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ORIGINAL ARTICLE

Who may benefit from prophylactic cranial irradiation amongst stage III non-small cell lung cancer patients?

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Summary

Purpose: *To identify a high risk group of non-small cell lung cancer (NSCLC) patients who may benefit from preventive strategies in order to reduce the rate of brain metastasis.*

Methods: *Two-hundred stage IIIA (47.5%) and IIIB (52.5%) NSCLC patients were analysed (median age 61 years, range 29-82). Pathological diagnosis consisted of 27% adenocarcinomas, 48.5% squamous cell carcinomas, and 24.5% non-small cell lung carcinomas. Brain metastasis rate was calculated and compared in relation to age, gender, stage, histology, chemotherapy and surgery.*

Results: *Median follow-up was 15 months (range 2-65), and the 2-year survival rate was 35%. Two-year incidence of brain metastasis was 23%. In univariate analysis, 32.9% of the patients younger than 60 years of age developed brain metastasis, in contrast to 15.3% of those older than 60 years (p=0.003). Brain was the first metastatic site in younger patients (44.4%) which was significantly higher than in the older age group (23%) (p=0.03). Adenocarcinoma had higher risk (39.6%) than squamous cell carcinoma (15.7%) for brain metastasis (p<0.0001). Patients 60 years old or younger with adenocarcinoma (53.3%) had higher risk for brain metastasis than all the others (18%; p<0.0001).*

Conclusion: *In locally advanced NSCLC patients, age and adenocarcinoma histology represent high risk factors for early development of brain metastasis. Many of the failures are isolated brain lesions and future studies are required to assess the benefit of preventive strategies in selected patients.*

Key words: *brain metastasis, non-small cell lung cancer, prophylactic cranial irradiation*

Introduction

NSCLC is a highly lethal disease and better local control and longer survival can be achieved with combined-modality therapies [1]. Tri-modality therapy [chemotherapy (CT), radiation (RT), and surgery] has been administered in several studies and the median and 2-year survival rates have been reported as 15-25% and 37-66% months [2-4]. Multimodality therapies reduce the extracranial metastasis rate, however, they have not any impact on intracranial relapse rates [5,6]. Hence, brain is still one of the most frequent sites of metastasis in lung cancer. Even more, brain is the first site of relapse in up to 30% of NSCLC patients during follow-up [6-8]. It is well-known that brain failure is high in limited stage small cell lung cancer (SCLC) and prophylactic cranial irradiation (PCI) is recommended in guidelines for decreasing the frequency of brain metastases [9]. This approach may also help reduce the rate of brain metastases in NSCLC patients. However, whole brain radiotherapy (WBRT) may have a negative impact on cognitive functions. Hence, defining a high risk group for brain metastasis development in order to administer PCI is crucial.

In this retrospective analysis, we aimed to identify the high risk group of NSCLC patients

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who might benefit from preventive strategies and improve the quality of life by reducing the rate of brain metastasis.

Methods

The medical records of pateints of our radiotherapy unit were retrospectively reviewed and 200 locally advanced (stage IIIA and IIIB) NSCLC patients treated between 1997 and 2010 were included in the study. Characteristics of patients, disease and treatments are depicted in Table 1. All of the patients received conventional RT in 1.8-3 Gy daily fractions, either 2-D (1997-2005) or 3D-conformal planning (2005-2010). Median thoracic RT dose was 5870 cGy (range 3000-7000) to the primary tumor with or without adjacent lymph nodes. Staging was done according to the TNM classification of 1997 [10,11]. Patients were treated with 3 modalities (RT, chemotherapy, surgery) in different sequence and periods during their follow-up: 22 (15%) were operated before or after chemoradiotherapy (CRT), 159 (73%) received chemotherapy alone. Chemotherapy was administered concurrently or sequentially in 63% of the patients, whereas RT alone was delivered to 26 (13%) patients. Before RT/CRT all patients had a metastatic work-up including brain evaluation with magnetic resonance imaging (MRI). Following primary treatment and during follow-up patients with any neurological and/or cognitive symptoms were evaluated with brain MRI.

Statistics

The endpoint of the study was overall survival which was calculated from the end of RT to death from any cause. Two-year actuarial brain metastasis development rate and the rate of first failure in the brain were also calculated. Factors were divided regarding to patient (age, gender), tumor (stage, histology) and treatment (surgery, chemotherapy), and chi-square test was used for comparison between groups in terms of brain failure. Univariate log-rank test and multivariate logistic Cox regression analyses were carried out to identify any relationship of the factors related to the development of brain metastasis. Median overall survival and 2-year actuarial brain metastasis development rate were calculated. Kaplan-Meier method was used to generate curves concerning survivals and time to brain metastasis development. All analyses were performed using the SPSS software, version 17 for Windows.

Results

The median follow-up time was 15 months (range 4-65). Five patients were lost to follow-up. The 2-year overall survival rate was 35.1% (Figure 1). All patients were subjected to RT to the primary tumor and the lymph nodes. Of 195 patients, 45 (23%) were diagnosed with brain metastasis after treatment and 2-year actuarial rate for brain metastasis development was 23%. Median overall survival after brain metastasis diagnosis was 4 months (range 1-18). Twenty-nine (64.4%) of these patients experienced brain metastases as the first site of distant failure. Nineteen (42.2%) of the patients with brain metastasis presented with 1-3 lesions and the remaining had more than 3 lesions.

Results of univariate and multivariate analysis are summarised in Table 2. The incidence of brain metastases was 32.9% in patients aged 60 years or younger, whilst it was 15.3% in patients older than 60 years of age (p=0.005; Figure 2). The

Table 1. Patients, disease and treatment characteristics

Characteristics	*N (%)*
Age (years)	
Median	61
Range	29 - 82
Gender	
Male	171 (85.5)
Female	29 (14.5)
Stage	
IIIA	95 (47.5)
IIIB	105 (53.5)
Histology	
Adeno	57 (28.5)
Squamous cell	114 (57)
Non-small cell	29 (14.5)
KPS*	
Median	80
Range	50 - 100
Radiotherapy (cGy)	
Median	5870
Range	3000 - 7000
Chemotherapy	
Yes	147 (73.5)
No	53 (27.5)
Chemotherapy regimens	
Platinum-based	74 (37)
Platinum and taxane-based	62 (31)
Other	40 (20)
Taxane-based	24 (12)
Surgery	
Yes	55 (27.5)
No	145 (32.5)

*Karnofsky performance status

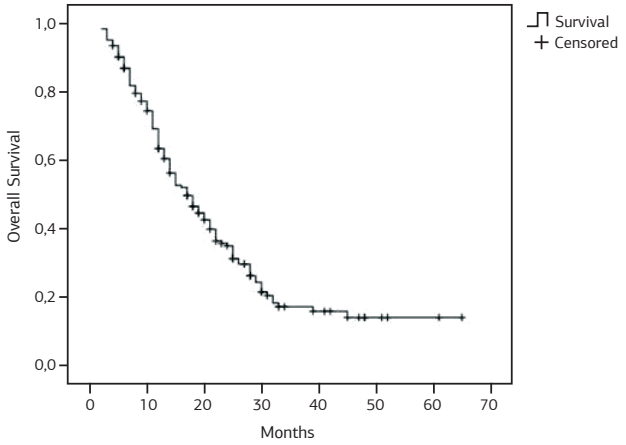

Figure 1. Kaplan-Meier overall survival of all patients.

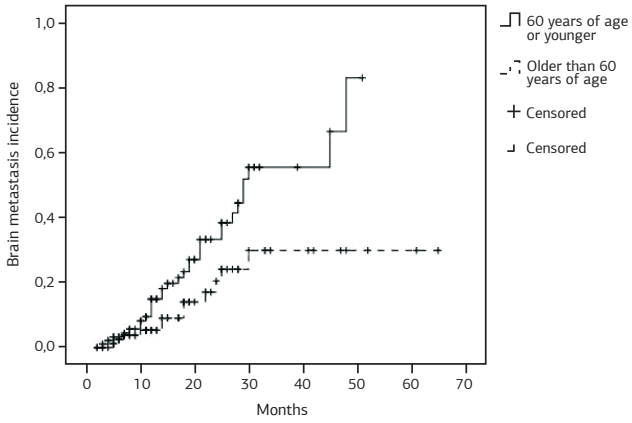

Figure 2. Time to brain metastasis development according to age (p=0.005).

first site of metastasis was the brain in 44.4% of the patients who were 60 years or younger and 23% in patients older than 60 years (p=0.03). According to histology, the incidence of brain metastasis was 39.6% for adenocarcinoma and 15.7% for squamous cell carcinoma (p<0.0001; Figure 3). In adenocarcinoma brain was the first site of metastasis in 55% of the patients and 23.5% in squamous cell cancer patients (p=0.01). Other factors including gender (p=0.15), stage (p=0.15), chemotherapy administration (p=0.11) and surgery of the primary disease (p=0.37) were not associated with significant univariate risk for brain metastasis. In patients aged 60 years or younger and having adenocarcinoma histology the incidence of brain metastasis was 53.3% and this was significantly higher compared with older patients who had squamous cell or non-small cell lung cancer histology (18%; p<0.0001; Figure 4). However, none of the parameters showed statistical significance in multivariate analysis

Discussion

Despite improvements in the local management of NSCLC, patients may still face brain failure and PCI can be a strategy for those patients who have a high risk for development of brain metastasis. Previously, a clear positive effect of PCI has been shown in SCLC patients [12,13] with significant reduction of brain metastasis without noticeable neurotoxicity [14,15]. In randomized controlled trials the incidence of brain metastasis was reduced from 12-54% to 0-14% [3,16-22]. Several prospective studies without brain metastasis as primary endpoint and retrospective studies evaluating PCI for NSCLC have been published [16,23]. These studies have consistently shown a decrease and/or delay in brain metastasis development with PCI. Stuschke et al. [16] showed that 30 Gy external RT decreased brain metastasis rate from 54 to 13% with PCI. Most brain metastases occur within 2 years of diagnosis [5,8,24-26].

According to our study, patients at greater

Table 2. Results of univariate and multivariate analyses

Variables	*2-year survival rate from brain metastasis development %*	*Univariate p-value*	*Multivariate p-value*
Age (years)			
≤60	32.9	0.005	0.06
>60	15.3		
Gender			
Male	22.5	0.15	0.91
Female	33.3		
Stage			
IIIA	32.7	0.15	0.07
IIIB	21.1		
Histology			
Adeno	42.3	<0.0001	0.33
Non adeno	12.9		
Surgery to primary			
No	23	0.37	0.31
Yes	16		
Chemotherapy			
No	13.6	0.11	0.12
Yes	27.6		
Age (years) and histology			
(adenoCa)≤60	53.3	<0.0001	0.11
All others	18.4		

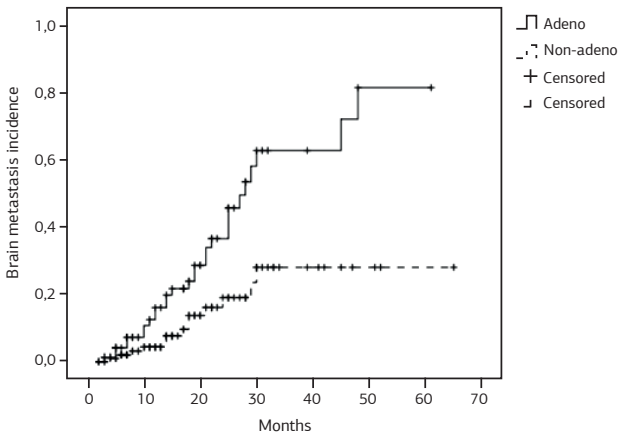

Figure 3. Time to brain metastasis development according to histology (p<0.0001).

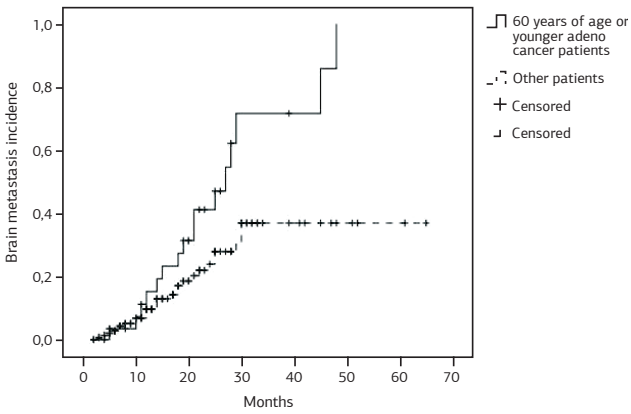

Figure 4. Time to brain metastasis development according to age and histology (p<0.0001).

risk are relatively younger and they mainly have adenocarcinoma histology. In these patients, brain is the first site of distant failure, having more aggressive disease with multiple brain metastases. Most of our patients (63%) received either concomitant or sequential CRT and 73% of them received chemotherapy at any time of progressive disease. So, even with multiple and intense cycles, chemotherapy may not prevent micrometastasis to the brain. In order to avoid brain failure, recommending PCI might be a reasonable option, especially for patients that are 60 years old or younger and/or have adenocarcinoma histology. One may say that the most important concern is the decline of the cognitive functions and quality of life in these patients. However, brain metastasis itself may worsen the patients' quality of life due to the development of a broad spectrum of severe/grave symptoms. Despite these concerns for irradiation, PCI may improve the quality of life by achieving partial or complete responses and reducing new intracranial relapses. In addition, cognitive functions can be avoided with protection of the hippocampal area with modern RT techniques like intensity modulated radiation therapy (IMRT).

In terms of protecting the normal brain functions and quality of life, the high risk group of patients for PCI in NSCLC should be well defined. Median time for relapse in the brain is 5.7-11.7 months [5,8,24,25]. Therefore, PCI can be immediately recommended when the hopefully curative treatment to the primary site has been completed.

Several factors have been associated with increased risk of brain metastasis, including histology (squamous vs nonsquamous), age (younger than 50 years vs older), nodal status at resection (pN0 vs residual nodal disease), and induction chemotherapy protocols (taxane-platinum combination vs other platinum-based regimens) [7,15,16,24-30]. The influence of histology on the risk of brain metastasis had been observed by other authors as well [25,26,28,30]. Gaspar et al. [26] showed that patients in stage IIIA and B NSCLC, with non squamous histology and age less than 50 years had increased risk for brain metastasis. The 2-year cumulative risk of failure in the brain for patients with adenocarcinoma and squamous cell carcinoma were 22% and 10%, respectively. Similar to our study, Ceresoli et al. [28] reported that stage IIIA and B NSCLC patients were more likely to develop brain metastases when younger than 60 years of age.

In conclusion, our study demonstrated a high risk for early relapse in the brain in stage IIIA and B NSCLC patients, particularly in those younger than 60 years and adenocarcinoma histology, with high probability of being isolated brain metastasis. Future studies are required to assess the benefit of PCI in selected high risk patients.

Authors' contributions

IAC was involved in the conception and design of the study; acquisition, analysis and interpretation of data; drafting the manuscript and revising it critically for important intellectual content and giving final approval of the version to be published.

ZA was involved in the design of the study; acquisition and analysis of data; drafting the manuscript and giving final approval of the version to be published.

BMA was involved in the conception and design of the study; acquisition, analysis and interpretation of data; drafting the manuscript and revising it critically for important intellectual content and giving final approval of the version to be published.

PFY was involved in drafting the manuscript and revising it critically for important intellectual content and giving final approval of the version to be published.

UA was involved in the conception and design of the study; acquisition, analysis and interpretation of data and giving final approval of the version to be published.

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