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Evaluation of postoperative radiotherapy in patients with non-small cell lung cancer. A retrospective study

Ocena wyników pooperacyjnej radioterapii u chorych na niedrobnokomórkowego raka płuca. Badanie retrospektywne

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Abstract

Introduction: Surgery remains the most important treatment modality in non-small cell lung cancer. Indications for postoperative radiotherapy in this patient population have been the subject of debate for many years. Currently, patients with metastatic mediastinal lymph nodes (pN2) or with micro- or macroscopically non-radical resection are offered adjuvant radiotherapy in many institutions. The aim of this study was to retrospectively evaluate the results of postoperative radiotherapy in non-small lung cancer patients.

Material and methods: Between December 1993 and November 2005, 366 patients underwent radical radiotherapy in the Department of Radiotherapy of Institute of Oncology at Wawelska St. in Warsaw, following surgical procedures. Indications for radiotherapy included non-radical resection in 192 patients, mediastinal lymph node metastases in 174 patients, or a combination of both in 26 persons. Stage I or II was assigned to 96 patients (I — 9 pts, 2.4%; II — 87 pts, 24%). Stage IIIA disease was present in 252 patients (69%), and stage IIIB in 18 persons (5%). Zubrod performance status 0 was noted in 302 patients (82.5%), score 1 in 54 patients (14.8%), and score 2 in 10 persons (2.7%). The results of treatment were analysed retrospectively. Major end-points in the study were survival and time to local recurrence. The percentage of surviving patients was calculated using the Kaplan-Meier estimator. The prognostic impact of various factors was analysed using multivariate analysis according to the Cox proportional hazard model.

Results: One-year survival was reached by 78.02 $\pm$ 2% patients in the studied group, with two-year survival in 54.14 $\pm$ 2%, and five-year survival in 31.03 $\pm$ 2% patients. Two-year local recurrence-free survival was 45.62% $\pm$ 4%, and a five-year period free from recurrences was reached by 27.37 $\pm$ 4% patients. The probability of survival was significantly better in patients with better performance status, with a median survival of 2.75 years in patients with Zubrod score 0 and 1.67 years in Zubrod 1 + 2. Patients receiving $>$ 50 Gy irradiation had significantly better prognosis; median survival was 4.42 years in the $>$ 50 Gy group and 2.25 years in the $\leq$ 50 Gy group. Furthermore, local recurrences were less frequent in patients irradiated with $>$ 50 Gy. Patients planned for therapy using the 3D radiotherapy technique did not experience local recurrences; however, most of them received higher radiation doses compared to the others. A significant negative prognostic impact was found for radiation dose $\leq$ 50 Gy, worse performance status, and older age in univariate analysis. Good performance status (0) was prognostically beneficial. Multivariate analysis confirmed a significant adverse prognostic impact of total radiation dose lower than 50 Gy and older age, with good performance status being an independent good prognostic factor.

Conclusions: 1. The efficacy of postoperative radiotherapy depended on radiation dose, patient age, and performance status. Total radiotherapy dose $>$ 50 Gy, younger age, and better performance status significantly correlated with longer survival. 2. Application of the 3D technique resulted in an optimal local control of the disease.

Key words: adjuvant radiotherapy, non-small cell lung cancer, survival, local control

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Introduction

Lung surgery was the only modality of radical treatment of non-small cell cancer in the 1930s. In October 1933, Graham and Singer, for the first time, performed and described a pneumonectomy, and the first such procedure in Poland was performed on July 29th 1947 by Leon Manteuffel-Szoege [1].

Surgery remains a fundamental treatment method for non-small cell lung cancer [2]. Adjuvant radiotherapy is still the subject of controversy and debate, as many clinical studies have shown increased mortality or worsened quality of life in patients undergoing adjuvant radiotherapy after radical thoracic surgery [3–7].

Adjuvant radiotherapy is currently considered for patients with confirmed mediastinal lymph node metastases (pN2), positive surgical margins, or lymph node metastases with extracapsular extension [7, 8]. Meta-analyses clearly advise against radiotherapy as the treatment modality of choice after completed surgical procedures, showing a mortality increase of 18%, an adverse effect on overall survival, and uncertain outcomes in stage III and N2.

The aim of the presented study was to retrospectively analyse the outcomes of adjuvant radiotherapy following surgical treatment of non-small cell lung cancer in a patient population treated in the authors' institution.

Material and methods

Between December 1993 and November 2005, 366 patients were qualified for adjuvant radiotherapy in the Department of Radiology of the Institute of Oncology in Warsaw. The group included 73 women (19.9%) and 293 men (80.1%), aged 34–78 years (mean age 60 years). The clinical characteristics of the studied group are presented in table 1.

Performance status was assessed according to 5-grade Zubrod score. Three hundred and two patents in the studied group had performance status 0 (82.5%), 54 patients had score 1 (14.8%), and 10 patients were assigned score 2 (2.7%).

Staging was assessed according to the TNM classification (tumour, nodes, metastases). The following distribution of disease stages was found in the studied patient group: stage I — 9 patients (2.5%), II — 87 patients (24%), IIIA — 252 patients (69%), and IIIB stage in 18 persons (5%). Three patients with N3 stage (metastases in contralateral hilar lymph nodes) were included.

Table 1. Clinical characteristics of the studied patient group

Feature	n	%
Sex		
Male	293	80.1
Female	73	19.9
Age		
Mean	60.2	
Range	34–78	
Performance status according to the WHO (Zubrod score)		
0	302	82.5
1	54	14.8
2	10	2.7
TNM stage		
T1	27	7.4
T2	183	50.0
T3	126	34.4
T4	20	5.5
N0	81	22.1
N1	118	32.2
N2	174	47.5
N3	3	0.8
Histopathological tumour type		
Squamous cell carcinoma	219	59.8
Adenocarcinoma	115	31.4
Large cell carcinoma	19	5.2
Non-small cell cancer, not otherwise specified	13	3.6
Clinical stage		
I	9	2.5
II	87	24
IIIA	252	69
IIIB	18	5
Type of surgical procedure		
Wedge resection	9	2.5
Lobectomy	235	64.2
Pneumonectomy	122	33

WHO — World Health Organization; TNM — tumour, nodes, metastasis

In the described group, 155 patients had tumour of less than 5 cm in the largest dimension (42.3%). Tumour size was 5–8 cm in 205 patients (56.0%), and a further 6 patients had tumours larger than 8 cm (1.6%).

Fifty-six patients (15.3%) had non-malignant comorbidities, all of them adequately controlled. Cytostatics were administered in 66 patients, and all protocols included cisplatin. Adjuvant chemotherapy was administered in 41 patients, and neoadjuvant treatment in 25 patients. In each case, chemotherapy was administered in other institutions, not in the Institute of Oncology.

Resection of lung parenchyma was carried out in all patients, and the performed procedures included wedge resection in 9 cases (2.5%), lobectomy in 235 cases (64.2%), and pneumonectomy in 122 cases (33%).

Adjuvant radiotherapy was assigned for patients with non-radically resected tumours or N2 lymph node status. Radical resection was assessed according to the R scale, with R1 assigned when neoplastic infiltrates were microscopically identified in resection margins of the bronchial stump or vessel wall, and R2 assigned if tumour elements were identified macroscopically. In the studied group, 192 patients (52.5%) were irradiated due to positive surgical margins (93 cases with R1 and 99 cases with R2 resection), and 174 (47.5%) patients received adjuvant radiotherapy for N2 node status in histopathological evaluation.

R1 resection in stage I disease was constated in 4 patients, and R2 margins were found in 5 patients with the same stage. In stage II disease, 41 patients had R1, and 46 patients R2 margins, respectively. In the group of patients with stage III tumours, 43 persons had R1, and 48 patients R2 margins.

Adjuvant radiotherapy was performed in patients in general good condition with no weight loss of more than 10% in the previous six months and no history of unstable coronary heart disease, cardiovascular failure requiring hospitalization, or heart infarct under the last six months. Good lung function was another requirement, and patients had to have spirometric volume indices of more than 50% of predicted value. Radiation therapy was commenced 4–6 weeks after operation. The irradiated area included former tumour lodge, with neighbouring lymph node groups or mediastinal field in patients with N2 status. Conventional fractionating was planned, with a daily dose of 2 Gy applied 5 times per week.

Irradiation was planned using the conventional 2D technique for Co-60 unit (166 patients), linear accelerator delivering 4–15 MEV (143 patients), mixed source technique (30 patients), or using the 3D technique (27 patients). The clinical characteristics of the studied patient group, in view of the applied radiation techniques, are presented in table 2. Irradiation by Co-60 unit was performed on anterior and posterior fields. In the case of linear accelerator-delivered radiotherapy, simple fields up to 44 Gy were used, then oblique fields were irradiated up to maximal dose, using fields calculated based on computed tomography scans. Mixed technique used Co-60 photon irradiation on simple fields up to 44 Gy, followed by oblique field irradiation to the total dose of 50 Gy under linear accelerator, with spinal cord protection. 3D multifield technique was used for the linear accelerator, planned by a team of physicists.

Beginning in 2000, conformal 3D irradiation was introduced, using single-stage multifield technique with coplanar beams, delineated based on CT scans and taking into account variegated tissue densities.

Three-dimensional radiotherapy planning permits maximal protection of normal tissues, with delivery of a higher maximal dose to the selected area. Dose homogeneity in treatment plans in the studied group ranged between 95–107% for clinical target volume (CTV), and 85–110% planning target volume (PTV). Critical organs in patients with lung cancer were irradiated up to the maximal possible doses, i.e. 37% lung volume, not exceeding 20 Gy dose; the heart was irradiated up to 66% volume, up to 60 Gy; the oesophagus was irradiated up to 30% volume, with maximal dose of 50 Gy for patients receiving chemotherapy and 60 Gy for those who did not receive cytostatics. The maximal dose applied to the spinal cord (with 4 mm margin) was 50 Gy. Verification of correct planning was carried out via X-ray volume imaging (XVI) procedure, performed at the time of the first and the third fraction, followed by control on a weekly basis. In cases of discrepancy of more than 5 mm, doses were corrected.

In the studied group, 318 patients were irradiated with the maximal dose of 50 Gy, 26 persons received 60 Gy, and the remaining 22 patients received 52–58 Gy radiation doses.

Patients were followed up every three months. In cases of suspected locoregional recurrence in chest X-ray, computed tomography was performed. When

Table 2. Clinical characteristics of respective patient subgroups by different radiation techniques

Technique	Performance status			Total	Stage			
	0	1	2		I	II	IIIA	IIIB
Co-60	139	24	3	166	1	38	123	4
Linear accelerator	128	13	2	143	7	33	93	10
Mixed technique	15	10	5	30	0	10	17	3
3D	20	7	0	27	1	6	19	1

distant metastases were considered, abdominal ultrasound, CT of the head, or radiological and scintigraphic skeletal investigations were carried out.

Clinical data were retrieved from patient journals. The date of last follow-up in the study was 30th June 2010. For all the patients, the alive/dead status was verified. In case of patient death, date of death was retrieved using a death certificate obtained from the patient's family or from the central database. The main endpoint in the study was overall survival, calculated from the date of first radiotherapy fraction until time of death or last follow-up. The probability of survival was calculated according to the Kaplan-Meier estimator, with level of statistical significance set at 0.05 and graphical verification. Multivariate analysis was carried out using Cox proportional hazard model, and the analysed variables included treatment results, patient age, performance status, and disease stage, as well as radiation dose and technique. Variables with p value > 0.1 were then stepwise eliminated for the final analysis.

Results

Local recidives under the follow up period were found in 128 patients (34.9%), distant metastases were detected in 72 patients (19.67%), and both local and distant disease relapse was observed in 10 persons (2.7%). Cerebral metastases were identified in 23 patients, bone metastases in 22 patients, and supraclavicular lymph node in 12 persons. Further distant metastatic sites included adrenal glands, contralateral lung, or liver; these were single tumour foci, detected in a total of 15 patients. Patients with both local and distant recidives had bone metastases (4 persons), supraclavicular lymph node lesions (4 persons), or contralateral lung lesions (2 persons). At the time of last follow-up 156 patients (42.6%) were free from disease.

Signs of radiation injury were detected in 67 cases in the studied patient group. These cases included oesophageal burning sensation or skin erythema, found in 10 persons irradiated by linear accelerator, 52 persons irradiated by Co-60 units and mixed technique, and in 5 persons undergoing 3D irradiation.

Median survival in the studied patient group was 2.33 years (range 2–2.9 years), and mean survival time was 4.3 years. Survival at one year was reached by 78.02 ± 2% patients, at two years 54.14 ± 2%, and at five years by 31.03 ± 2% patients. Two-year period to local recurrence was reached by 45.62 ± 4%, and five-year period was obtained in 27.37 ± 4% of patients. The mentioned results are presented in figures 1 and 2.

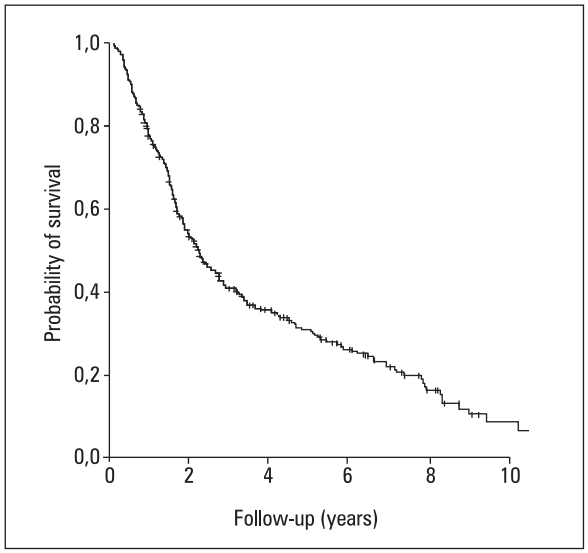


Figure 1. Overall survival in the group of 366 patients receiving adjuvant radiotherapy

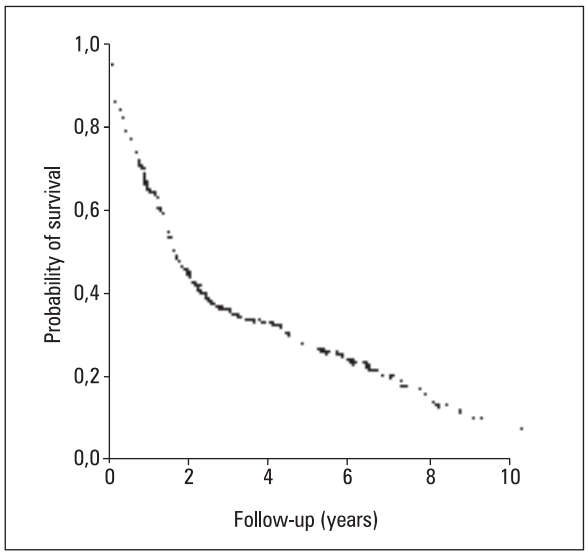


Figure 2. Disease-free survival in the group of 366 patients receiving adjuvant radiotherapy

Radiation dose, patient age, Zubrod performance status, clinical stage, T and N stage, and tumour size were the variables included in the potential prognostic factor analysis.

Patients irradiated with > 50 Gy had significantly better prognosis. Median survival time was 4.42 years in the > 50 Gy group and 2.25 years in the ≤ 50 Gy group, respectively (table 3). Curves depicting overall survival and time to local relapse are presented in figures 3a and 3b.

Patients with a good performance status (0) had significantly longer survival as compared to the other subgroup (Zubrod 1+2), with median survival times of 2.75 and 1.67 years, respectively

Table 3. Median survival time (years) by irradiation dose and selected clinical parameters

Parameter	Patient number	Median value	95% CI	
Stage I + II	96	2.67	2.2–3.4	
Stage III (A + B)	270	2.16	1.6–2.83	
Zubrod 0	302	2.75	2.17–3.42	
Zubrod (1+2)	64	1.67	1.5–2.25	
≤ 50 Gy cumulative dose	318	2.25	1.92–2.75	
> 50 Gy cumulative dose	48	4.42	2.25–7.83	
Age				
[34–53]	97	4.58	2.25–6.41	
[54–60]	80	2.12	1.58–2.83	
[61–67]	98	1.95	1.5–2	66
[68–78]	91	2.58	1.83–4.1	

CI = confidence interval

(table 3). Patient survival by performance status is depicted in figure 4.

Analysis of survival time by disease stage did not reveal statistically significant differences, with median survival times of 2.67 and 2.16 years, respectively (tab. 3, fig. 5).

Younger patients (34–53 years of age) experienced significantly longer survival periods compared to older ones (figure 6).

Correlations between radiotherapy technique and time to local recurrence or survival were analysed in the studied patient group. Local recidives occurred in 97 Co-60 irradiated patients (58.4%), 21 patients irradiated under linear accelerator (14.7%), and 33% patients receiving mixed technique irradiation. However, no local recurrences were found in patients receiving 3D irradiation. The latter patient subgroup had the best prognosis in the analysed population, but the differences were not statistically significant (fig. 7).

Univariate and multivariate analyses were used for assessment of survival prognostic factors (tab. 4). Older patient age and radiation dose of ≤ 50 Gy were two independent adverse prognostic factors, whereas performance status was a good prognostic factor.

Discussion

Indications for adjuvant radiotherapy in patients operated on for non-small cell lung cancer have been a subject for debate for many years now.

Most published studies concerning adjuvant radiotherapy confirm no need of such intervention after radical surgical excision [7, 8, 10]. Meta-analysis including results of 9 randomized studies showed a negative impact of adjuvant radiotherapy on survival and mortality, especially in stage I and II cases [7–9, 11]. Given these results, oncologists from many institutions choose not to irradiate patients who have undergone radical surgery. Some authors, however, point to the necessity of radiotherapy in cases with confirmed mediastinal lymph node metastases (pN2) detected following a radical surgical procedure [5, 10]. These studies showed improvement of two-year survival by 7%, especially in the setting of N2 nodes or stage III disease. Adjuvant chemotherapy also improved patient survival through decreased incidence of distant metastases. Moreover, better prognosis was observed in irradiated patients with N2 lymph nodes who received adjuvant chemotherapy [12–15].

In many institutions, adjuvant radiotherapy is applied after surgical procedure in patients with pN2 lymph nodes, alternatively R1 or R2 resection. Data from literature confirm that irradiation may destroy subclinical tumour foci, thus improving time to local recurrence and long-term survival [7, 11, 16]. Average survival of patients with tumour recurrence after R1 or R2 resection was 9 months; therefore, adjuvant radiotherapy is important to prevent development of overt local recurrences [17, 18].

In the presented study, adjuvant radiotherapy was administered in half of all the patients, following non-radical excision or, in the remaining population, due to N2 status. Radiation was administered as monotherapy in most cases, and not more than 66 patients (18%) received chemotherapy.

The results from the presented study are in accordance with published data concerning long-

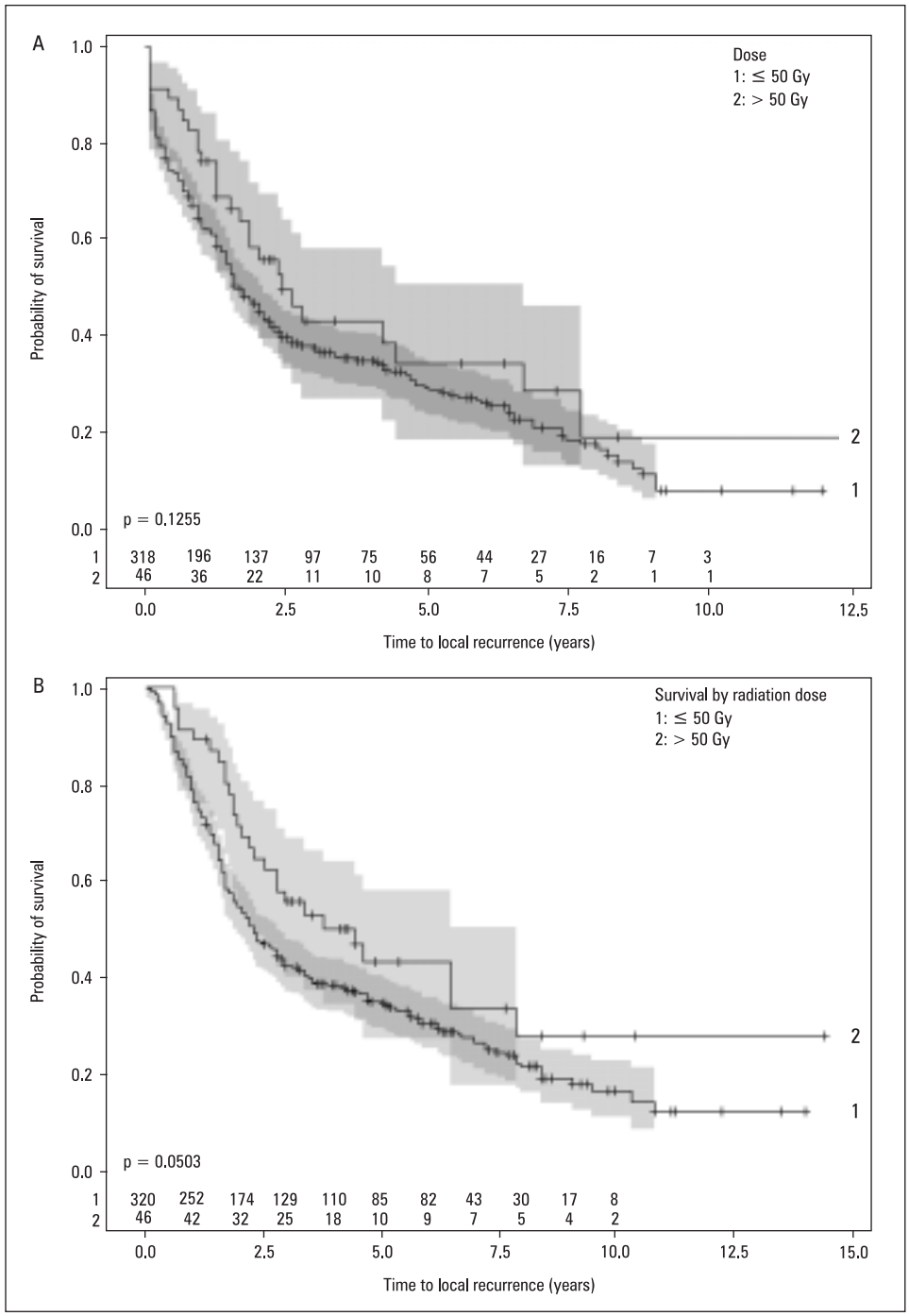


Figure 3. A — time to local recurrence by radiation dose ≤ 50 Gy versus > 50 Gy. B — overall survival by radiation dose ≤ 50 Gy versus > 50 Gy.

term survival rates. In the literature, reported rates range between 48-70% for two-year survival [6–8, 19], whereas in the presented study 54.14 ± 2% patients survived two years and 31.03 ± 2% patients lived for five years.

Patient age, performance status, and total radiation dose had the strongest prognostic impact in the studied group. Younger patients with performance status 0 and receiving a radiation dose of more than 50 Gy had a significantly longer survival. Radiation dose of over 50 Gy and younger age were independent prognostic factors.

According to published data, total radiation doses of 55–60 Gy are most efficient [10, 11, 15, 16]. Introduction of modern radiotherapy planning techniques, dosimetry, and improvement of the radiotherapy procedure itself permitted safe administration of higher doses. Further options include reduction of the irradiated area, 3D planning, and contemporaneous administration of chemotherapy [17–19].

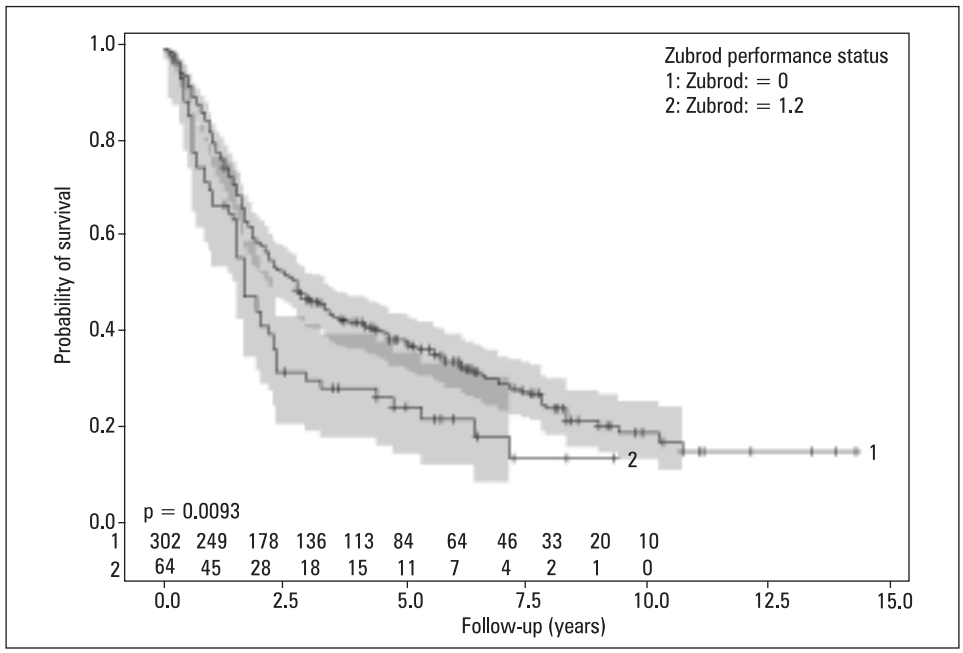


Figure 4. Overall survival by Zubrod performance status in the group of 366 patients receiving adjuvant radiotherapy

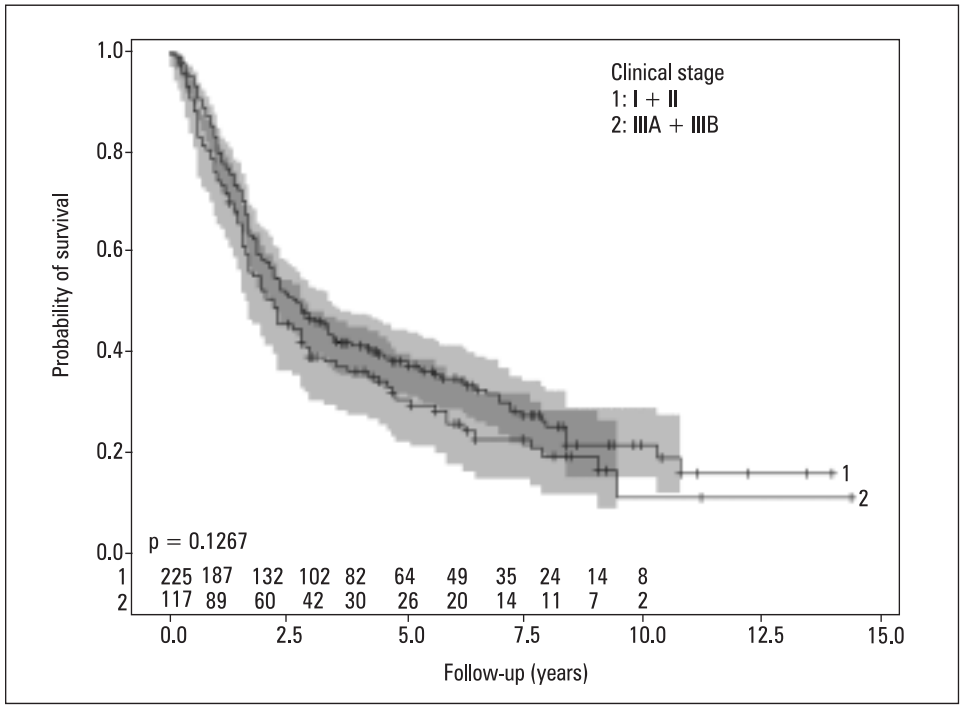


Figure 5. Probability of survival by disease stage in the group of 366 patients receiving adjuvant radiotherapy

The three-dimensional technique turned out to be most efficient in the presented study group; however, the small number of patients receiving this radiation modality (27 patients) limits the significance of the study results. Most studied patients were irradiated using two-dimensional techniques (339 patients, of which 30 received mixed therapy). Dose distribution in the latter population may be the reason for insufficient radiation delivery into certain areas, which then led to local recurrences (fig. 8 and 9).

Data from the literature suggest that the most clinically grave treatment failures in lung cancer patients receiving adjuvant radiotherapy are di-

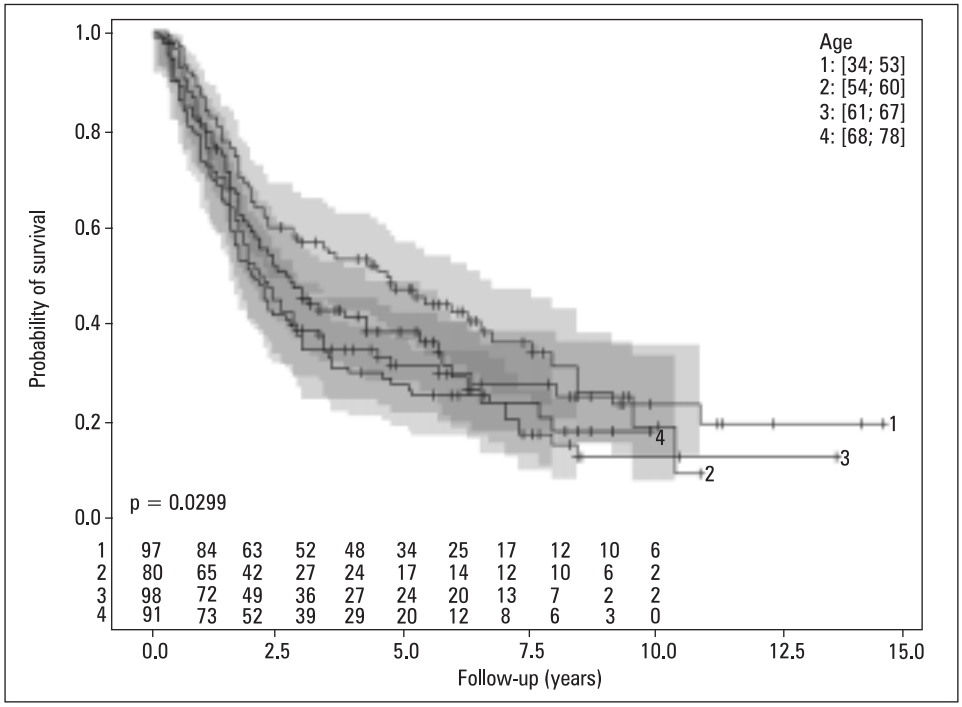


Figure 6. Overall survival by patient age

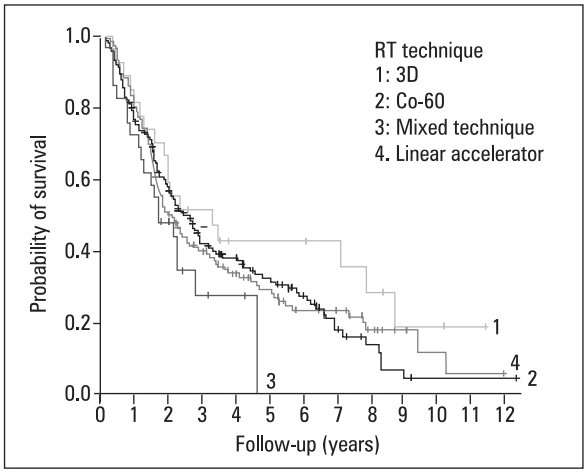


Figure 7. Overall survival by radiotherapy technique (RT)

stant metastases. In the presented study, however, local recurrences played the most important role. The high incidence of local recurrences in the presented material could probably be explained by the total radiation dose being too low, which was 50 Gy in as many as 318 patients (86.8%). Total received radiation dose of > 50 Gy correlated with longer time to local recurrence and significantly improved survival. Radiation doses applied in the presented study were in accordance with current guidelines [20, 21]. Recently, total radiation dose of 60 Gy has been applied in the authors' institution. Data from the literature show varying incidences of local recurrences after adjuvant radiotherapy, ranging from 11% [10, 11] to 41% [5] for the total dose of 54 Gy.

In the presented study, all radiation techniques correlated with a high incidence of local recurrences, with the exception of 3D technique. No patients receiving three-dimensional radiation therapy experienced this type of treatment failure. However, two patients under 3D treatment died due to cerebral metastases, and another one due to heart infarct. The other patients who received this variant of therapy are still alive.

The incidence of local recurrences was significantly higher for Co-60 technique as compared to linear accelerator (58.4% vs. 14.7%). Analysis of the isodose curves in these two techniques gives a probable explanation for the higher local recurrence incidence in patients irradiated with Co-60. The tumour area in patient mid-body thickness was not fully covered by the isodose (fig. 8). Adjusting this curve to the tumour cross section shape would require application of much larger radiation fields, thus bearing a much greater risk of irradiating normal tissues. A linear accelerator does not impose similar restrictions, and the isodoses cover the tumour mass more precisely (fig. 9). These results have mostly historical value, as cobalt units are no longer in use in the authors' institution.

Table 4. Significant prognostic factors in univariate and multivariate analysis

Univariate analysis				Multivariate analysis			
Prognostic factor	**HR**	**95% CI**	**p**	**Prognostic factor**	**HR**	**95% CI**	**p**
Age	1.013	1.0–1.027	0.057	Age	1.016	1.003–1.03	0.019
≤ 50 Gy dose	1.561	1.044–2.333	0.03	≤ 50 Gy dose	1.497	1.005–2.231	0.047
Performance status	0.668	0.49–0.91	0.0106	Performance status	0.636	0.46–0.87	0.005

HR = hazard ratio, CI = confidence interval

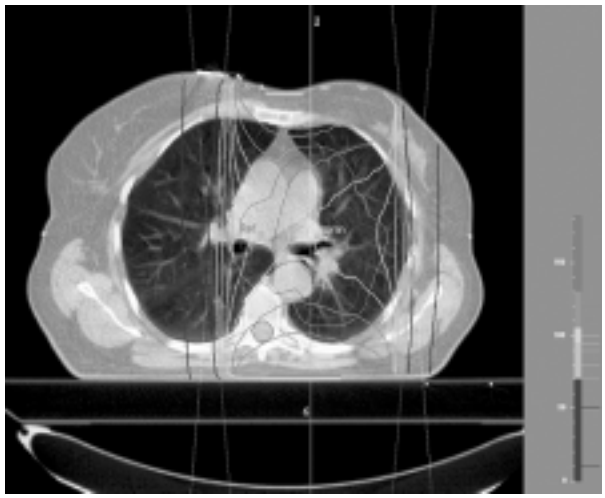


Figure 8. Isodoses for Co-60 irradiation

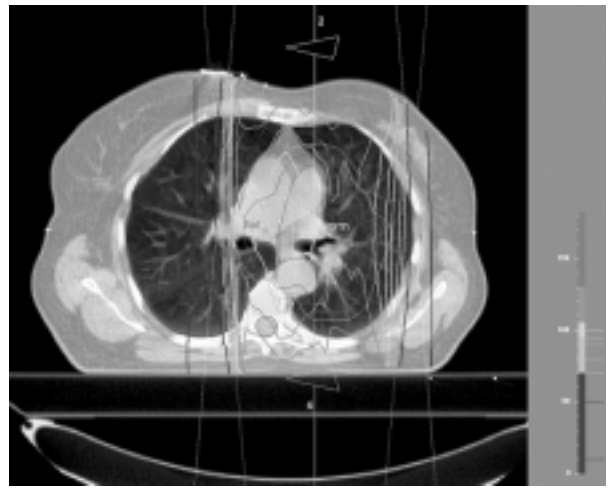


Figure 9. Isodoses for accelerator irradiation

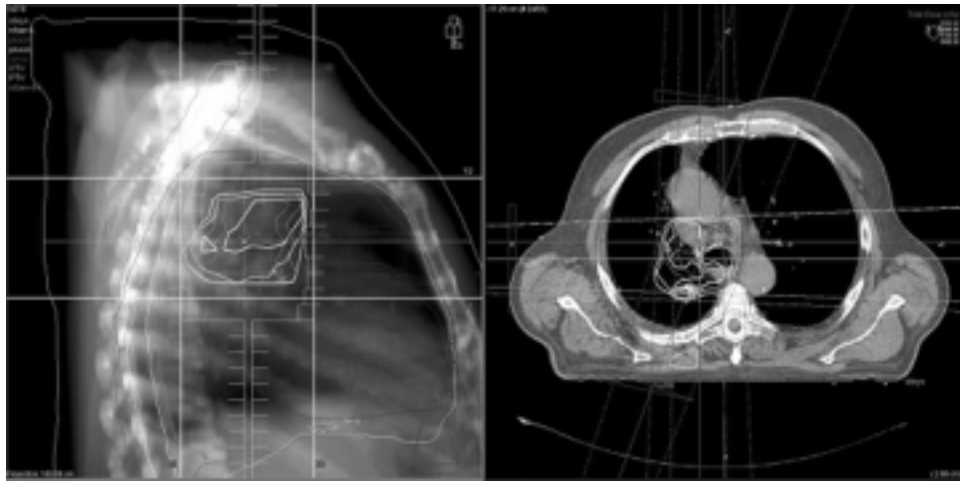


Figure 10. Isodoses for 3D technique

Three-dimensional techniques provide optimal isodose distribution (fig. 10). Many institutions are currently equipped with modern 3D planning devices and electronic portal imaging. Radiotherapy for lung cancer, with greater attention to organ respiratory mobility, can therefore be carried out with the intention of improving therapeutic benefit and reducing toxicity. Some authors report that computer-based treatment planning leads to a change in selected radiotherapy technique in the thoracic area in as many as 35% cases (26–67%) [22, 23].

The presented results suggest that escalation of total radiation dose, with complete reproducibility of three-dimensional treatment plan and thus protection of normal tissues and vital organs, can be of value in a selected population of patients (younger, with a good performance status).

Conclusions

1. Efficacy of radical adjuvant radiotherapy depended on total radiation dose, patient age, and performance status in the presented patient group. Radiation dose >50 Gy, younger patient age, and better performance status significantly correlated with longer survival.
2. Three-dimensional technique contributed to a better locoregional control of the disease.

Conflicts of interest

The authors declare no conflicts of interest.

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