

STUDY PROTOCOL

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Study protocol: watchful observation of patients with limited small cell lung cancer instead of the PCI—prospective, multi-center one-arm study

Sergiusz Nawrocki* and Anna Sugajska

Abstract

Background: Prophylactic cranial irradiation (PCI) is a current standard of care after confirmed response to radical chemoradiotherapy for limited disease small cell lung cancer (LD-SCLC). This standard is mostly based on results of old randomized studies when brain imaging with magnetic resonance (MRI) was not available. Survival benefit of PCI in extended disease SCLC was recently challenged by the results of randomized phase III study from Japan.

Methods: Eighty patients with LD-SCLC after response to chest chemoradiotherapy will be enrolled. Patients will be followed up by brain MRI every 3 to 6 months up to 3 years. Neurocognitive function tests will be performed at baseline and after 12 and 24 months. Patients who develop brain metastases will be irradiated with stereotactic (SRT) or whole brain RT (WBRT). The primary endpoint is overall survival. The secondary endpoints are: response rate to radiotherapy of early detected brain metastases, analysis of efficacy of SRT and WBRT; assessment and analysis of neurocognitive functions and QoL in the studied cohorts: QLQ-C30 questionnaire and the California Verbal Learning Test, Color connection test, Benton visual retention test, and verbal fluency test will be carried out.

Discussion: The results of this trial may contribute to changing of LD-SCLC clinical management by deescalating the treatment. There is a lack of prospective, recent studies in LD-SCLC patients with omission of PCI and modern radiation therapy technologies for developed brain metastases. The comprehensive neurocognitive function testing will help to assess the impact of modern radiotherapy (SRT) compared with WBRT and no-PCI in SCLC patients. A subgroup of long-term survivors, who will not develop brain metastases, will not be exposed to unnecessary brain irradiation with its deleterious consequences. The limitation of our study is a lack of parallel randomized control arm. This is a potential source of bias; however, randomized study will be difficult to complete for two major reasons: (1) limited population of LD-SCLC eligible for the study and (2) opinions of our patients, who after information and discussion about benefits and potential harms of PCI, often choose to omit PCI in our practice.

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Keywords: Small-cell lung cancer, Prophylactic cranial irradiation, PCI, Stereotactic radiotherapy, SRT

* Correspondence: sergiusz.nawrocki@uwm.edu.pl

Katedra Onkologii, Wydział Lekarski, Collegium Medicum, Uniwersytet
Warmińsko-Mazurski w Olsztynie, Olsztyn, Poland



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Background

About 15% of patients with lung cancer are diagnosed with SCLC, one third of whom are patients with LD. According to the current standard clinical practice, patients with known LD-SCLC after a radical treatment (chemotherapy and chest radiotherapy) are eligible for prophylactic cranial irradiation (PCI) in case of a good response to treatment and lack of CNS dissemination. PCI aims to reduce the risk of brain metastases development and to improve survival, however, at the expense of possible losses of cognitive functions (attention, perception, memory, executive functions) because of brain irradiation.

This wide clinical acceptance of PCI is based mainly on the results of the meta-analysis published in 1999, which summarizes the observations of patients treated in the 70's and 80's [1]. At that time, the staging of the patient's disease was mostly based on X-ray, biopsy and computed tomography (CT) scans were not performed. The treatment of patients was varied, and the methods (especially radiotherapy) differed significantly from those used nowadays. Three years after randomization, cerebral metastases occurred among 60% of patients in the non-PCI group, whereas only 40% of the patients in the PCI group were diagnosed with metastases to the brain. Based on the results of this meta-analysis, it has been demonstrated that there is a reduction in the risk of brain metastases by 20% after PCI, and an overall survival improvement of about 5% was observed. The patients analyzed in the meta analysis formed a heterogeneous group, which is difficult to compare with patients treated today mainly due to the phenomenon of stage migration. Certainly, in the prophylactically treated PCI cohort, there were some patients with already developed brain metastases.

In 2007, the results of a prospective study evaluating the influence of PCI on the survival and progression of the disease in the group of patients with disseminated small cell lung cancer were published [2]. Similarly, the irradiated group was compared with the group without PCI. It has been shown that after PCI treatment, there is a 2-time reduction in the risk of symptomatic metastases to the brain and an improvement in overall survival.

The introduction of CT and, more importantly, MRI as methods of brain metastases imaging in the last two decades has important implications for interpretation of results of trials with PCI. Even in the era of the common use of CT of the brain in LD SCLC, if in 90% of the cases there were no detected metastases, 6% single metastasis was found and 4% multiple metastases were found when CT was used, whereas in the same group of patients evaluated with the MRI of the brain, 76% were observed as no metastases, 14% were seen with multiple metastases, and 10% for single metastasis [3]. This

comparison of CT and MRI sensitivity in SCLC suggests that many patients treated with PCI in pre-MRI era have had asymptomatic metastases to the brain so that their irradiation was indeed not prophylactic but selective which might influence the reported results upon which current clinical guidelines are based.

Recently, in Japan, a randomized, 3-phase study was performed using MRI imaging [4] in a group with disseminated SCLC (ED-SCLC), in which the PCI in the experimental arm was replaced with watchful observation with regular MRI follow-up. In the group closely followed up without PCI, MRI was performed at regular intervals. PCI reduced the number of diagnosed brain metastases by about 20% in the 24-month follow-up. At the same time, it was demonstrated that PCI does not improve the overall survival of patients. On the contrary, PCI could even have had negative effect on survival (HR = 1,27; statistically non-significant). It could be that patients qualified for PCI experienced significant neurotoxicity of treatment, deterioration of cognitive functioning [5], which might contribute to non-cancer deaths. This study confirmed the belief prevailing in Asian countries about avoiding the PCI in standard treatment of SCLC.

In conclusion, the standard of treatment for patients after radical treatment of small-cell lung cancer is a consequence of research conducted before universal access to MRI, and MRI examination reveals much more metastatic changes to the brain than CT.

To our knowledge, no prospective studies using current diagnostic and therapeutic options for patients with LD small-cell lung cancer have been performed assessing the omission of PCI. In recent years, two retrospective studies evaluating the group of patients in the localized stage have been published. In the Ozawa study in 2015 [6], it was shown that performing PCI in the group of LD SCLC patients may bring questionable benefit in the situation when there is wide access to MRI research, and at the time of recurrence it is possible to perform SRT. A 2016 study [7] has shown that more research is needed to detect patient group with no benefits from PCI. Probably, these are patients older than 70 years and with a tumor larger than 5 cm in the lung. In clinical practice, these criteria are met by most our patients.

Our trial is aimed to fill this gap and to answer several important questions regarding the need of PCI in LD-SCLC in current clinical practice.

Brain irradiation is associated with both acute and chronic toxicity. Acute toxicity associated with PCI is fatigue, alopecia, redness of the scalp, and to a lesser extent, headache and nausea of low intensity. All of these are self-limited [8]. Long-term toxicity, especially delayed neurocognitive disorders are important especially in the group of LD patients with long survival or cure.

Significant neurological and intellectual deficits were observed historically when brain irradiation was performed with simultaneous chemotherapy, in high fractions (3.0 or 4.0 Gy), or to a high total dose, all of which have been shown to be associated with significant late neurotoxicity [9–11].

The probability of severe deficits appears to be much lower with the use of modern irradiation techniques, lower fractions, and total doses. Two historical randomized studies monitored patients after PCI. In the first trial, patients underwent a neuropsychological examination and CT of the head, which were repeated during the follow-up in the group of patients with and without PCI (total dose 24 Gy in 2-Gy daily fractions) [12]. No significant differences in neuropsychological functioning have been described. In the second trial, the cognitive functions and QoL of patients were evaluated both before and after the treatment with the PCI and in the control group [13]. None of these studies showed statistically important PCI-related adverse events; however, the treatment was performed before MRI era so the relevance of these historical results today is limited.

More recently, RTOG 0212 study evaluated a group of 265 patients with LD-SCLC after therapy which included PCI with different total dose and fractionations (25 Gy in ten fractions vs 36 Gy in 2 Gy daily or 24 twice-daily fractions) [14]. A detailed neurocognitive and quality of life assessment was conducted in the studied population. The initial assessment before PCI detected abnormalities in many parameters (language, visual-spatial scan, attention, sequencing, and quickness). The progression of neurological dysfunction was observed in the 12-month evaluation, but chronic neurotoxicity was less common in patients treated with a lower dose (60 vs. 85–89%, $p = 0.02$).

As the treatment of SCLC will hopefully become more and more effective so the potential neurotoxicity of PCI should be minimized or better eliminated in patients who would never develop brain metastases. Research efforts aimed at reducing the neurotoxicity of PCI included, among others, hyperfractionation (1.5 Gy $2 \times$ daily to 30–36 Gy), WBRT with hippocampal sparing, as well as the use of pharmacological methods (cytoprotection), such as memantine [15, 16]. Trials with hippocampal sparing and memantine were small and underpowered so that these methods have not been widely accepted in clinical practice.

The aim of our study is to limit the irradiation of the brain to a group of patients who develop metastases to the brain. The primary end-point of the trial is the assessment of patients' overall survival at 24 months after starting radical treatment with chemoradiotherapy. We assume that careful follow-up with regular MRI and the use of modern irradiation technologies in case of diagnosed early brain metastases will not worsen survival in LD-SCLC patients without PCI. The second primary

endpoint is intracranial tumor control at 12 and 24 months after patient recruitment.

The secondary goals are (1) to assess the risk of developing brain metastases without PCI; (2) to assess the efficacy of radiotherapy of detected early brain metastases, including the feasibility and efficacy of SRT (stereotactic radiotherapy); (3) to monitor patients with neurocognitive tests and QoL questionnaires to assess and compare the influence of treatment on their performance and QoL in subgroups.

Methods/design

Patients diagnosed with LD-SCLC after completed radical treatment (chemoradiotherapy according to current international clinical guidelines) will be eligible for the study (Table 1). Eligible patients should have brain MRI at initial diagnosis with contrast before chemoradiotherapy and after completion of chemoradiotherapy. MRI studies will be acquired on a 1.5-T scanner using a dedicated coil for brain imaging using standard brain imaging MRI protocol: T1-, T2-, diffusion-weighted, and fluid-attenuated inversion recovery (FLAIR)], followed by T1-GD images.

The eligibility criteria and doses for SRT: 1–3 asymptomatic or minimally symptomatic metastatic lesions up to 30 mm in longest diameter, with sum of volumes less than 15 ml (the largest lesion must have less than 30 mm in longest diameter and its volume should be less than 10 ml); SRT doses, specified at 80% isodose: 20 Gy for lesions with diameter equal or less than 20 mm, 18 Gy for 21–30 mm lesions.) PTV will be obtained by adding 2-mm margin to GTV.

Standard WBRT will be performed for patients who do not qualify for SRT; 30 Gy in 10, 2-Gy fractions will be given in 2 weeks.

Statistical assumptions

The sample size of the studied group of patients was calculated using the online SWOG data calculator (Southwest Oncology Group). Based on the published data (in 2013) from our cancer center reporting the survival of patients with SCLC treated in our institution in 2003 to 2006, the expected number of patients was calculated. The 2-year survival was 36% for a group of 138 LD-SCLC treated in our institution [17]. We assumed that the 2-year survival in the studied group will be at least 50%. Taking $\alpha < 0.1$ and a power of 0.80, the required sample size is 80 patients. Patients with diagnosed LD-SCLC, after radical treatment with remission or at least a good response after radical therapy, will be eligible for the study. Patients would have had radical radiotherapy to the chest with chemotherapy according to current international guidelines and institutional protocols. A detailed medical history will be collected regarding SCLC and comorbidities. During the qualification

Project documentation will be protected so that undesirable persons will not have access to it. At any time during the project, the patient has the right to resign from further participation.

There are 3 radiotherapy centers that have declared to take part in this study: (1) Szpital MSWiA z Warmińsko-Mazurskim Centrum Onkologii w Olsztynie, (2) Ośrodek Radioterapii i usprawniania NU-MED w Elblągu, (3) Klinika Onkologii i Radioterapii Gdańskiego Uniwersytetu Medycznego w Gdańsku. The planned enrollment time is 24 months. The first patient was enrolled in Szpital MSWiA z Warmińsko-Mazurskim Centrum Onkologii w Olsztynie in September 2019. In case of enrolment rate slower than expected, additional radiotherapy centers in Poland will be approached to participate in the study.

Abbreviations

PCI: Prophylactic cranial irradiation; LD-SCLC: Limited disease small cell lung cancer; MRI: Magnetic resonance imaging; SRT: Stereotactic radiotherapy; WBRT: Whole brain radiotherapy; QoL: Quality of life; CNS: Central nervous system; CT: Computed tomography; HR: Hazard ratio; ED-SCLC: Extensive disease small cell lung cancer; RTOG: Radiation Therapy Oncology Group; SWOG: Southwest oncology group; RECIST: Response Evaluation Criteria in Solid Tumors; CVLT: California verbal learning test; CCT: Color connection test; BNRT: Benton retention test; VFT: Verbal fluency test

Acknowledgments

None.

Declarations

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Authors' contributions

SN have designed the conception, developed the protocol, wrote, and submitted the manuscript. AS is a doctorate student who took part in designing, wrote a protocol draft and drafted the manuscript, AS together with SN has presented the protocol to the bioethics committee and obtained the approval for the study. AS and SN approved final version of this manuscript. AS's doctorate thesis is going to be based on clinical study results.

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The study is non-commercial (no external commercial funding) academic clinical trial. The Department of Oncology of the University of Warmia and Mazury in Olsztyn has received internal funds to cover study-related procedures (study-related diagnostics and neurocognitive testing) which are not part of routine clinical management of LD-SCLC. Standard diagnostics and treatment is reimbursed by the state agency - National Health Fund). The personnel involved in the study from the Department of Oncology is collecting the data as one of the academic tasks, Dr. Anna Sugajska who is a coauthor of the paper is a PhD student who is responsible for coordination and administration of the study which is her PhD thesis but without additional financial compensation.

Availability of data and materials

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The trial received ethical approval from the local medical university Bioethical Review Board (Komisja Bioetyczna, Uniwersytet Warmińsko-

Mazurski w Olsztynie, Uchwała nr 46/2019). Written informed consent will be obtained from all participants.

Consent for publication

Not Applicable.

The results of the trial will be disseminated through peer-reviewed publications and conference presentations.

Competing interests

The authors declare that they have no competing interests.

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