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## Failures of radical radiotherapy in patients with non-small cell lung cancer

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*Introduction.* Lung cancer is the most frequent malignant neoplasm in man. In Poland the morbidity indicators for lung cancer are larger than the world average. The yearly increase of this factor in men in Poland is twice that in any other European country. The basic method of treatment of non-small cell lung cancer is surgery, however, under Polish conditions, only about 15% of patients qualify for it. Therefore, still a large group of patients become potential candidates for radiotherapy. In the early period, radiotherapy had mainly a palliative character. The possibilities of radical treatment emerged in the fifties, together with the application of megavoltage apparatus. However, five-year survivals do not surpass the level of 6–10%. Therefore, analyses of the results of radical radiotherapy are carried out in order to find the reasons of its failures, as this implies the direction of search for improving the efficiency of the therapy.

*The aim of the study.* The aim of the study was to assess the failures of radical radiotherapy in patients with non-operable, non-small cell lung cancer. The results obtained will be the basis for revision and rationalisation of the present indications to radical radiotherapy in patients with non-small cell lung cancer.

*Material.* Between January 1, 1990, and December 31, 1995, 2330 patients with non-small cell lung cancer attended the Out-patient Clinic of the The Maria Skłodowska Curie Memorial Cancer Center in Warsaw. Basing on the results of clinical examination and additional analyses, 260 patients qualified for radical radiotherapy (31 women (12%) and 229 men (88%)). In a majority of cases the stage of the disease was advanced: stage IIIA was found in 114 patients (44%), and stage IIIB in 73 patients (28%).

*Methods.* The survival time and the time to local progression were the basis for the analysis. The survival probability was calculated with the Kaplan-Meier method. As a failure of treatment the first information on progression, local or distant, was assumed. The frequency of failure in the first and the second year of observation was compared. To this end, the McNemar test for related observations was used.

*Results.* Survival probability at two years was  $32 \pm 2\%$  and at five years  $10\% \pm 2\%$ . Two-year local control was observed in  $16\% \pm 2\%$  and five-year in  $6 \pm 2\%$  of cases.

In the two-year observation local recurrence was the more frequently observed failure ( $p=0.002$ ) (113 cases), than the distant metastases (47 cases).

*Conclusions.* 1. Loco-regional failure of cancer control is the main failure of treatment in radical radiotherapy of patients with non-operable, non-small-cell lung cancer. 2. The majority of failures emerges in the first two years of observation. More frequently this is local recurrence ( $p=0.002$ ). 3. Radical radiotherapy with total doses of 60–70 Gy in patients with non-operable, non-small-cell lung cancer allows to obtain two-year survivals in  $33 \pm 2\%$  of cases, and two-year survivals without symptoms of the disease in  $16 \pm 2\%$  of cases.

### Analiza niepowodzeń radykalnej radioterapii u chorych na niedrobnokomórkowego raka płuca

*Wstęp.* Rak płuca jest najczęstszym nowotworem złośliwym u człowieka. W Polsce wskaźniki zachorowalności na raka płuca kształtują się powyżej średniej światowej. Roczne tempo wzrostu współczynnika umieralności na raka płuca u mężczyzn w Polsce jest w ostatnim dwudziestolecu dwukrotnie szybsze niż w jakimkolwiek innym kraju Europy. Podstawową metodą leczenia niedrobnokomórkowego raka płuca jest zabieg chirurgiczny, jednak w warunkach polskich może być do niego zakwalifikowanych tylko około 15% chorych. Z tych przyczyn ciągle duża grupa chorych staje się potencjalnymi kandydatami do ra-

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dioterapii. W początkowym okresie miała ona głównie charakter paliatywny. Możliwości leczenia radykalnego pojawiły się w latach 50. wraz z zastosowaniem aparatów megawoltowych. Przeżycia pięcioletnie nie przekraczają jednak 6–10%. W takiej sytuacji prowadzone są analizy wyników radykalnej radioterapii celem ustalenia jej niepowodzeń, ponieważ implikuje to kierunek poszukiwań zwiększania skuteczności terapii.

**Cel pracy.** Celem pracy była ocena niepowodzeń radykalnej radioterapii u chorych na nieoperacyjnego, niedrobnokomórkowego raka płuca. Uzyskane wyniki będą podstawą do zrewidowania i zrjonalizowania dotychczasowych wskazań do radykalnej radioterapii u chorych na niedrobnokomórkowego raka płuca.

**Materiał.** W okresie od 1 stycznia 1990 r. do 31 grudnia 1995 r. do Ambulatorium Centrum Onkologii-Instytutu na Ursynowie zgłosiło się 2330 chorych na niedrobnokomórkowego raka płuca. Na podstawie badania klinicznego i badań dodatkowych, do radykalnego leczenia napromienianiem zakwalifikowano 260 chorych. W powyższej grupie znajdowało się 31 kobiet (12%) i 229 mężczyzn (88%). W większości przypadków stwierdzano znaczne zaawansowanie procesu nowotworowego: stopień IIIA ustalono u 114 chorych (44%), a stopień IIIB u 73 chorych (28%).

**Metody.** Podstawą do oceny niepowodzeń był czas przeżycia oraz czas przeżycia bez progresji choroby. Prawdopodobieństwo przeżycia i przeżycia wolnego od choroby obliczano metodą Kaplana-Meiera [17]. Jako niepowodzenie leczenia przyjęto pierwszą informację o progresji, lokalnej lub odległej. Porównano częstość występowania niepowodzenia leczenia w pierwszym i drugim roku obserwacji. Do tego celu użyto testu dla obserwacji powiązanych McNemar'a.

**Wyniki.** Dwuletnie przeżycie w całej grupie chorych wyniosło  $33 \pm 2$  %, a pięcioletnie  $10 \pm 2$  %. Dwuletnie przeżycie bez cech choroby wyniosło  $16 \pm 2$  %, a pięcioletnie  $6 \pm 2$  %.

W dwuletniej obserwacji częściej obserwowanym niepowodzeniem był miejscowy nawrót choroby ( $p=0,002$ ), który miał miejsce w 113 przypadkach, niż przerzuty odległe, które odnotowano w 47 przypadkach.

**Wnioski.** 1. Niewyleczenie loko-regionalne raka jest zasadniczym niepowodzeniem radykalnej radioterapii chorych na nieoperacyjnego, niedrobnokomórkowego raka płuca. 2. Większość niepowodzeń leczenia pojawia się w ciągu pierwszych dwóch lat obserwacji. Częściej ( $p=0,002$ ) jest to nawrót miejscowy. 3. Radykalna radioterapia z zastosowaniem całkowitych dawek promieniowania 60-70 Gy u chorych na nieoperacyjnego, niedrobnokomórkowego raka płuca, pozwala uzyskać dwuletnie przeżycie w  $33 \pm 2$  % przypadków, a prawdopodobieństwo dwuletniego przeżycia bez cech choroby wynosi  $16 \pm 2$  %.

**Key words:** radical radiotherapy, failure, non-small cell lung cancer

**Słowa kluczowe:** radykalna radioterapia, niepowodzenia, niedrobnokomórkowy rak płuca

## Introduction

Lung cancer is the most frequent malignant neoplasm in man. For the last 20 years it has been the most frequent malignant neoplasm in Polish men and is now it the third found in Polish women [1-3]. In the United States it holds the second place among malignant neoplasms (preceded by prostate cancer in men and breast cancer in women) [4]. The morbidity indicators for lung cancer in Poland surpass the world average [2]. In the last two decades, the yearly increase of this factor in men in Poland is twice that in any other European country [2].

One of the established methods of treatment of non-small cell lung cancer is radiotherapy. In the early period, radiotherapy had mainly a palliative character [5]. The possibilities of radical treatment emerged in the fifties, together with the application of megavoltage apparatus. However, five-year survivals do not exceed 6-10% [6-8]. Such results stem from quick local recurrences, as well as from distant metastases [9-15]. Therefore, analyses of the results of radical radiotherapy are carried out in order to find the reasons of its failures, as this implies the direction of research for improving the efficiency of the therapy.

## The aim of the study

The aim of the study was to assess the failures of radical radiotherapy in patients with non-operable, non-small

cell lung cancer. The earliest information on progression, local or distant, was considered failure of treatment. The results thus obtained constituted the basis for revision of the present indications for radical radiotherapy in patients with non-small cell lung cancer and rationalisation of the follow-up system in this group of patients.

## Material

Between January 1, 1990 and December 31, 1995, 2330 patients with non-small cell lung cancer attended the Outpatient Clinic of the Maria Skłodowska-Curie Memorial Cancer Center in Warsaw. After clinical and additional examination 260 patients qualified for radical radiotherapy. The group constituted of 31 women (11.9%) and 229 men (88.1%), aged between 24 and 79 (mean 61, median 62).

Clinical stage was assessed according to TNM classification. In the considered group there were 16 patients (6.2%) in stage I and 57 (21.9%) in stage II of the disease. In a majority of cases the neoplastic process was considerably advanced: stage III A was found in 114 patients (43.8%) and stage III B in 73 patients (28.1%).

Blood count and chemistries were analysed in all the cases. In 200 patients chest tomography was performed to assess tumour size, in 47 other patients the information on the size of the lesion was obtained during exploratory thoracotomy. In the remaining patients the tumour size was estimated from the chest X-rays. The largest transversal dimension of the tumour was between 10 mm and 90 mm (mean 54 mm, median 50 mm).

## Clinical characteristics

The overall performance status score was assessed according to Zubrod. There were 19 patients with score 0 (7.3%), 216 with score 1 (83%) and 25 with score 2 (9.6%).

Weight loss during the last six months before treatment was reported by 98 patients (37.7%). Losses between 1 kg to 20 kg (mean 2,25 kg). In 67 patients (25.8%) weight loss of at least 5 kg was observed. Of the 260 patients, in 47 (18%) exploratory thoracotomy was performed before irradiation. All these interventions were performed outside our Cancer Center. In a majority of patients surgeons performed pulmonary function tests. Sixty three patients disqualified from the surgery as they revealed the features of dyspnoea. More detailed information on the assessed group of patients had been presented in our previous paper [16].

## Method of treatment

The patients who qualified for radical irradiation treatment presented the following characteristics: good overall state, no significant dyspnoea (easily climbs two flights of stairs), no severe circulatory insufficiency resistant to treatment, weight loss not exceeding 10% during last six months, disease with local advancement, no involvement of the supraclavicular lymph nodes, no oesophagus infiltration and no infiltration of the entire wall of the myocardium, the chest wall and the spine (excluding the Pancoast tumour), no presence of neoplastic cells in the pleural or pericardial cavity liquid. The basic qualification criterion was the tumour size. Patients with the transversal dimension of the tumour not exceeding 6-7 cm were treated.

The irradiation treatment was carried out according to a uniform treatment protocol, under the supervision of the same group of physicians. The treatment was carried out in two stages. In the first stage a 44-46 Gy dose was administered to the tumour site with the neighbouring mediastinum using the AP fields. In the second stage the dose to the tumour was increased up to 64-69 Gy, with the use of oblique fields, while avoiding the spinal cord. The technique of large fields, *i.e.*, fields including the tumour and the neighbouring mediastinum region was applied to 234 patients. A 2 cm margin of normal tissue around the tumour and the involved mediastinum lymph nodes was added. The mediastinum of the normal side was surrounded by a 1 cm margin on the left in the case of the right lung tumour and a 2 cm margin on the right in the case of the tumour in the left lung. In nine cases the supraclavicular region on the side of the tumour was included, due to the tumour of lung top. In 26 patients (10%) the treatment was carried out with small fields including the tumour and the nearest lymph nodes. This was the group in which the overall state or the impaired pulmonary function created a risk of severe complications. For all the patients the total dose was calculated according to the ICRU recommendations in the middle of the AP dimension in the central radius for the AP fields and in the isocentre for the oblique fields.

Conventional irradiation, 2 Gy per day, 5 times per week was applied to 254 patients. Also 6 patients in whose cases the first stage of treatment was carried out with non-conventional fractionation were included in the analysis. This was the group initially qualified for palliative therapy. In this group after the first stage of treatment significant tumour regression was observed in the computer tomography tests and the qualification was altered from palliative to radical. The equivalent dose for the first stage of treatment was recalculated with the linear-quadratic formula.

Irradiation was carried out with the Cobalt 60 gamma beams or photon X beams with energies of 4, 9 and 15 MeV obtained in linear accelerators. In the cases where the first stage of treatment was performed with Cobalt or photons of 4 MeV, the second stage was carried out with higher energy.

## Follow-up examinations

After the treatment was completed the patients were obliged to present themselves for a follow-up examination every three months, if the clinical stage did not imply the necessity for more frequent examinations. During each examination a chest X-ray was made. Each six months an ultrasound examination of the abdominal cavity and basic blood tests were carried out. Other diagnostic tests were made according to individual requirements. In the case of absence of a patient for longer than six months, either he was called upon by telegraph, or his doctor or family were contacted.

## Statistical methods

The source for the retrospective analysis of the clinical material were the case histories. The observation was closed on December 31, 1997. For all the patients information whether they were alive, or, in case of the contrary, the date of death was established. The material comprised information on 260 patients.

The basic information for the assessment of results was the survival time and the time to local progression. Local progression was assessed from the chest X-ray. The survival time was measured from the starting date of irradiation to the date of death or the date of the last information that the patient lives. Time to local progression was measured from the starting date of irradiation to the date of finding the features of progression or, if the progression was not found, the date of the last clinical examination. Bronchoscopy for confirming the restoration was not carried out in any case. Survival probability and disease-free survival probability was calculated with The Kaplan-Meier method [17]. As the failure of treatment the first information on progression, local or distant, was assumed. The frequency of failure in the first and the second year of observation was compared. To this end, the McNemar test for combined related observations was used. Neither observation was shorter than two years. For 64 patients a detailed reason of death was not known (in the last clinical examination carried out at the Center of Oncology no features of illness were found).

## Results

The time of observation varied between 2 and 98 months, median 16 months. Two-year survival in the entire group of patients was  $33 \pm 2\%$  and five-year survival was  $10 \pm 2\%$ . Two-year survival without symptoms of the disease was  $16 \pm 2\%$ , and five-year survival was  $6 \pm 2\%$ . The results obtained are shown in Tab. I and Figs. 1 and 2. In the two-year observation the more frequently observed failure was local recurrence of the disease, present in 113 cases ( $p=0.002$ ), and distant metastases, found in 47 cases, were less frequent. In the second year of observation the symptoms of local recurrence were found in

**Tab. I. Survival probability and probability of survival without the symptoms of the disease in the analysed group of 260 patients, with a 95% confidence interval**

| Time of observation (months) | Survival probability (95% CI) | Probability of survival without the symptoms of the disease (95% CI) |
|------------------------------|-------------------------------|--|
| 12                           | 0.60 (0.540.66)               | 0.40 (0.340.46)  |
| 24                           | 0.33 (0.290.37)               | 0.16 (0.120.20)  |
| 60                           | 0.10 (0.060.14)               | 0.06 (0.020.10)  |

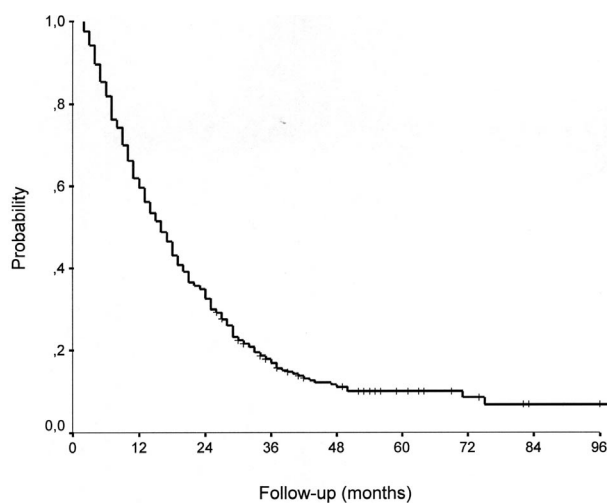


Fig. 1. Survival in the group of 260 patients with the non-small cell lung cancer, treated with the radiotherapy alone as a radical treatment

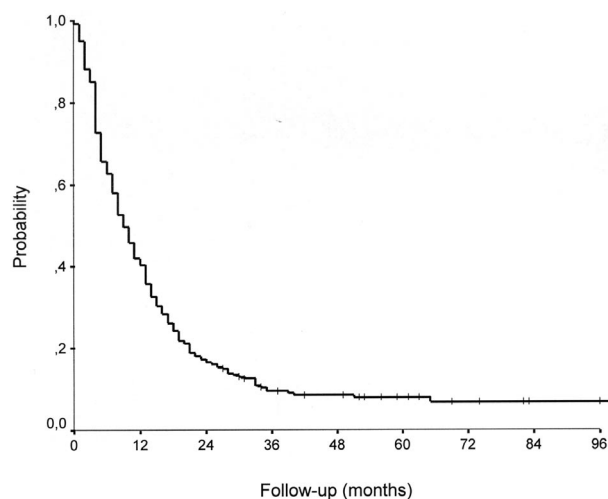


Fig. 2. Survival without progression of the disease in the group of 260 patients with the non-small cell lung cancer, treated with the radiotherapy alone as a radical treatment

84% of the patients. The probability of survival without local recurrence between the third and fifth year of observation stayed at a nearly constant level – after 36 months it was 27% and after 60 months – 24%. The probability of survival without distant metastases remained at a nearly constant level during the entire period of observation. It was 88% after six months, 78% after 12 months, 63% after 24 months, and remained constant after 36 and 60 months, equalling 59%. In the analysed material during the two-year observation in five patients local recurrence and distant metastases occurred simultaneously. These cases were assigned to the category of local recurrences. This is the “pessimistic” option for the examined material. During the entire observation the symptoms of local recurrence and distant metastases appeared in 46 patients (17.7%). In this case the time factor is not taken into consideration, hence, its interpretation is doubtful.

Among the 64 patients who had died without the symptoms of the disease, in 15 cases the cause of death was determined. In nine patients the direct cause of death was infarctus, in one – apoplectic stroke without symptoms suggesting metastases (the patient had no computed tomography and the diagnosis was established basing upon neurological examination), in two patients – car accident, in two – suicide, in one – haemorrhage from

gastric ulcer. In this group correspondence contact was established with all the families of the patients or their general practitioner doctors. In some ten to twenty cases information on the recurrence, either local or distant, was received, but without a precise date of this event. Consequently, these patients could not be included in any significant analysis.

## Discussion

In the present study an assessment of failures of radical radiotherapy applied as the sole method of treatment in 260 patients with non-operable, non-small-cell lung cancer was carried out. The analysis has a retrospective character, it therefore bears all the limitations of such a method: difficulties in a comparative analysis with other published experiments, limited credibility of information contained in the case histories due to subjectivity of interpretations, and lack of full information on the group of patients not qualified to the treatment.

In Tab. II the own results are confronted with those obtained elsewhere in patients treated with comparable methods. The analysis of these results does not lead to optimistic conclusions. Local efficiency is poor, two-year survivals reach the level of 20% [6, 10, 18], and in a vast majority of cases five-year survivals do not exceed 10%

Tab. II. Comparison of the results of radical radiotherapy of the non-small-cell lung cancer

| Author           | Number of patients | 2-year survival | 2-year local control | 5-year survival | 5-year local control |
|------------------|--------------------|-----------------|----------------------|-----------------|----------------------|
| Perez [27]       | 105                | 19.0%           | –                    | –               | –                    |
| Katz [18]        | 115                | 17.0%           | –                    | 6%              | –                    |
| Johnson [16]     | 106                | 12.5%           | –                    | 3%              | –                    |
| Durci [9]        | 81                 | 24.0%           | 28%                  | 9%              | 15%                  |
| Morton [26]      | 58                 | 16.0%           | 15%                  | 7%              | –                    |
| Hazuka [13]      | 88                 | 37.0%           | 44%                  | –               | –                    |
| Koukourakis [19] | 153                | 25.0%           | 19%                  | 13%             | 10%                  |
| Wigren [36]      | 134                | 14.8%           | –                    | –               | –                    |
| Chmielewska      | 260                | 33.0%           | 35%                  | 10%             | 23%                  |

[6-8, 18]. For a radiotherapist the results of local control after radiotherapy are frustrating, as in the majority of published papers it oscillates between slightly above ten and 30% after two years, and after five years attains merely 10-15%. The basic failure of treatment is local recurrence, observed in nearly 80% of patients. Blood-related dissemination is found in around 75% of patients [7, 9-15, 19].

The attempts to improve local control consisted of increasing the total dose, applying non-conventional fractionation methods and using combined treatment: chemo-radiotherapy. Higher percentages of local control were received with the increase of the administered total dose, conventionally fractionated [1, 10, 13, 20, 21] and non-conventionally fractionated [22-28]. A clear dose-effect relation was demonstrated by many authors. Hazuka observed higher percentages of full regression for total doses larger than 67.6 Gy ( $p=0.018$ ) [10], and Martel for doses larger than 70 Gy ( $p=0.055$ ) [29]. A similar relation between the total dose and the result of treatment was demonstrated by Soresi and Ansari, who achieved 15% and 20% of two-year survivals with conventionally fractionated doses of 50 Gy and 60 Gy, respectively, in combined treatment with cisplatin [30, 31].

Investigations on the application of non-conventional fractionation gave an improvement of overall survivals. In the studies by Brindle [26], Byhard [23] and Cox [24] the two-year survivals were between 21 and 29%. Definitely the most interesting results were published by Saunders [27]. In a group of 62 patients irradiated with the CHART technique (Continuous, Hyperfractionated, Accelerated Radiotherapy: 3 fractions of 1.5 Gy daily, with a break of 6 hours, during subsequent 12 days; total dose 54 Gy) she observed that the probability of a one-year survival equal to 64%, and that of a two-year survival equal to 34%. The results of combined treatment, and especially the concurrent radio-chemotherapy, focused the research in a new direction. Five-year observations, and longer, demonstrated a statistically significant difference of survivals in favour of the combined treatment ( $p=0.02$ ), and also a statistically significant decrease of distant metastases ( $p=0.002$ ) [7, 12, 14].

The performed analysis demonstrated that the basic reason of failure of the treatment was local recurrence of cancer, while distant metastases emerged in a considerably smaller number of the patients. Therefore the trials aimed principally at improving local results seem important. These can be carried out either in the way of further improvement of the biological value of the administered dose, or by combining radiotherapy with such cytostatics which have a radiosensitizing action or suppress the repair of post-irradiation damages in cancer cells. The following drugs belong to this group: cisplatin, docetaxel, winorelbine and gemcytabine. The results of the performed analysis seem to imply that in a selected group of patients it is advisable to increase the total irradiation doses, even to 76-80 Gy, in combination with a full repetitiveness of a three-dimensional therapy plan, providing for sparing normal anatomical structures. The authors of

many studies indicate that shortening the total irradiation time improves local control and long-term results of the treatment in a significant way [32-34].

The unsatisfactory results of treatment of patients with non-small cell lung cancer remain a constant challenge to oncologists and constitute an incentive for a future search of more efficient therapeutic methods.

## Conclusions

1. Loco-regional failure of cancer therapy is the principal failure of radical radiotherapy in patients with non-operable, non-small-cell lung cancer.
2. The majority of failures of the therapy emerge during the first two years of observation. Local recurrence is more frequent ( $p=0.002$ ) than distant metastases.
3. Radical radiotherapy with total doses of 60-70 Gy in patients with non-operable, non-small-cell lung cancer allows to achieve two-year survivals in  $33\pm 2\%$  of cases, and the probability of a two-year survival without the symptoms of the disease is  $16\pm 2\%$ .

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