

Small cell lung cancer and brain metastasis

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10 Summary

Small cell lung cancer (SCLC) is a relatively common lung malignancy and generally has a bad prognosis. This cancer can be accompanied by a wide range of neurologic diseases, ranging from paraneoplastic syndromes to brain metastases. This thesis focuses mainly on the brain metastases related to SCLC.

Chapter 1 comprises a brief general introduction and outlines this thesis' objectives.

Chapter 2 details the results of a longitudinal neurologic follow-up of 203 consecutive patients with SCLC. The most recurring neurologic complication was brain metastasis. A total of 79 patients were diagnosed as having brain metastases, of these 27 had been diagnosed prior to any treatment, and in the remaining 52 the diagnosis was made either during or after treatment of the lung carcinoma. The cumulative risk of developing brain metastasis was 47% in limited disease patients and 69% for extensive disease patients. Patients diagnosed with brain metastases prior to SCLC treatment had a significantly higher survival rate than patients diagnosed with brain metastases in later stages of the disease. Histopathologic examination of the brain metastases in 15 patients resulted in a different diagnosis for 2 patients (13%); other primary tumor n=1, no SCLC after having achieved complete remission for SCLC n=1. The discrepancy of the initial histologic diagnosis and that of the brain metastases might be explained by tumor heterogeneity,

tumor changes influenced by treatment or time, and the development of an other primary tumor in the same patient. The other neurologic complications of SCLC are briefly described.

Using the guidelines provided by the Pathology Panel of the International Association for the Study of Lung Cancer the predictive value of the histologic subclassification for neurologic complications are discussed in chapter 3. A retrospective revision was made of the material used to establish the initial SCLC diagnosis of the 239 patients participating in a longitudinal neurologic follow-up study. The subclassification of the histologic as well as cytologic material of these patients resulted in the following: classic cell type n=178, variant cell type n=32 (mixed cell type n=31, combined cell type n=1), and non-classification n=29 (only autopsy material available n=14, initial diagnosis altered n=8, and slides missing n=7). The relationship between developing brain metastases or the duration of brain metastatic-free intervals and the histologic subtyping did not appear to be of any statistical significance. Those patients suffering neurologic complications of paraneoplastic syndromes all had classic small cell subtype. Notwithstanding that this result coincides with the result of the experimental research where classic subtype was characterised by a greater manifestation of neuro-endocrine signs, this finding merely represents a trend. Other non-metastatic complications appeared not so much related to the subtype, but

more so dependant on treatment method or coincidence. The conclusion being that we find no clinical significance for histologic subclassification.

Chapter 4 and 5 continues with a discussion of the validity of using cranial computed-tomography (CT) scan and magnetic resonance (MR) imaging in staging patients with SCLC. As part of the initial staging research 57 consecutive patients underwent an examination by a neuro-oncologist and a cranial CT scan. These patients remained under the controlled supervision of the neuro-oncologist (during the first year quarterly, and biannually thereafter). A cranial CT scan was repeated if there was any suspicion of brain metastases. Three patients were excluded from the trial for various reasons (cerebrovascular accident n=2, leptomeningeal metastases n=1). Of the remaining 54 patients, 50 were neurologically asymptomatic and 4 were symptomatic. In 3 patients the use of CT scan showed aberrations symptomatic to brain metastases. The remaining patients showed no signs of possible metastases.

The same trial was carried out in 40 consecutive patients but this time using MR scan. Movement artefacts excluded 1 patient from this trial. Of the 11 patients in which the MR scan showed deviations similar to metastases 3 were neurologic asymptomatic. The clinical staging of these 3 patients did not change since they already had extensive disease. Of the 14 patients with deep hyperintensive non-Gadolinium enhanced white matter

lesions, 4 were neurologic symptomatic. Two of these 4 developed brain metastases within 6 months. In the interim, part of the deep hyperintensive non-Gadolinium enhanced white matter lesions became contrast enhanced. We concluded that the CT scan is not superior to neurologic examination for detection of brain metastases in SCLC patients. A MR scan, however, can contribute significantly to the early detection of brain metastases and contribute to the primary staging procedure. Deep white matter hyperintensities can make brain metastases undetectable in neurologically symptomatic patients.

Chapter 6 reports on the effectiveness and safety of prophylactic cranial irradiation (PCI) in a prospectively followed group of 203 consecutive SCLC patients. Of the 37 limited disease patients who had achieved complete remission, brain metastases developed in 3 of 17 treated with PCI, versus 8 of 20 non-PCI treated patients. The number of brain metastases did not differ significantly. Patients who underwent PCI treatment did have a considerably longer brain metastatic-free interval and survival rate. It should be noted that this was a non-randomized study, and that the remaining treatment course of the SCLC was not totally equal, as well as the fact that the patient population was too small to show any signs of the effects of PCI. Whether brain metastases developed or not seemed largely dependant on the behavior of the primary tumor.

The early as well as the later possible adverse effects of the treatment are covered in detail. Half of the 18 long-term surviving patients had undergone PCI. These patients had a marked increase in cognitive function associated complaints. There was also an increase in cranial CT scan or MR abnormalities, all of which maybe attributed to PCI treatment. When taken in conjunction with existing literature concerning the use and adverse effects of PCI, it becomes plausible that PCI treatment at least has a synergetic effect on the potential neurotoxic treatment of SCLC. The extent and severity of toxicity to the central nervous system as well as the effectiveness of PCI remains unknown.

Cognitive functioning of SCLC patients is the subject matter of chapter 7. In this study 32 consecutive patients underwent neuropsychologic testing, prior to, during, and after treatment with chemotherapy and/or PCI. During the same period these patients were examined neurologically. Patients with brain metastases were excluded from the neuropsychologic follow-up study. The pretreatment average results were compared to those of a control group with similar age, sex, and intelligence quotient. As a result of either brain metastases or premature death only 14 patients participated in the second trial session, 11 patients in the third and fourth trial session, and 5 patients in the last session. In patients with no indication of brain metastases neurologic deviations were not present. Less serious complaints

of concentration and memory, word finding problems, and libido deficiency were indicated. When compared to the matched control group, the patient group clearly performed worse on the 15 Word Auditory Verbal Learning task, the Stroop color-word test and the Trailmaking test. No further treatment-related negative consequences were established. We concluded that the disease itself can negatively the patients cognitive functioning abilities. Precluding a longitudinal follow-up the effects of the disease and those of the treatment are interchangeable.

Chapter 8 presents the results of research on 59 long-term SCLC survivors. Various long treatment centres in the Netherlands were approached and long-term survivors were asked to voluntarily take part in neurologic, neuropsychologic, and neurologic testing. Since the primary objective of the study was to determine the neurotoxicity of the treatment 8 patients were not able to take part for various reasons (cerebrovascular accidents $n=4$, no chemotherapy or PCI treatment $n=2$, Korsakov syndrome $n=1$, severe head trauma $n=1$). The neurologic findings are described in 21 patients treated solely with chemotherapy (group 1), 19 patients treated with PCI subsequent to chemotherapy (group 2), and 11 patients treated with concurrent or sandwiched PCI and chemotherapy (group 3). A statistical comparison is made of the quantifiable neuropsychologic and neuroradiologic data. The neuropsychologic test

results were compared between the study groups and also to the results of a healthy group matched for age, gender, and education level. Even though PCI treated patients complained more of cognitive dysfunction and though neurologic abnormalities were more often present in this group of patients (in group 3 more than in group 2), statistically these group differences could not or at best only partially be explained when neuropsychologic and neuroradiologic data were compared. Among the three patient groups there were no neuropsychologic differences. There was, however, a statistically significant difference with the control group. The statistics for the severity of cortical atrophy and the presence of ventricular enlargement and cerebellar atrophy between the three groups was not representative. Yet patients in group 3 did show meaningful statistic differences where white matter lesions are concerned. Namely they had more white matter lesions than the two other groups. Patients in group 3 had a significantly longer survival rate. The three patients groups did not differ in age, gender, education level, cardiovascular risk factors or research methods. The retrospective study of these long-term SCLC survivors concludes that no indications were found for serious PCI related toxicity. The neuropsychologic differences with the healthy control group and the lack of significant disparity among the three patient groups may be indicative of the fact that the patient groups were suffering from SCLC and/or chemotherapy related effects.

The general discussion once again examines the results of all the studies and draws the following conclusions:

- the most frequent neurologic complication of small cell lung cancer are brain metastases.
- the course of the disease when compounded by brain metastases is related to the point when the brain metastases are diagnosed.
- histologic subclassification of the International Association for the Study of Lung Cancer is of no significance in predicting neurologic complications.
- in contrast to computed tomography scanning, is magnetic resonance imaging clearly superior to neurologic examination in helping to establish an early diagnosis of brain metastases.
- hyperintensive white matter lesions impede the identification of brain metastases in neurologic symptomatic patients.
- a longitudinal study is necessary to adequately determine the neurotoxicity of the treatment in small cell lung cancer.
- the overall diminished condition of the patients, either due to the disease small cell lung cancer itself or chemotherapy must be taken into consideration when explaining the cognitive dysfunction in long-term survivors of small cell lung cancer
- retrospective study of 59 long-term survivors of small cell lung cancer could not establish indications of frequent and severe prophylactic cranial irradiation related toxicity.

- subtle cognitive impairment can have a huge impact on daily life functioning in long-term small cell lung cancer survivors.
- it is important to determine subtle changes in cognitive functioning in order to better understand and eventually prevent central nervous system toxicity associated with small cell lung cancer treatment.