Editorial

Prophylactic cranial irradiation for stage IV small cell lung cancer, live longer or reduce morbidity of brain metastases?

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After the publication of the results of the Japanese study (1) on the apparent lack of benefit by prophylactic cranial irradiation (PCI) it is worthwhile to reconsider all issues around this important clinical problem.

Awareness of the high frequency of symptomatic brain metastases in small cell lung cancer (SCLC) patients dates back to the seventies of the last century, and was estimated as being 80% in patients living at 2 years (2). At diagnosis the initially reported 10%, as detected by contrast-enhanced CT, is in reality >20% if magnetic resonance imaging (MRI) is used (3).

Symptomatic brain metastases cause considerable morbidity and greatly affect the quality of life of those affected (4). Attempts to prevent it by giving so-called PCI have been reported in a large number of studies (5), universally resulting in a reduction in incidence of brain metastases but not demonstrating survival benefit. As PCI was associated with acute and long-term side effects (6), there remained substantial reluctance to consider it as part of standard therapy. After prospective evaluation of neurocognitive functioning of PCI with lower fraction doses, lower total dose and no concomitant chemotherapy it was found that there was no increase in neurological sequelae (7,8). Finally, a meta-analysis of seven randomized studies demonstrated that patients achieving a complete response after systemic therapy +/– local radiotherapy (RT) benefitted from PCI, not only by a considerable lower incidence of brain metastases, but also with prolonged overall survival with an absolute increase at 3 years of 5.4% (9). This approach improved the outcome of the patients treated with curative intent, almost all been staged as having locoregional disease, formerly described as "limited disease" (10). However, for the majority of patients, morbidity due to brain metastases remained an important problem. Attempts of maintenance therapy with drugs supposed to cross the blood-brain barrier (11) failed, and also small brain metastases were not affected by standard dose chemotherapy, suggesting the presence of a still effective blood-brain barrier in this situation (12,13).

Despite the relatively good sensitivity of SCLC for RT, the response rate of symptomatic brain metastases after whole brain radiotherapy (WBRT) is only 50% and usually short-lived (14). Furthermore, systemic therapy has only limited efficacy, independent of the use of potentially non-cross resistant agents (15-17). The response rate became higher if adding WBRT to chemotherapy, but survival was not affected (18). Attempts to diagnose brain metastases before causing morbidity by computer tomographic surveillance failed as well (19).

All these studies clearly demonstrated that early detection methods, as well as available treatment options, except PCI, failed in preventing considerable morbidity caused by symptomatic brain metastases.

Based on these observations the EORTC initiated a

study (20) with as primary endpoint the development of symptomatic brain metastases. For this a list of key symptoms was specified: signs of increased intracranial pressure, headache, nausea and vomiting, cognitive or affective disturbances, seizures, and focal neurological symptoms. If any of these was found, this had to be followed by contrast-enhanced CT or MRI of the brain, confirmation by imaging was necessary to be considered as symptomatic brain metastases. Survival was only a secondary endpoint, based on the assumption that treating a single site, in a disease with usually progression at multiple sites (21) and rarely only in the brain (14), would not likely result in improved survival. The study clearly showed that PCI reduced the frequency of symptomatic brain metastases considerably, and—unexpectedly—resulted in a somewhat longer median survival of 6.7 *vs.* 5.4 months, as well as doubling of the 1-year survival rate from 13.3% to 27.1%. Based on this outcome PCI became part of the treatment guidelines for stage IV SCLC patients responding to chemotherapy (22,23). The explanation for the improved survival is not clear. The frequency of disease progression is identical in both arms, but there was a higher rate of 2nd line chemotherapy at progression in the PCI group. Apparently the patients in the PCI group were in a better condition at the time of PD and through that would more likely tolerate further therapy.

The EORTC study was performed in a way as close as possible to daily practice in the beginning of this century. It did not include any extra investigations before entry or during follow-up. More sensitive detection methods, such as MRI, were not advised, nor was imaging of the brain before PCI mandatory. This makes it likely that a substantial number of the patients in the study had at the time of PCI asymptomatic brain metastases. Although a new analysis of the EORTC dataset focusing on this aspect, showed that its impact on the overall outcome was not detectable (24), it still led to discussions on the role of PCI especially in stage IV SCLC (25).

The outcome of this new randomized study leads to further questioning whether PCI is needed (1). The major differences in design, compared to the EORTC study, are evaluation of the brain by MRI before the start of PCI and after chemotherapy, and evaluation by brain-MRI every 3 months for a year and subsequently at 18 and 24 months. The evaluation by MRI after chemotherapy excludes the possibility of possible benefit by PCI in patients with visible but still asymptomatic brain metastases, and as such this makes it a purer approach than accepting all chemotherapy responders as done within the EORTC study. However, the most important difference between the two studies is—amazingly—the choice of overall survival as the primary endpoint in the Japanese study. As stated above, treating a single site of an extensively disseminated disease with poor outcome after chemotherapy, will very unlikely result in overall survival benefit. The investigators decided to take time to brain metastases as secondary endpoint. Although the authors mention how this was defined, at the time of protocol specified brain MRI or MRI or brain CT for symptoms suggestive of brain metastases, they do not report specifically on the latter group but only give percentages of brain metastases at 6, 12 and 18 months. At all these points the PCI group has a lower incidence. The reirradiation in the PCI group (25 of 54 patients) suggests that these patients were suffering from symptomatic brain metastases, how many of the 64 (out of 77) patients in the observation group had at the time of RT symptomatic brain metastases, was unfortunately not reported. This lack of information makes it difficult to compare the EORTC and Japanese study on the for these patients most important issue: the morbidity related to symptomatic brain metastases. The number of patients treated with WBRT in the control arm is high compared to the EORTC study. Unfortunately, the authors of the Japanese study did not report whether giving WBRT or stereotactic RT (26) or both for, to MRI detected and still asymptomatic, brain metastases, results in the same delay of brain metastases to become symptomatic as PCI does. Additional information would be welcome.

A more general comment is the slow recruitment with a mean of 1.2 patients per center per year. The percentage of patients treated with WBRT in the control arm is high compared to the EORTC study. This, together with the high CR rate after chemotherapy, might indicate some selection bias.

Conclusions

The Japanese investigators confirmed that PCI does not, as expected, improve survival in stage IV SCLC. Unfortunately, it remains unclear whether prevention, or delay, of brain metastases to become symptomatic, can be achieved by the tested approach of careful monitoring by brain MRI. If that is the case, the approach of careful follow-up might be considered as standard. Implementation will be difficult due to financial constraints and capacity issues in many areas of the world.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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