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The retrospective evaluation of prophylactic cranial irradiation in patients treated for limited stage small-cell lung cancer — a single centre study

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Introduction. The standard treatment for patients with LD SCLC (limited stage small-cell lung cancer) is combined modality therapy that includes chemotherapy (ChT) with platinum-based regimens and thoracic radiotherapy (RT), followed by prophylactic cranial irradiation (PCI) in patients with a response in the thorax.

Objectives. The evaluation of PCI in patients with LD SCLC and the analysis of the effects of certain therapeutic factors on the frequency and occurrence of brain metastases.

Materials and methods. Between 2002 and 2015, a total of 271 patients with LD SCLC received chemo-radiotherapy (concurrently in 122 pts — 45% and sequential in 149 pts — 55%). PCI was administered in 167 pts (61.6%) with total dose of 30 Gy given to the whole brain; 86 pts (51.1%) received PCI after completed chemo-radiotherapy and in 81 pts (48.9%) PCI was administered immediately after the end of thoracic irradiation.

The following statistical methods were used: Kaplan-Meier method (evaluation of survival rates: overall survival — OS, and brain metastases-free survival — BMFS), log-rank test (for comparison of survival rates), Cox' proportional hazard model (for multivariate analysis), Pearson chi^2 test for independence (for categorized variables comparison) and variance analysis (for continuous variables comparison). All the calculations were performed using Statistica v. 13.3 software (TIBCO Software Inc.) and the significance level for all the statistical methods was $p < 0.05$.

Results. Complete response in thorax was observed in 172 pts (63.5%) and remaining 99 pts (36.5%) developed partial response. During follow-up, 120 pts (44.3%) developed distant metastases from which brain metastases were most frequent (61 cases — 60.8%). The cumulative 5-year incidence of brain metastases amounted to 18.9% (when PCI was administered) and 45.9% (when PCI was omitted) and these differences were significant ($p < 0.0001$). PCI was an independent prognostic factor for BMFS and for OS. Omitted PCI is related with HR amounted: 6.25 for BMFS and 1.81 for OS.

Conclusions. PCI significantly reduces the incidence of brain metastases and delays the development of brain metastases in patients treated for LD SCLC. PCI is a significant independent prognostic factor for brain metastases-free survival and overall survival. The development of brain metastases is the most common type of failure in patients with LD SCLC and 90% of such relapses occurred during the 24 months following the completion of chemo-radiotherapy.

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Key words: small-cell lung cancer, prophylactic cranial irradiation, chemo-radiotherapy, limited stage, brain metastases

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Introduction

Small-cell lung cancer (SCLC) is an aggressive neuroendocrine tumour which accounts for approximately 10–15% of all lung cancer cases. This disease is characterised by a rapid doubling time and a high degree of sensitivity to chemotherapy and radiotherapy. However, this disease has widespread metastatic potential [1–4]. Despite these facts, at the time of diagnosis only 30–40% of patients with SCLC can be classified as having the limited stage of the disease (LD SCLC) [5]. According to the Veterans Administration Lung Cancer Study Group Classification, limited stage SCLC is defined as being confined to one hemithorax and regional lymphatic nodes (mediastinum, homolateral and contralateral hilar regions, homolateral supraclavicular fossa) and theoretically responsive to radiotherapy. Though limited stage SCLC corresponds to stages I–III according to TNM classification, but some studies assessed treatment modalities have used the classical not the TNM classification [6–8].

The standard treatment for patients with LD SCLC is combined modality therapy that includes chemotherapy (ChT) with platinum-based regimens and thoracic radiotherapy (RT), followed by prophylactic cranial irradiation (PCI) in patients with a response in the thorax [2, 5, 8–10]. The results of randomised trials and meta-analyses showed that combined chemo-radiotherapy (ChT-RT) improved tumour control as well as overall survival (+5.4% at 2-years) [11, 12]. This benefit is observed when ChT-RT is applied as a concurrent modality. The results of meta-analyses showed a 5.4% absolute increase in the 2-year survival rate for concurrent ChT-RT and this effect is particularly evident when thoracic RT is administered immediately after the first or second cycle of ChT [2, 5, 10, 13–18].

Although SCLC responds to ChT-RT, which results in a lower risk of thoracic relapse, the most frequent site of disease progression is the brain. The cumulative incidence of brain metastases is higher than 50% at 2 years after diagnosis [19–21]. The results of clinical trials and meta-analyses showed that PCI diminish the incidence of brain metastases and this translates into a 5.4% increase in the 3-year overall survival rate [8, 19, 22–24]. Therefore, PCI remains the standard therapy for all patients with SCLC in whom a response to ChT-RT was observed.

The objective of the present study was to evaluate the effectiveness of PCI in patients with LD SCLC treated at a single centre and to analyse the effects of certain therapeutic factors (particular PCI) on the frequency and occurrence of brain metastases.

Materials and methods

Between 2002 and 2015, a total of 271 patients with LD SCLC received combined treatment (chemotherapy and thoracic radiotherapy) at the Maria Skłodowska-Curie Institute — Oncology Center (MSCI) in Kraków, Poland.

In our study LD SCLC was defined as a disease limited to the hemithorax and ipsilateral supraclavicular lymph nodes. The stage of the disease was determined on the basis of the patient's medical history, a physical examination, a pathology review, computed tomography (CT) of the chest, upper abdomen and brain, a magnetic resonance (MR) of the brain, chest radiography, laboratory tests and an evaluation of pulmonary, cardiac and renal function tests.

Patients and therapeutic methods

The clinical and therapeutic characteristics of 271 patients with LD SCLC as whole group and according to application of prophylactic cranial irradiation (PCI) are shown in Table I.

The mean age of our patients was 60.5 years (ranging from 32 to 79 years), and the performance status of 167 patients (62%) was evaluated as 1 according to the WHO scale. The majority of patients (64.2%) were males.

All patients received chemotherapy according to a PE (cisplatin 30 mg/m^2 intravenously and etoposide 120 mg/m^2 intravenously) schedule. The chemotherapy consisted of 4–6 cycles administered every 3–4 weeks; and 92.6% of the patients received 4 or more cycles of PE.

Thoracic radiotherapy was administered concurrently (122 patients — 45% of the total) with RT beginning to be administered during ChT, immediately after the first or second cycle of PE (106 patients — 86.9%) or after the third cycle (16 patients — 13.1%). The remaining 149 patients (55% of all) received thoracic radiotherapy on a sequential basis (i.e. after the completion of the chemotherapy). Radiotherapy was applied using a photon beam (6 MV or 18 MV) produced in a linear accelerator and a three-dimensional treatment planning system was adapted to the conformal radiotherapy technique. The gross tumour volume (GTV) was defined on the basis of CT scans and included primary tumour and involved lymph nodes. The clinical target volume (CTV) in the first phase included GTV and mediastinal and hilar lymph nodes as elective irradiated nodes, whereas in the second phase it covered GTV with adequate margins (8 mm added isotropically). The planning target volume (PTV) in both phases covered the CTV with margins: 7 mm axially and 12 mm longitudinally were added to account for tumour motion. The total dose administered ranged between 40 and 66 Gy (the fractional dose was 1.8–2.0 Gy) and amounted on average to 54.2 Gy (median: 54 Gy), and the majority of the patients (233 out of 271 — 86%) received a dose equal to or greater than 54 Gy.

Prophylactic cranial irradiation (PCI) was delivered to 167 patients (61.6%) as "late" PCI (when it was administered after ChT-RT; in 86 patients — 51.1%) or "early" PCI (when it was administered immediately after the end of thoracic irradiation; in 81 patients — 48.9%). During PCI, a total dose of 30 Gy in 2-Gy fractions was delivered to the whole brain.

Table I. The characteristics of 271 patients with LD SCLC in relation to application of prophylactic cranial irradiation (PCI)

Parameters		Whole group		PCI — yes		PCI — no		p-value
		N = 271 (100%)	%	N = 167 (61.6%)	%*	N = 104 (38.4%)	%*	
Age (in years)	range	32–79		32–79		35–79		
	mean ± SD	60.5 ± 9.1		58.8 ± 8.9		63.3 ± 8.7		0.0001[a]
	median	60.0		59.0		63.5		
Gender	male	174	64.2	103	61.7	71	68.3	0.2709[b]
	female	97	35.8	64	38.3	33	31.7	
Primary tumour localization at side	left	123	45.4	72	43.1	51	49.0	0.3408[b]
	right	148	54.6	95	56.9	53	51.	
Positive of supraclavicular nodes		14	5.2	11	6.6	3	2.9	0.1806[b]
Performance status (WHO scale)	1	168	62.0	107	64.1	61	58.7	0.3716[b]
	2	103	38.0	60	35.9	43	41.4	
Chemo-radiotherapy (ChT-RT)	concurrent	122	45.0	100	59.9	22	21.2	0.0000[b]
	sequential	149	55.0	67	40.1	82	78.9	
ChT — number of PE cycles	range	1–6		2–6		1–6		
	mean ± SD	4.9 ± 0.9		4.9 ± 0.8		4.9 ± 1.1		0.8140[a]
	median	5.0		5.0		5.0		
	4–6	251	92.6	157	94.6	94	90.4	0.1898[b]
	1–3	20	7.4	9	5.4	10	9.6	
Thoracic RT after PE cycle	1 or 2	106	39.1	92	55.1	14	13.5	0.0000[b]
	3 or more	165	60.9	75	44.9	90	86.5	
Thoracic RT — dose (in Gy)	range	40–66		40–66		40–60		
	mean ± SD	54.2 ± 3.9		54.3 ± 3.2		53.8 ± 4.8		0.2084[a]
	median	54.0		54.0		54.0		
PCI (yes)	early			81	48.5			
	late			86	51.5			

ChT-RT — chemoradiotherapy, ChT — chemotherapy, PE — cisplatin and etoposide, PCI — prophylactic cranial irradiation, SD — standard deviation, *percentage in relation to subgroup, [a]Variance analysis (Student t-test), [b]chi^2 test

The significant differences (Tab. I) between the group that received PCI and the group that omitted PCI concerned the mean age, the schedule of ChT-RT and the beginning of thoracic RT in relation to chemotherapy. The patients who received PCI in comparison to whom omitted PCI: (a) were significant ($p < 0.05$) younger (mean age: 58.8 vs 63.3), (b) most of them received concurrent ChT-RT (59.9% vs 21.2%), and (c) more frequent thoracic RT began earlier — immediately after the first or second cycle of PE (55.1% vs 13.5%).

The response of all the patients to treatment was evaluated 6–8 weeks after the completion of therapy and it was assessed on the basis of a chest CT. During the follow-up a physical examination was performed every 2 months for the first 24 months and every 3 months thereafter. A radiological examination (a chest CT and a brain MR) was performed to assess the chest (every 6 months) and the brain (every 12 months or when clinical symptoms are present).

Statistical methods

The results were evaluated as 5-year overall and brain metastasis-free survival rates. The survival rates were estimated using the Kaplan-Meier method. The influence of various parameters on survival rates was assessed using the log-rank test, as well as Cox's proportional hazards regression model to identify independent prognostic factors. The groups were compared using Pearson's chi^2 test for independence (for categorized variables) and variance analysis based on the Student's t-test (for continuous variables).

All the calculations were performed using Statistica v. 13.3 software (TIBCO Software Inc.) and the significance level for all the statistical methods was $p < 0.05$.

Results

Following treatment, complete response (CR) to thoracic disease was observed in 172 patients out of a total of 271 (63.5%), while the remaining 99 patients (36.5%) developed partial response (PR). The follow-up period ranged from 3 to 183 months with a mean of 33.2 months. During this period, 220 patients (81.2%) died. The causes of death were as follows: progression of small-cell lung cancer in the thorax (88 pts; 40%), the development of distant metastases (77 pts; 35%), and coexistent diseases (17 pts; 7.7%). In the remaining 34 patients (15.5%) the cause of death was unknown.

During the follow-up period, 84 patients (32.7%) developed failure in the thorax: recurrence (41 patients out of a total of 172 with CR, 23.8%) or progression (43 patients

out of a total of 99 with PR — 43.4%). The mean time it took for the above thoracic failures to develop was 17.2 months in the case of recurrence and 5.4 months in the case of progression.

Distant metastases occurred in 120 patients (44.3%), and the mean time of this type of failure was 8.2 months. The most common location of distant failure was the brain (61 pts, 50.8%), where metastases developed after a mean time of 11.4 months following ChT-RT (range: 1–96 months). Other locations of distant metastases were as follows: lymph nodes (36 pts, 30%), liver (19 pts, 15.8%), bones (16 pts, 13.3%), suprarenal glands (9 pts, 7.5%), lungs (8 pts 6.7%), pancreas (2 pts, 1.7%), and the skin (1 pt, 0.8%).

The 5-year overall (OS) and brain metastases-free (BMFS) survival rates were 23% and 60.3%, respectively.

Figure 1 shows the probability of (a, c) overall survival and (b, d) brain metastasis-free survival both for the whole group (a, b) as well as in relation to the administration of PCI (c, d).

The cumulative 5-year incidence of brain metastases in relation to PCI amounted to 18.9% (when PCI was administered) and 45.9% (when PCI was omitted). This difference was statistical significant (p = 0.0000, log-rank test).

The results of the multivariate Cox' proportional hazard model showed that one statistically significant independent factor affecting survival rates (OS and BMFS) was the administration of prophylactic cranial irradiation (Tab. II). The risk increased when PCI was omitted: brain metastases-free survival (HR = 6.25, p = 0.0000), and overall survival (HR = 1.81, p = 0.0000).

The role of the administration of PCI was also evident when evaluating the frequency of brain metastases in relation to time intervals following ChT-RT (Fig. 2). The majority of the brain metastases (90.2%) occurred within twenty-four months of treatment. A significant correlation was observed between the administration of PCI and the reduction rate (11.4% vs 40.4%, p = 0.0000, chi^2 test) and occurrence delay (27.6 vs 4.0 months, p = 0.0017, Student' t-test) of brain metastases compared to when PCI was not administered.

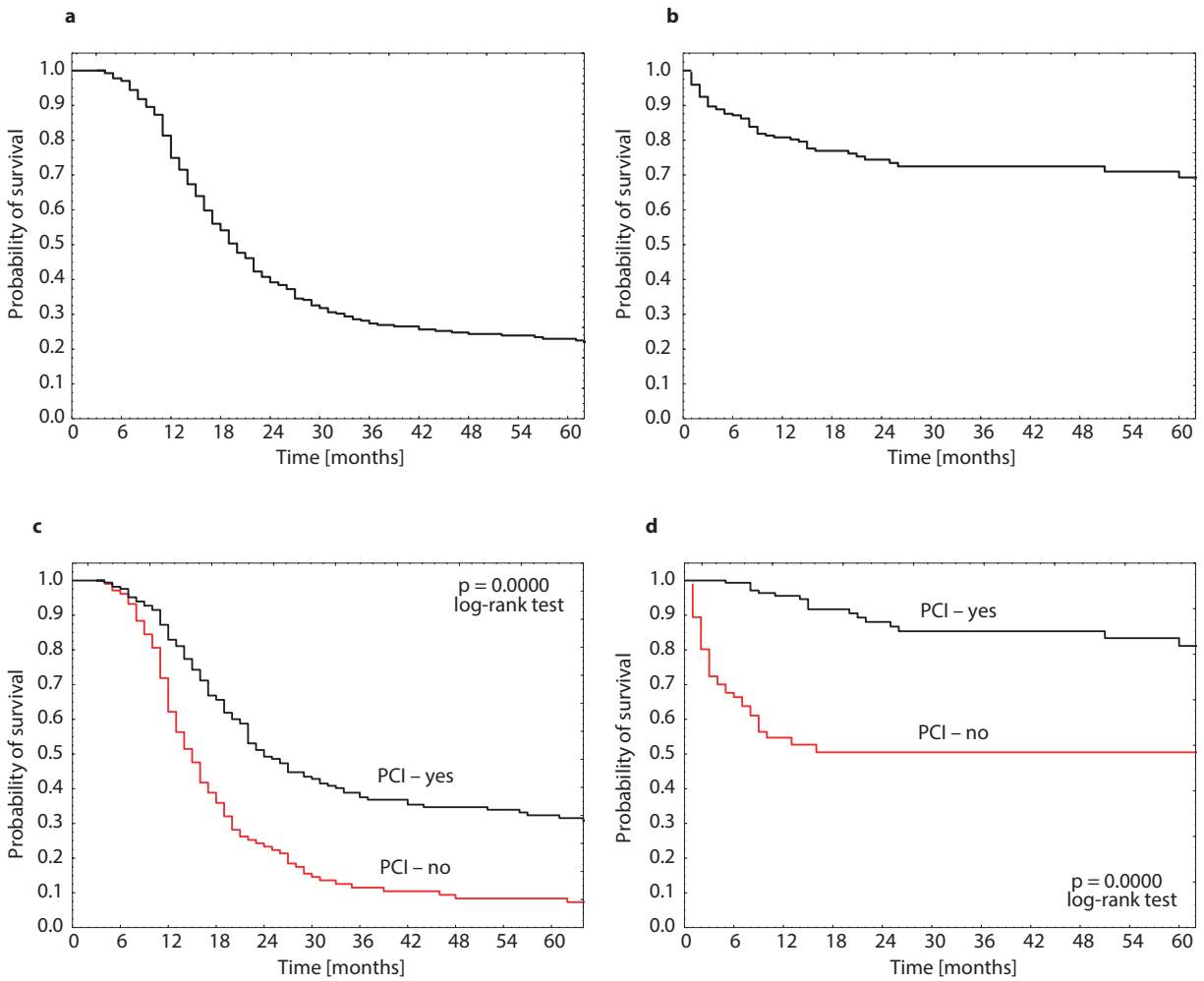

Figure 1. The probability of (**a, c**) overall survival and (**b, d**) brain metastasis-free survival in the whole group (**a, b**) as well as in relation to the administration of PCI (**c, d**)

Table II. The results of multivariate proportional hazard Cox' model

Parameter	HR	95% CI	p-value
Overall survival			
PCI: no vs yes	1.81	1.36–2.40	0.0000
response: PR vs CR	2.50	1.86–3.37	0.0000
Brain metastases-free survival			
PCI: no vs yes	6.25	3.59–10.87	0.00000

HR — hazard ratio, CI — confidence interval, PCI — prophylactic cranial irradiation, PR — partial response, CR — complete response

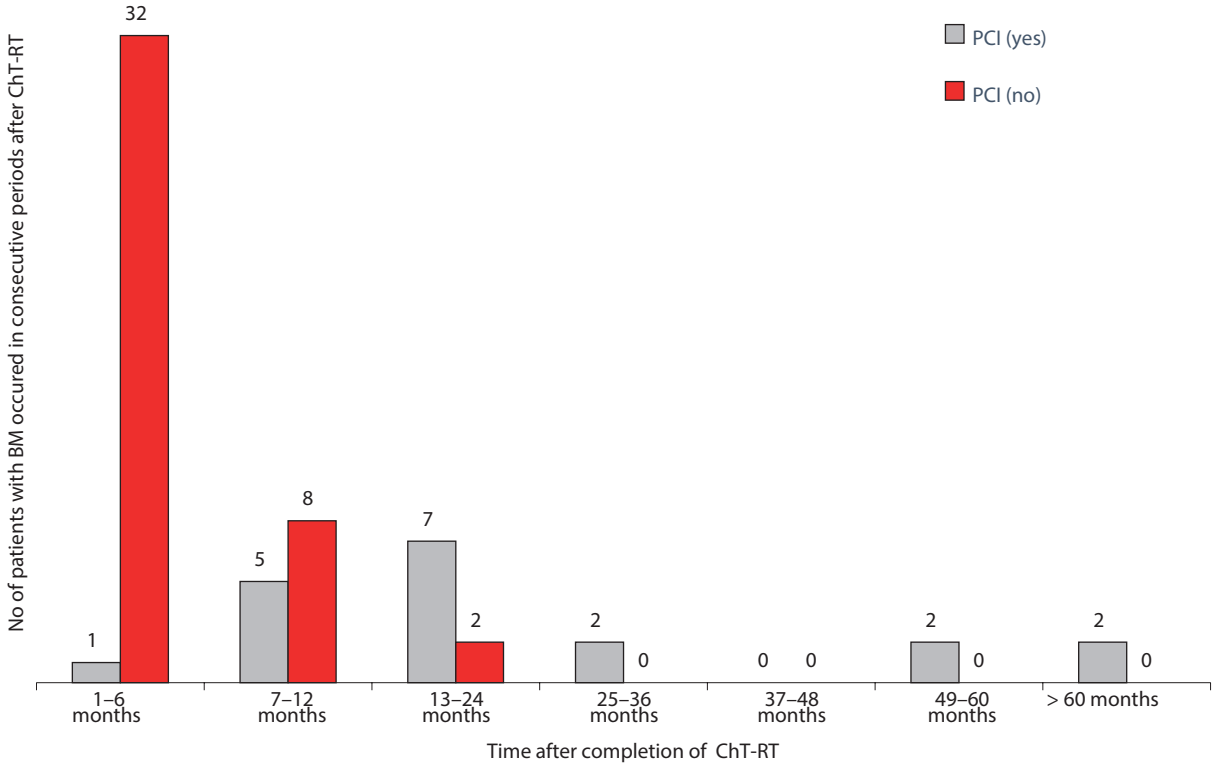

Figure 2. The frequency of brain metastases in time intervals following chemo-radiotherapy (ChT-RT) in relation to application of prophylactic cranial irradiation (PCI)

Table III. The influence of PCI and other therapeutic factors and treatment results for frequency and time of brain metastases occurrence in patients with LD SCLC

Features		Brain metastases				p-value chi^2 test	Time period between ChT-RT and occurrence of brain metastases (mean ± SD)	p-value Student's t-test
		yes N = 61 (22.5%)		no N = 210 (77.5%)				
		No of pts.	%	No of pts.	%			
ChT-RT	concurrent	18	14.8	104	85.3		34.5 ± 40.9	
	sequential	43	28.9	106	71.1	0.0057	19.9 ± 26.8	0.0008
RT after PE cycle	1 or 2	15	14.2	91	85.9		23.9 ± 25.8	
	3 or more	46	27.9	119	72.1	0.0083	7.3 ± 14.4	0.0027
Response in chest	CR	37	21.5	135	78.5		15.8 ± 23.2	
	PR	24	24.2	75	75.8	0.6043	4.6 ± 4.2	0.0067
PCI	yes	19	11.4	148	88.6		27.6 ± 27.8	
	no	42	40.4	62	59.6	0.0000	4.0 ± 3.6	0.0017
PCI (yes)	early	10	12.4	71	87.7		38.4 ± 44.1	
	late	9	10.5	77	89.5	0.7021	31 ± 29.2	0.4970

ChT-RT — chemoradiotherapy, RT — radiotherapy, PE — cisplatin and etoposide, CR — complete regression, PR — partial regression, PCI — prophylactic cranial irradiation, SD — standard deviation

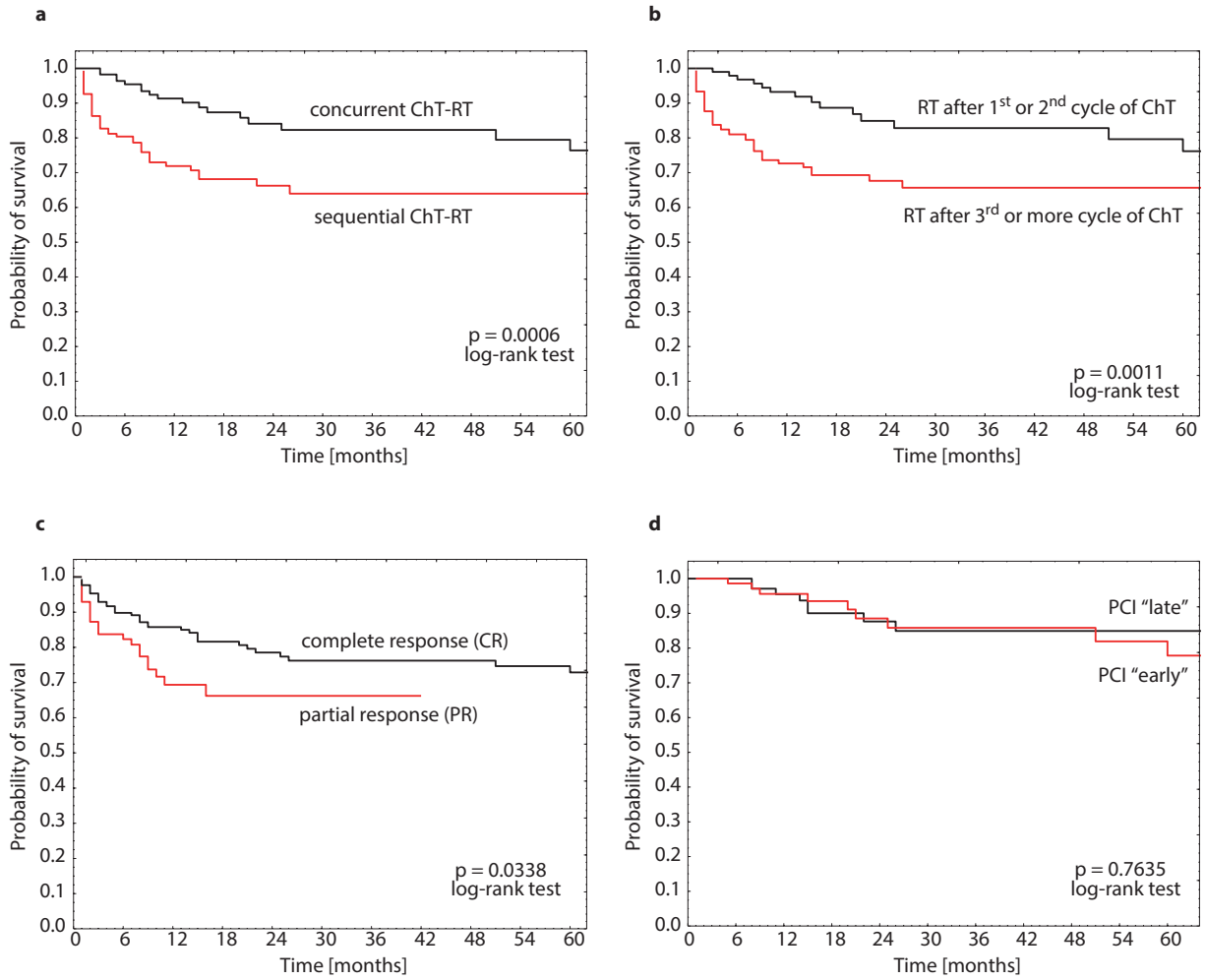

Figure 3. The probability of brain metastases-free survival (BMFS) in relation to: (**a**) schedule of chemo-radiotherapy: concurrent vs sequential, (**b**) beginning of thoracic radiotherapy: after 1st or 2nd cycle vs later, (**c**) response to treatment: complete vs partial, and (**d**) time of PCI application: "early" vs "late"

The influence of certain therapeutic factors on the frequency and timing of the brain metastases is summarized in Table III, and Figure 3 shows the probability of brain metastases-free survival (BMFS) curves in relation to: (a) schedule of chemo-radiotherapy: concurrent vs sequential, (b) beginning of thoracic radiotherapy: after 1st or 2nd cycle vs 3rd cycle chemotherapy, (c) response to treatment: complete vs partial, and (d) time of PCI application: "early" vs "late".

The brain metastases were rare and developed later when: (a) ChT-RT was performed concurrently, (b) thoracic RT commenced immediately after the 1st or 2nd cycle of PE (early thoracic RT), and when (c) prophylactic cranial irradiation was used, and these differences were significant. Furthermore, the achievement of complete response after ChT-RT was associated with a delay in brain metastases compared with patients with partial response (15.8 vs 4.6 months, p = 0.0017). On the other hand, despite the significant role of prophylactic cranial irradiation, the timing of PCI ("early" or "late" PCI) did not have major influence on the frequency and occurrence of brain metastases.

The 5-year brain metastases-free survival (BMFS) rates were as follows: 60.3% (for the group as a whole), 81.1% vs 50.5% (respectively, for PCI vs no PCI, p = 0.0000, log-rank test), 76.4% vs 64% (concurrent vs sequential ChT-RT, p = 0,0006, log-rank test), 76.2% vs 65.7% (thoracic RT after 1 or 2 cycles of ChT vs after 3 or more cycles of ChT, p = 0.0011, log-rank test). Significant differences in BMFS were also observed in relation to the post ChT-RT response; the 5-year rates were 72.9% and 66.2%, respectively, for CR and PR (p = 0.0338, log-rank test).

Discussion

Brain metastases (BM) are the most common form of SCLC relapse. The 2-year cumulative risk of brain metastases is higher than 50% in patients with LD SCLC [19–21].

In the case of our material, brain metastases developed in 61 (22.5%) out of a total of 271 patients with LD SCLC.

Papers published in 2017 presented similar results. According to data from Wu et al. [25] and Farooqi et al., [26] brain metastases were observed in 19% and 21.1% of all cases, respectively.

The efficacy of combined (ChT-RT) treatment reduces the risk of thoracic failure and brain metastases become the main type of relapse. The hypothesis that the brain is a pharmacological sanctuary for microscopic tumours against systemic chemotherapy suggests that prophylactic cranial irradiation may be considered as a strategy for eradicating non-detectable brain metastases. This treatment method has been shown to reduce the incidence of brain metastases and to help improve the survival rate. The role of PCI in reducing brain metastases has been assessed extensively in patients with LD SCLC. The results of clinical trials and meta-analyses showed that PCI not only significantly decreases the incidence of brain metastases, but also results in higher overall survival rates [23, 24, 27, 28]. Auperin's meta-analysis showed that PCI reduces the risk of brain metastases (from 59% to 33% at 3 years) and at the same time improves the 3-year survival rate (a 5.4% gain for overall survival and an 8.8% gain for disease-free survival) [23]. Similar observations reported by other authors confirmed the significant role played by the administration of PCI in decreasing (an average of 14–36%) the incidence of brain metastases [22, 27, 29–31]. Patel et al. [24] performed a retrospective analysis of 7995 patients and showed that PCI is a significant predictor of survival; the 5-year survival rate was 19% when PCI was administered compared with 11% when PCI was omitted.

Our observation confirmed the significant benefits of administering PCI. Brain metastases developed in 11.4% of patients who received PCI as compared with 40.4% of patients when PCI was omitted. Moreover, we observed that brain metastases developed significantly later in patients with PCI compared with cases in which no PCI was administered (mean time: 27.6 vs 4.0 months, respectively; $p = 0.0017$, Student's t-test). Another benefit of PCI was an improvement in survival rates; the 5-year overall survival rates were as follows: 32.4% (with PCI) and 8.4% (without PCI) and this difference was significant ($p = 0.0000$, log-rank test).

Farooqi et al. [26] observed that the administration of PCI was associated with a significantly lower frequency and delayed occurrence of brain metastases compared with cases that did not involve PCI (frequency: 18.1% vs 24.8%, mean time of occurrence: 16.8 vs 8.2 months, respectively). Instead, Tai et al. [32] showed that PCI significantly delayed the mean time at which brain metastases occurred (20.7 vs 10.6 months in cases with or without PCI, respectively).

The administration of PCI was an independent prognostic factor affecting survival rates both in the case of brain metastases-free survival and overall survival [25, 26, 29]. We showed that the hazard ratios for cases where PCI was omitted were 6.25 for brain metastases-free survival and 1.81 for overall survival. A similar observation presented Eze et al. [29] who showed that patients without PCI had poorer overall survival — the hazard ratio in their multivariate analysis averaged 1.899. The recently published results of other authors confirmed that the administration of PCI not only significantly decreases the risk of brain metastases, but also it is an independent significant factor for survival rates [25, 26].

Another analysis of the effectiveness of PCI concerned the total dose and time of delivery. The results of an EORTC phase 3 randomized trial comparing the effect of standard versus higher PCI doses on the incidence of brain metastases showed that there was an insignificant reduction in the total incidence of brain metastases after a high dose of PCI and there was also a significant increase in mortality [33]. On the other hand, the early administration of PCI was based on Auperin's clinical observations and theoretical conditions (Suwinski's group) that revealed an almost linear dose-response relationship in relation to a reduction in brain metastases which is evidence in favour of early PCI application [23, 34, 35]. Our previous observation confirmed that early administered PCI (immediately after the completion of thoracic radiotherapy) lowered the incidence of brain metastases compared with the later application of PCI (7.3% vs 20% respectively for early vs late PCI) [36]. Unfortunately, our present results did not confirm what influence the timing of PCI delivery has on the development of brain metastases. It is conspicuous that the current group in comparison to early presented group is nearly twice as large (271 vs 129 cases) and the mean time of the follow-up is longer (33 vs 19 months).

Restricting PCI carries the risk of the development of neurotoxicity. According to data from the literature, neurotoxicity affects 10–70% of patients treated for SCLC. The most common neurological dysfunctions include cognitive impairment and memory problems [37–39]. It is important to note that these neuropsychological problems may not only be a consequence of PCI, but might also result from the cancer itself and the anticancer therapy. Therefore, in patients with LD SCLC the earliest possible administration of chemotherapy in combination with chest radiotherapy should be considered the standard treatment, followed by prophylactic cranial irradiation for patients with tumour response and no contraindications for this procedure.

Conclusions

1. Prophylactic cranial irradiation (PCI) significantly reduces the incidence of brain metastases and delays the development of brain metastases in patients treated for LD SCLC. The cumulative 5-year incidence of brain metastases amounted to 18.9% (when PCI was administered) and 45.9% (when PCI was omitted).
2. Prophylactic cranial irradiation is a significant independent prognostic factor for brain metastases-free survi-

val (BMFS) and overall survival (OS). The relative risk of omitting PCI amounted 6.25 for BMFS and 1.81 for OS.

3. The development of brain metastases is the most common type of failure in patients with LD SCLC and 90% of such relapses occurred during the 24 months following the completion of chemo-radiotherapy. In the case of the present group, brain metastases affected 22% of all patients and 51% of all cases involving distant metastases.

Conflict of interest: none declared

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