

Frequency of Silent Brain Metastasis Before Prophylactic Cranial Irradiation in Small Cell Lung Cancer

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Abstract

OBJECTIVES: Prophylactic cranial irradiation (PCI) decreases incidence of brain metastasis and improves survival in patients with limited disease-small cell lung cancer (LD-SCLC) who achieved complete response (CR) after treatment. There is no satisfactory evidence about the necessity of new brain imaging for asymptomatic metastasis immediately prior to PCI. The present study aimed to evaluate the frequency of brain metastasis in SCLC patients without neurological symptoms who are candidates for PCI.

MATERIAL AND METHODS: The data files of 243 patients with SCLC referred for cranial irradiation were retrospectively reviewed. The patients with following characteristics were enrolled to the study; 1) LD-SCLC patients with CR after chemoradiotherapy who are candidates for PCI. 2) No neurological signs or symptoms of brain metastasis after chemoradiotherapy. 3) Having brain imaging at initial diagnosis and before PCI.

RESULTS: Ninety-nine patients (83 male, 83.3%) were included in this study. Median age was 60 years. Time interval between initial and reevaluation for brain metastasis was median 5.5 months (range; 4.7-7.1). Asymptomatic brain metastasis rate was 20.2% (18/99).

CONCLUSION: Even if local disease is under control, asymptomatic brain metastasis is not rare. Therefore, patients who are candidates for PCI after completion of chemoradiotherapy should be reimaged for brain metastasis before PCI.

KEYWORDS: Prophylaxis, brain, imaging, SCLC, metastasis

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INTRODUCTION

Approximately 30% of patients with small cell lung cancer (SCLC) initially staged as limited disease (LD) are candidates for combined model treatment (CMT) with curative intent. CMT with sequential or concurrent chemoradiotherapy (CRT) achieves complete response (CR) in 50%-60% of patients. However, the blood-brain barrier precludes the penetration of chemotherapeutic agents to the brain. The risk for brain metastasis occurrence is approximately 50% in the first 2 years after diagnosis [1]. Silent brain metastasis may develop at some point during the treatment course even in patients with a CR of intrathoracic disease. Emerging evidence suggests that prophylactic cranial irradiation (PCI) in patients with LD-SCLC who have achieved CR after CRT reduces the incidence of brain metastasis and improves survival [2,3]. However, the recommended dose for whole brain radiotherapy in patients with brain metastasis differs from the preferred dose for PCI [2].

Lung cancer guidelines recommend routine initial evaluations for brain metastasis with contrast-enhanced (CE) magnetic resonance imaging (MRI) or computed tomography (CT) in patients with SCLC [4,5]. The necessity of radiological reevaluation to detect asymptomatic brain metastasis before PCI has not been remarked on the guidelines, contrary to recommendations for the initial staging of SCLC.

Manapov et al. [6] detected silent brain metastasis in 32.5% of small patients size with LD-SCLC who were complete responders to CRT with pre-PCI second CE-MRI. However, there is a paucity of data on the frequency of asymptomatic brain metastasis in patients who are candidates for PCI. The present study aimed to evaluate the frequency of brain metastasis in SCLC patients without neurological symptoms who are candidates for PCI.

MATERIAL AND METHODS

Medical records of all consecutive patients with histologically proven SCLC, who were referred for palliative and prophylactic cranial irradiation to the Department of Radiation Oncology at the Chest Disease and Surgery Training and Research Hospital between January 2012 and December 2013, were retrospectively reviewed. Patients who were referred for PCI

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among these patients were extracted and further evaluated according to inclusion criteria. Patients who met the following inclusion criteria were included in the study: LD-SCLC patients who have achieved near CR or CR after CRT, patients without any neurological signs or symptoms of brain metastasis after CRT, patients who underwent CE brain imaging at initial diagnosis and before PCI.

In our hospital, standard work-up for initial staging in patients with lung cancer includes CE-CT of the chest/upper abdomen, bone scintigraphy, and CE-CT/MRI of the brain or CE-CT of the chest, PET/CT scans with [18F]-fluorodeoxyglucose, and CE-CT/MRI of the brain. CE-MRI is used as a problem solving tool for patients in whom CE-CT of the brain did not provide sufficient information for metastasis. Response evaluation (RECIST 1.1 criteria) is done with CE-CT of thorax/upper abdomen in 3-4 weeks after completion of the treatment and physical examination. Patients who are candidates for PCI are reevaluated with CE-CT and MRI of the brain and neurological symptom and signs.

The study was planned according to the World Medical Association Declaration of Helsinki (2013).

Statistical Analysis

Data were analyzed by using the Statistical Package for the Social Sciences version 16.0 (SPSS Inc.; Chicago, IL, USA) statistical software.

RESULTS

Treatment data of 243 patients with SCLC who were referred for cranial irradiation to the Department of Radiation Oncology were reviewed. Ninety-nine patients (83 males, 83.3%) who met the inclusion criteria were included in this study. Median age was 60 years (44-81). Initial evaluation for brain metastasis was performed with CE-CT in 85.9% (85/99) and with CE-MRI in 14.1% of the patients (14/99). One patient with abnormal CT findings with suspected brain metastasis underwent further MRI testing. This patient was assessed in the MRI group. CRT was performed sequentially in 76% (75/99) and concurrently in 14% (14/99) of the patients. All patients received platinum-etoposide combination chemotherapy. Prior to PCI, reevaluation for brain metastasis was performed with CE-CT in 58.6% (58) and with CE-MRI in 41.4% (41) patients. We were skeptical of three cases included in the MRI group due to the cranial CT of these patients in terms of metastasis. Fourteen patients who had cranial MRI at initial staging were reevaluated with MRI. Median time interval between initial staging and reevaluation for brain metastasis was 5.5 months (range: 4.7-7.1).

Asymptomatic brain metastasis was detected in 20.2% (18/99) of the patients before PCI. In 50% (9/18) of them, metastasis was detected with MRI. Only 1 of 9 who had cranial MRI at reevaluation also had MRI at the first staging.

DISCUSSION

In our study, the frequency of asymptomatic brain metastasis was 20.2% in patients with CR after CRT and who were candidates for PCI.

Most chemotherapeutic agents cannot pass through the blood-brain barrier [7,8]. Because of that, the brain is considered the first site of recurrence in an aggressive tumor such as SCLC. Many randomized studies showed that in patients with LD-SCLC exhibiting CR after CRT, PCI reduces the incidence of brain metastasis and improves survival rate [2,9-12]. Timing of PCI is a matter of debate. There was a tendency toward a decrease in the incidence of brain metastasis with early PCI [2,12]. However, early PCI is not possible in all patients for various reasons. The likelihood of developing brain metastasis increases with the increased interval between the start of treatment and assessment of PCI. This interval is mostly more than 4 months in patients with SCLC [3]. Therefore, brain metastasis might develop during the combined treatment for SCLC. In our patient group, the median interval was 6.3 months. Manapov et al reported the time between SCLC diagnosis and second cranial imaging as 7 months (range: 4-10 months) [6].

Manapov et al. [6] detected silent brain metastasis in 32.5% (13/40) of LD-SCLC complete responders to CRT with pre-PCI second CE-MRI. In our study, we detected asymptomatic brain metastasis in 20.2% (18/99) of LD-SCLC patients with CR in the pre-PCI period. The lower frequency in our study population may be due to the shorter interval between SCLC diagnosis and the second cranial imaging.

There are several important limitations to our study mainly due to the retrospective study design. Different imaging methods were used at the initial staging and pre-PCI period in some patients. Owing to the low accessibility of cranial MRI in daily practice, half of our patients were evaluated with cranial CT at initial diagnosis. Guidelines recommend cranial CT or MRI at initial staging evaluation [4]. However, some studies show that cranial MRI is superior to CT in detecting silent brain metastasis [13].

Consequently, even if local disease is under control, asymptomatic brain metastasis is not rare. Therefore, patients who are candidates for PCI after completion of CRT should be reimaged for brain metastasis before PCI.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: This is a study analyzing of the patient data files. Because of that, patient informed consent was not obtained.

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REFERENCES

1. Seute T, Leffers P, Ten Velde GP, Twijnstra A. Neurologic disorders in 432 consecutive patients with small cell lung carcinoma. *Cancer* 2004;100:801-6.
2. Auperin A, Arragiada R, Pignon JP, et al. Prophylactic cranial irradiation in small cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999;341:476-84.
3. Tai P, Assouline A, Joseph K, et al. Prophylactic cranial irradiation for patients with limited-stage small-cell lung cancer with response to chemoradiation. *Clin Lung Cancer* 2013;14:40-4.
4. Gaspar LE, Gay EG, Crawford J, et al. Limited-stage small-cell lung cancer (stages I-III): observations from the National Cancer Data Base. *Clin Lung Cancer* 2005;6:355-60.
5. Jett JR, Schild SE, Kesler KA, et al. Treatment of Small Cell Lung Cancer. *Diagnosis and Management of Lung Cancer*, 3rd ed: American College of Chest Physicians. Evidence-Based Clinical Practice Guidelines. *Chest* 2013;143:e400S-e419S.
6. Manapov F, Klautke G, Fietkau R. Prevalence of brain metastases immediately before prophylactic cranial irradiation in limited disease small cell lung cancer patients with complete remission to chemoradiotherapy: A single institution experience. *J Thorac Oncol* 2008;3:652-5.
7. Wilhelm I, Molnár J, Fazakas C, et al. Role of the blood-brain barrier in the formation of brain metastasis. *Int J Mol Sci* 2013;14:1383-411.
8. Svokos KA, Salhia B, Toms SA. Molecular biology of brain metastasis. *Int J Mol Sci* 2014;15:9519-30.
9. Bunn PA Jr, Kelly K. Prophylactic cranial irradiation for patients with small-cell lung cancer. *J Natl Cancer Inst* 1995;87:183-90.
10. Gregor A, Cull A, Stephens RJ, et al. Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC). *Eur J Cancer* 1997;33:1752-8.
11. Meert AP, Paesmans M, Berghmans T, et al. Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis. *BMC Cancer* 2001;1:5.
12. Sas-Korczynska B, Korzeniowski S, Wójcik E. Comparison of the effectiveness of „late“ and „early“ prophylactic cranial irradiation in patients with limited-stage small cell lung cancer. *Strahlenther Onkol* 2010;186:315-9.
13. Seute T, Leffers P, Ten Velde GP, Twijnstra A. Detection of brain metastases from small cell lung cancer. Consequences of changing imaging techniques (CT versus MRI). *Cancer* 2008;112:1827-34.