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The impact of the dose time ratio on the outcomes in postoperative radiation therapy for non small cell lung cancer

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Introduction. The aim of the study was to analyse the results of irradiation and the prognostic factors related to clinical, pathological and therapeutic characteristics observed in patients with non-small cell lung cancer.
Material and method. We analysed the cases of 64 patients with primary non-small cell lung cancer treated between the years 1994-2000, who were operated on in the Lower Silesian Lung Disease Center and underwent postoperative irradiation at the Lower Silesian Oncology Center. Dose fractionation was 2 Gy or 2.66 Gy per day, with five fractions per week; total dose was 39.9 to 64 Gy. The results were analysed statistically. We examined the correlations between the following parameters and their influence on survival and disease-free survival – gender, age, type of operation, radicality of operation, pTNM, histologic subtype, grade of histologic malignancy, number of chemotherapy cycles, total dose of radiotherapy, dose intensity, fractionation dilution and the dose time ratio.
Results. Only the grade of histologic malignancy and parameters connected with the intensity of radiotherapy influenced patient survival. Local Disease Free Survival (LDFS) and Disease Free Survival (DFS) were statistically significantly shorter among patients with Dose Intensity (DI) <1.35 and Local Disease Free Survival (LDFS) – among patients with Fractionation Dilution (FD) >1.47. The Dose Time Ratio (DTR) on Local Disease Free Survival (LDFS) and Disease Free Survival (DFS) exhibited the strongest statistical power, but there was no influence on Overall Survival (OS).
Conclusion. Interruptions during postoperative radiotherapy are detrimental for disease-free survival and survival free of locoregional relapse in patients with NSCLC.

Wpływ współczynnika dawka – czas na wynik pooperacyjnej radioterapii u chorych na niedrobnokomórkowego raka płuca

Cel. Celem pracy była analiza wpływu wybranych czynników klinicznych i patologicznych na przeżycie chorych na niedrobnokomórkowego raka płuca, leczonych z zastosowaniem pooperacyjnej radioterapii.
Materiał i metoda. Materiał do badania pochodził od 64 pacjentów z rozpoznaniem niedrobnokomórkowego raka płuca, leczonych operacyjnie w Dolnośląskim Centrum Gruźlicy i Chorób Płuc w latach 1996-2000, a następnie poddanych uzupełniającej radioterapii w Dolnośląskim Centrum Onkologii. W trakcie radioterapii stosowane były dawki frakcyjne 2 Gy i 2,66 Gy dziennie, przez 5 dni w tygodniu do dawki całkowitej między 39,9 Gy a 64 Gy. Analizie statystycznej zostały poddane korelacje między następującymi parametrami – płeć, wiek, typ operacji, stopień radykalności operacji, stopień zaawansowania choroby pTNM, podtyp histologiczny raka, stopień złośliwości histologicznej nowotworu, liczba cykli chemioterapii, dawka całkowita radioterapii, Wskaźnik Intensywności Dawki, Wskaźnik Powtarzalności Frakcji i Współczynnik Dawka-Czas, oraz ich wpływ na przeżycie pacjentów.
Wyniki. Spośród badanych czynników jedynie stopień złośliwości histologicznej guza i parametry związane z intensywnością radioterapii miały wpływ na przeżycie pacjentów. Stwierdziliśmy istotne statystycznie skrócenie czasu Przeżycia Wolnego od Nawrotu Miejscowego Choroby (LDFS) i Przeżycia Wolnego od Nawrotu Choroby (DFS) wśród pacjentów ze Wskaźnikiem Intensywności Dawki (DI) <1,35, oraz skrócenie Czasu Przeżycia Wolnego od Nawrotu Miejscowego Choroby (LDFS) wśród pacjentów o Wskaźniku Powtarzalności Frakcji (FD) >1,47. Współczynnik Dawka-Czas wykazywał silny statystycznie wpływ na czas Przeżycia Wolnego od Nawrotu Miejscowego Choroby (LDFS) i Przeżycia Wolnego od Nawrotu Choroby (DFS), jednakże nie miał wpływu na Przeżycie Całkowite (OS) pacjentów.
Wnioski. Wyniki te potwierdzają negatywny wpływ przerw w trakcie pooperacyjnej radioterapii na przeżycie wolne od choroby u pacjentów z rozpoznaniem niedrobnokomórkowego raka płuca.

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Key words: non-small cell lung cancer, postoperative radiotherapy, Dose Time Ratio, Fractionation Dilution, Dose Intensity
Słowa kluczowe: niedrobnokomórkowy rak płuca, pooperacyjna radioterapia, Wskaźnik Intensywności Dawki, Wskaźnik Powtarzalności Frakcji, Współczynnik Dawka-Czas

Introduction

Lung cancer was the most common cause of cancer deaths in 1996 in the region of Lower Silesia in Poland. It accounted for 10.8% of all malignancies among women, second only to breast cancer. Among men it was the most common type of cancer – 28.1% of all cancer morbidities. Five-year survival among men reached 7%, and among women – 12.1% [1]. Surgery remains the basic treatment modality and offers the best chance to cure patients with NSCLC. However, less than 1/3 of these patients are suitable for surgery and the results of treatment are poor, because even if radical surgery is possible still a majority of patients are not free of the disease. Supplemental therapy remains a necessity. However, the efficiency of postoperative radiotherapy is controversial [2-13]. Some authors suggest that postoperative radiotherapy may not only decrease the rate of local recurrences but also positively influence the survival of patients with resected N2 disease [2, 3, 7, 10, 11]. In case of incomplete resection, postoperative radiotherapy has a positive impact on survival [4, 9]. Despite the lack of obvious evidence, most experts continue to recommend post-operative irradiation for patients with NSCLC in the N2 setting and after incomplete resection (defined as the presence of microscopic or macroscopic residual disease or disease in the highest resected paratracheal lymph node).

Material and methods

We have analysed the cases of 64 patients with primary non-small cell lung cancer, who were operated on in Lower Silesian Lung Disease Center and postoperatively underwent radiation therapy at the Lower Silesian Oncology Center. The study covered the years from 1996 until 2000. Histopathologic types of primary tumours and treatment modalities are presented in Table I. TNM classification of the patients and the radicality of the operation are presented in Table II. All patients were irradiated postoperatively. The time from operation to radiotherapy varied between 3 and 29 weeks (the difference was brought on by the administration of postoperative chemo-therapy). Fractionation was 2 Gy or 2.66 Gy per day, with five fractions per week; total dose was 39.9 to 64 Gy. Postoperative chemotherapy was administered to 35 patients and was delivered before radiotherapy. The most common chemotherapy regimens were: cisplatin with etoposide, and mitomycin with ifosfamid and cisplatin. Because of the two different fractionation schedules we re-calculated the Normalized Total Dose (NTD) using the linear – quadratic formula; where TD is the total physical dose delivered by fractionation of d Gy per day, and a/b characterises the tissue under consideration (35Gy for lung cancer) [14, 15].

Table II. TNM classification of patients and surgical radicality

Radicality of the operation	pTNM stages			
	I	IIA	IIB	III
radical operation	0	0	2	0
uncertain radicality	0	0	5	11
incomplete resection	5	4	10	27

$$NTD = TD\ (a/b + d)/(a/b + 2.0)$$

Furthermore, because of interruptions in the course of radiotherapy caused by machine breakdowns, we also took into consideration loss of part of the dose to defray repopulation [16]. We calculated the Normalised Total Dose with time correction (NTD-T) assuming a loss of 0.6 Gy per each day of the break. These calculations were used in case of breaks during treatment if the overall time of radiotherapy was longer than 28 days. The next parameters which characterised radiotherapy were the Dose Intensity Factor (Total Dose/Overall Time of Radiotherapy), the Fractionation Dilution Factor (Overall Time of Radiotherapy/Number of Fractions) and the Dose Time Ratio (Dose Intensity Factor/ Fractionation Dilution Factor) which defines the degree of interdependency between the first two [17, 18].

Table I. The histopathologic types of primary tumours and the treatment modalities

No of patients		Histopathology			In total
		squamous ca.	adenoca.	large cell ca.	
		24	23	17	64
Type of operation	wegde resection	0	1	0	1
	lobectomy	10	17	10	37
	bilobectomy	2	2	0	4
	pulmonectomy	12	3	7	22
No of chemotherapy cycles	0	14	9	5	28
	1-2	2	3	7	12
	3	5	9	5	19
	4-6	3	2	0	5
fractionation of postoperative radiotherapy	df=2Gy	21	14	13	48
	df=2.66Gy	3	9	4	16

Overall cancer-specific survival was defined as the period from the date of the operation to the date of cancer-death. An observation was made at the last follow-up to determine whether the patient was alive or had died of a cause other than NSCLC. Disease Free Survival was defined similarly. Kaplan-Meier curves were calculated for each variable. The log-rank test and Cox's proportional hazards model were used to examine the relationship between cancer-specific survival, disease-free survival and various potential prognostic factors. The level of significance was set at $p<0.05$. The association of all markers with clinicopathological parameters was evaluated using the Chi-square Test. Statistical analysis was performed using STATISTICA software, ver. 6.

Results

We examined the association between the following parameters and their influence on overall survival and disease-free survival – gender, age, type of operation, radicality of operation, pTNM, histologic subtype, grade of histologic malignancy, number of chemotherapy cycles, total dose of radiotherapy, dose intensity, fractionation dilution and the dose time ratio.

Table III shows mean DFS and OS. Only the grade of histologic malignancy (Figure 1) and parameters connected with the intensity of radiotherapy achieved statistical significance as factors affecting patient survival. There was no correlation between the time lapse between surgery and radiotherapy, or between overall duration of radiotherapy and patient survival. Patients were divided into three groups (according to the level of the Normalised Total Dose): those who received low doses (40.6-42 Gy), medium doses (46-52 Gy), and high doses (54-60 Gy). There was no difference in Local Progression-Free Survival (LPFS), Disease Free Survival (DFS), or Overall Survival (OS) between these three groups. Similarly, patients were categorised according to the level of Normalised Total Dose with time correction, which also failed to influence patient survival.

According to the Dose Intensity Factor (DI) patients were divided into two groups:
0 – 27 patients with DI below 1.35
1 – 37 patients with DI above 1.35.

Patients with DI higher than 1.35 had statistically longer DFS (Figure 2) and LPFS (Figure3). There was no difference in OS between these groups.

According to the Fractionation Dilution Factor (FD) patients were divided into two groups:
0 – 32 patients with FD above 1.47
1 – 32 patients with FD below 1.47.

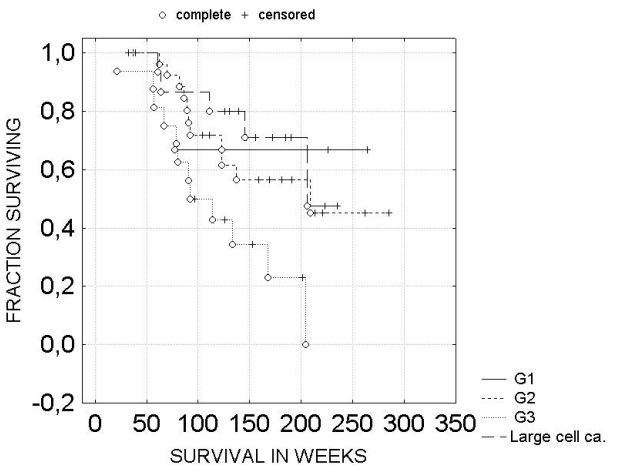

Figure 1. Overall survival of the patients according to the grade of cancer malignancy

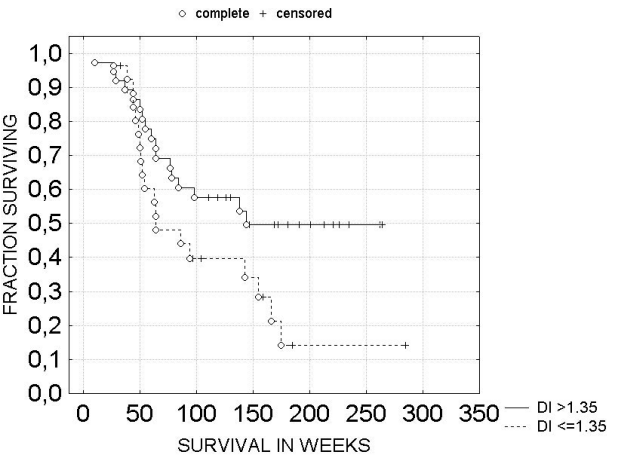

Figure 2. Disease free survival of patients according to the level of the Dose Intensity Factor (DI) (p = 0.047)

Table III. Disease Free Survival (DFS) and Overall Survival (OS) in weeks from the date of the operation

	Women	Men	Medium (weeks)		Minimum (weeks)		Maksimum (weeks)		Standard deviation	
			DFS	OS	DFS	OS	DFS	OS	DFS	OS
Healthy	6	14	182	182	104	104	285	285	53.0	53
Distant progression	6	13	59	105	10	21	155	223	31.4	51
Loco-regional progression	2	7	95	129	44	62	175	209	52.4	54
Loco-regional progression and distant progression	1	5	68	98	27	56	143	153	42.0	38
Another cancer	0	2	96	141	54	92	138	190	59.3	69
Death without cancer progression	0	8	85	85	32	32	213	213	65.0	65
In total	15	49	107	130	10	21	285	285	69.5	63

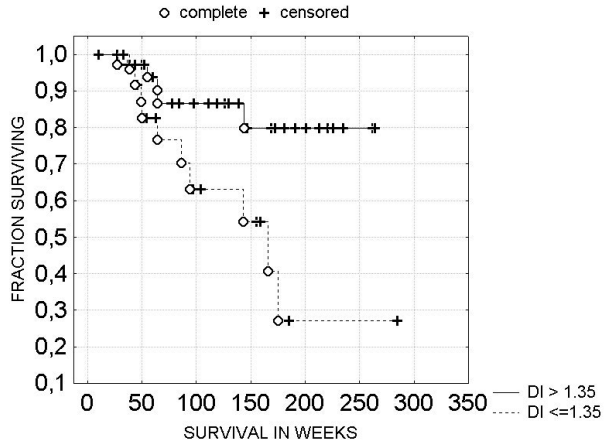

Figure 3. Local progression-free survival of patients according to the level of the Dose Intensity Factor (DI) (p = 0.013)

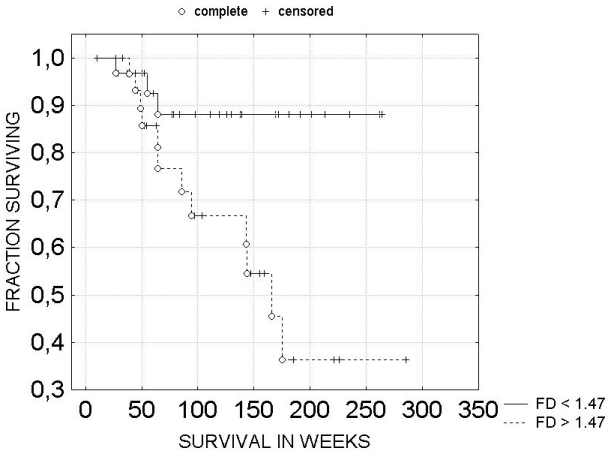

Figure 4. Local progression-free survival of patients according to the level of the Fractionation Dilution Factor (FD) (p = 0.012)

There was a statistically important difference in LPFS between patients with FD <1.47 and FD > 1.47 (Figure 4). There was no difference in DFS and OS between these groups of patients.

The Dose Time Ratio (DTR) categorised patients into two groups: one group of 22 patients with DTR lower than 0.95, and another group of 42 patients with DTR higher or equal to 0.95. LPFS (Figure 5) and DFS (Figure 6) were statistically significantly shorter among patients with DTR <0.95. There was no difference in OS between these two groups.

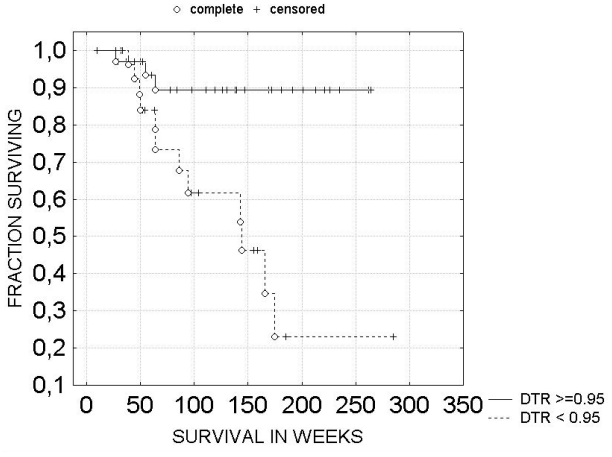

Figure 5. Local progression-free survival of patients according to the level of the Dose Time Ratio (DTR) (p = 0.0012)

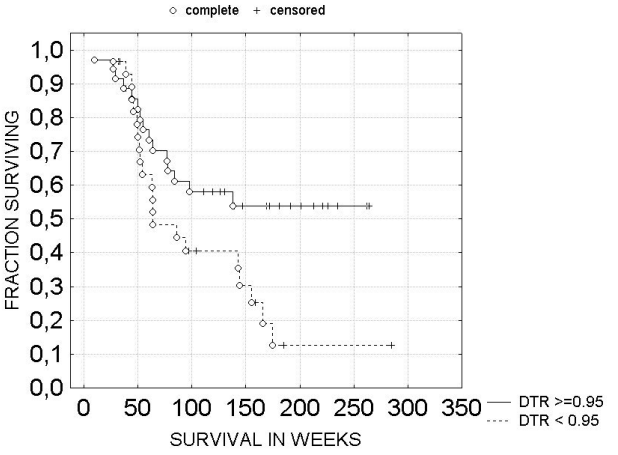

Figure 6. Disease free survival of patients according to the level of the Dose Time Ratio (DTR) (p = 0.028)

Discussion

The aim of this study was to analyse the efficiency of postoperative radiotherapy in patients treated for non-small lung cancer in one institution.

The probability of sterilizing a tumour after radiotherapy is influenced by a number of factors, the most important among them being tumour volume, tumour kinetics, intrinsic cellular radiosensitivity, dose and fractionation of radiotherapy, and overall time of radiotherapy. The influence of all these parameters is directly related.

We observed no influence of the level of the Normalised Total Dose nor of the Normalised Total Dose with Time correction on patient survival in the analysed group. However, we suppose that these results may be, to some extent, erroneous, because factor *a*/*b* considered in these calculations has not been estimated precisely and because the dose equivalent of repopulation was based on records obtained also from head and neck cancer patients. Therefore in order to compare the results of different fractionations of radiotherapy (different doses per fraction and interruptions during treatment), we used Maciejewski's conception of simple factors – Dose Intensity, Fractionation Dilution and Dose Time Ratio [17, 18].

We observed significantly shorter LDFS and DFS in patients with DI <1.35 and shorter LDFS in patients with FD >1.47. DTR on LDFS and DFS exhibited the strongest statistical power, but failed to influence OS.

If the dose per fraction (d) is not altered in the course of radiotherapy, we can describe DTR as:

$$DTR = d/(FD)^2$$

Thus DTR decreases when there are breaks in the course of radiotherapy (increased FD). Decreased DTR negatively influences DFS and LDFS. Our patients were administered two different doses per fraction: 2 Gy and 2.66 Gy. Because DTR 0.95 correlated with poorer survival, in the case of 2 Gy per fraction it corresponded to FD higher than 1.45 or to interruptions in radiotherapy lasting at least two days. In the case of 2.66 Gy per fraction it corresponded to FD higher than 1.67 or a five day break.

In view of these results one may assume that the time-table of radiotherapy is more important than the level of the total dose. However, the negative correlation between the total dose and the effect of radiotherapy should be approached cautiously, as we lack credible calculations of the *a*/*b* factor and the dose – equivalent of repopulation for different histologic subtypes of lung cancer. The dose – equivalent of repopulation was estimated from records of head and neck cancers. Even in the case of this type of cancer, quantitative estimates of the time factor are problematic and should be used with caution [19].

The CHART study confirmed the great significance of the accelerated repopulation of clonogenic tumour cells during the course of radiotherapy. The outcome after CHART was better than after conventional treatment, despite the 6 Gy reduction of the total dose, but overall treatment time was shortened from six weeks to 12 days. The conclusion of this study was the suggestion that repopulation is an important factor to be considered when planning the management of NSCLC and that the overall duration of treatment should be kept as short as possible [20]. Cox and others have been the first to show that interruptions lasting more than five days during high – dose (>69.6 Gy) radiation therapy decreased long term survival in favourable patients with unresectable NSCLC [21]. The result of this study indicated the exceptional role of the time factor in the radiotherapy of lung cancer [22]. A paper by Koukourakis et al. also proves that prolonged treatment time had a negative impact on survival [23]. In 2000 Chen et al. observed a statistically significant decrease of survival among patients whose overall treatment time was longer than 45 days. They calculated that overall treatment time prolonged for one week causes a 9% decrease in the three year Local Disease Free Survival [24].

Although it seems likely that accelerated tumour cell repopulation does occur during radiotherapy for NSCLC, there is lack of sufficient data to estimate it quantitatively. For this reason, it seems appropriate to compare the results of radiotherapy using simple factors, which characterise the intensity of radiotherapy at the time of its application.

There is a little data in literature concerning the influence of prolonged time of postoperative radiotherapy on the survival of NSCLC patients. We have shown that interruptions during postoperative radiotherapy are detrimental for disease-free survival and locoregional relapse-free survival in patients with NSCLC.

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