite change. Seven patients died from distant metastases and two from other causes. It is possible that the treatment volume was too small in two of the cases in this group.

4. *Viable carcinoma tissue in the treatment area.* The fourth group comprised 26 cases. Treatment had to be discontinued in four of them, and thus viable carcinomatous tissue was demonstrable both macroscopically and microscopically in the treatment area in 22/60 cases, i.e. 37 per cent of those that received roughly the planned dosage. The histologic distribution is given in Table 4.

Table 6

Correlation between autopsy findings and radiation dose

	> 4 000 rad	> 5 000 rad	> 6 000 rad	Total
No carcinoma	8	8	2	18
Fibrosis	3	7	4	14
Necrosis	4	2	—	6
Viable carcinoma	6	11	5	22
Total	21	28	11	60

Exploratory thoracotomy was performed in three cases and partial resection of the tumour in one case; the growth was 6 to 9 cm in diameter and the dosage 4 000 to 6 000 rad. The split-course technique was employed in fifteen cases and continuous radiotherapy in eleven cases. The therapy was completed according to schedule in only thirteen cases, and in the other thirteen complications (anemia, fever, etc) interfered and in three of the latter cases prolonged the treatment time to 114—133 days.

Roentgenography at the termination of the primary treatment indicated improvement in seventeen and no obvious change in nine cases. A recurrence was observed roentgenologically in four cases 3 to 6 months after the primary therapy. The treatment fields may have been too small or the tumour may not have been precisely localized in these cases. One of the cases was treated with cobalt 60 therapy with the breathing of pure oxygen 20 minutes prior to therapy and during it. The fractionation was 600 rad twice a week, total dosage 4 700 rad/54 days (split-course technique).

Nineteen of the patients in this group died of the primary disease or distant metastases. Seven patients died from other causes.

Metastases were demonstrated in fifty-six cases of the total autopsy material; the locations appear in Table 5. The ratio between the autopsy finding and the radiation dose is given in Table 6.

Discussion

The prognosis of inoperable carcinoma of the lung treated with radiotherapy is generally considered to be poor (e.g. GUTTMANN 1955, 1958, 1961, HAAS et coll. 1957, KUTZ 1958, COCCHI 1961, 1964, BELING & EINHORN 1965, HOLSTI 1965, 1967a). Some authors are completely pessimistic about the treatment (WATSON 1956). Almost invariably, the starting point for radiotherapy is unfavourable. The tumour is often of considerable size, as well as infiltrating, and thus inoperable. The subjects are frequently elderly, in poor condition and anemic,

Table 7

Autopsy findings and histologic features in the split-course group

	Squamous cell carcinoma	Anaplastic carcinoma	Small cell carcinoma	Unclassified carcinoma	Adenocarcinoma	Total
No carcinoma tissue	6	2	4	1	1	14
Fibrosis + carcinoma	1	1	2	—	—	4
Necrosis + carcinoma	3	1	1	—	—	5
Viable carcinoma tissue	7	3	3	1	1	15
Metastases	12/(17)	5/(7)	10/(10)	1/(2)	1/(2)	29/(38)

Table 8

Autopsy findings and histologic features in the continuous therapy group

	Squamous cell carcinoma	Anaplastic carcinoma	Small cell carcinoma	Unclassified carcinoma	Adenocarcinoma	Total
No carcinoma tissue	1	—	2	1	—	4
Fibrosis + carcinoma	3	4	3	—	—	10
Necrosis + carcinoma	2	2	—	—	—	4
Viable carcinoma tissue	6	3	2	—	—	11
Metastases	11/(12)	8/(9)	7/(7)	1/(1)	—	27/(29)

with infection as a prominent feature. In addition, metastases are often already present. However, in the present material, which was of a wholly random character, the carcinoma had actually disappeared microscopically in eighteen (30 per cent) of the cases that received the full planned therapy of at least 4 800 rad. There were no complicating factors in these cases. Fourteen (78 per cent) of these cases were treated by the split-course technique, which suggests that the method has definite advantages. Bearing in mind that there was no true random selection of cases for split-course or continuous therapy in this series, comparison of the two methods (Tables 7 and 8) indicate that the primary tumour disappeared completely in 37 per cent of the cases treated by the former and in only 14 per cent of those treated by the latter method.

Both macroscopic and microscopic regression frequently occurs during the interval of the split-course therapy (Holsti 1967c), which may contribute to the good end-result. Metastases were encountered in 76 per cent of the cases treated by the split-course technique and in 93 per cent of those given continuous therapy.

The distribution of the metastases in the total material concurred on the

whole with that reported by ROSENBLATT & LISA (1956). All the cases with complete loss of malignant tissue had received over 4 800 rad. Fourteen cases (23 per cent) had islets of carcinoma cells in the fibrotic areas. Recurrence might well arise from such residual foci, as has been stressed in radiobiologic studies based on cell survival observations (FOWLER 1966). In those groups in which viable carcinomatous tissue, or necrotic areas with islets of malignancy, were found at autopsy in the therapeutic area, over half the number of cases (67 per cent in group 3, 50 per cent in group 4) had complications during therapy. This prevented the realisation of the radiotherapeutic plan and thus impaired the end-results.

The treatment had to be interrupted in seven cases by the time the patients had received 2 000 to 3 000 rad. All still showed evidence of malignancy, in three of the cases in addition to necrotic tissue. The dose administered had obviously been incapable of destroying the tumour tissue. Prolongation of the treatment time on account of protracted or recurrent complications, such as pyrexia or anemia, considerably hinders the chances of recovery.

However, it was only in a few rare cases in which the therapeutic programme could be completed without noteworthy complicating factors (at a dosage of 4 000 to 6 000 rad) that viable carcinomatous tissue was demonstrated. Only the individual radiosensitivity of the tumour can properly account for this, an important factor being the anoxic cells. THOMLINSON & GRAY (1955), in pulmonary carcinoma in human subjects, regularly observed small necrotic anoxic areas more than 180 μ from the nearest capillary. The proportion of anoxic cells in tumours is extremely important in relation to the radiation dosage needed for radical treatment and can make all the difference between success and failure (FOWLER et coll. 1963). Viewed against this background, it is perhaps not always most purposeful to aim at homogeneous 'dose distribution' in radiation therapy. Anoxic areas need larger doses than well oxygenated areas. The roentgenologic appearances were improved in 18/18 cases in group 1, in 12/14 cases in group 2, in 2/9 cases in group 3 and in 17/26 cases in group 4. These observations suggest that roentgenologic evidence of decrease or disappearance of the growth is an indication that local control of tumour is possible.

Obviously, the smaller the tumour, the greater are the chances of success. This is borne out too by the fact that the fully healed cases included six that had been subjected to palliative surgery. But even if the tumour is destroyed completely, latent or subsequent metastases may impair the end-result so that the final clinical results deteriorate as the patient succumbs to the metastases. In any event it would appear that it is possible under favourable conditions to destroy the primary focus of pulmonary carcinoma by megavoltage therapy at a dosage of 4 800 to 6 000 rad.

In summary, two-thirds of the patients in the present material died of the primary growth or metastases. In eighteen cases, i.e. 30 per cent, the tumour was sterilized by radiotherapy and the patients died from other diseases, though eight of these even had distant metastases. The study confirms the view that the greatest problem in the treatment of carcinoma of the lung is its readiness to form metastases. The individual radiosensitivity of the tumours (e.g. the number of anoxic cells) obviously also play an important role.

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SUMMARY

The autopsy findings in 67 cases of inoperable carcinoma of the lung treated with megavoltage therapy were analysed to determine whether the primary tumour had been destroyed. Seventy-eight per cent of the cases of complete cure had been treated by the split-course technique. Forty-four of the total of 67 patients, i.e. 66 per cent, died from the original condition or metastases and twenty-three (34 per cent) from other causes.

ZUSAMMENFASSUNG

Die Autopsiebefunde in 67 Fällen von nicht operierbaren Lungenkarzinomen wurden analysiert, um festzustellen ob der Primärtumor vollständig durch die Megavolt-Röntgenbestrahlung zerstört wurde. In 78 % der Fälle, die mit unterbrochener Serienbestrahlung behandelt wurden, konnte eine vollständige Heilung erreicht werden. Primärtumore oder Metastasen verursachten den Tod in 66 % (44 Patienten) während 34 % (23 Patienten) infolge anderer Ursachen starben.

RÉSUMÉ

Les auteurs ont étudié les résultats d'autopsie de 67 cas de cancer du poumon inopérable, traités par radiothérapie à méga-voltage pour savoir si la tumeur primitive avait été détruite. Soixante-dix-huit pour cent des cas de guérison complète avaient été traités par la technique de fractionnement du traitement (split-course). Quarante-quatre des malades sur un total de 67, c'est-à-dire 66 pour cent, sont morts du cancer primitif ou de métastases et 23 (34 pour cent) sont morts d'autres affections.

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