or S. Given that SRS is minimally invasive, is able to treat lesions in surgically inaccessible locations, and is potentially more cost-effective than surgery, it is reasonable and more attractive alternative to surgery in the management of single brain metastasis.

Prognostic variables in patients with brain metastases include KPS, number of brain metastases, and absence or presence of extra-cranial disease. Absence of extra-cranial disease, KPS > 70, and single (rather than multiple) metastasis in the brain usually predict longer survival. Patients who fulfill all these criteria will survive longer following SRS and will most likely benefit from the increased local control achieved by SRS. Survival in patients who do not meet any of these criteria is very poor in survival, and these patients are less likely benefit from SRS and should be treated with WBI alone. The Pros and Cons of each modality will be discussed at the conference.

M18-03 Hot Issues in the Management of Brain Metastases, Thur, Sept 6, 10:30 - 12:00

Prophylactic cranial irradiation in patients with locally advanced non-small cell lung cancer

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In most common solid tumours, such as lung and breast cancer, the brain is at a high risk of metastatic dissemination. Until now, small cell lung cancer (SCLC) has been the most studied clinical entity in this matter. Previously overlooked, we know now that the brain is the most common site of dissemination for this disease, reaching a metastasis rate of more than 50% at 2 years. In the early 1970's, prophylactic cranial irradiation (PCI) was proposed to be included in the treatment strategy for SCLC and since then several randomised trials were conducted [1] to evaluate this treatment. Until recent years, it was thought that PCI was only effective in decreasing the brain metastasis rate, but without a significant effect on overall survival. This issue has been clarified since the publication of the PCI overview [1] that analysed all randomised trials conducted in patients with SCLC in complete remission (CR). It is tempting to extrapolate this effect to other tumour sites with a high risk of brain metastases. However, SCLC is a unique tumour because of its extreme chemo and radiosensitivity. The other important issue to take into consideration is the potential toxic effect on the normal brain parenchyma. Even if it has been demonstrated that total radiation doses in the range of 24 to 30 Gy given with a fraction size of 3 Gy or less are not deleterious up to 3-4 years [2-3], only limited experience is available with a longer follow-up [4].

The rationale to propose a PCI in high risk patients is similar to that established for SCLC patients, i.e., the brain, as a natural sanctuary to the drug action is a common first site of failure, most brain metastases are symptomatic with a significant impact on quality of life, and preventive treatment might have an impact on overall survival.

The main issues to be addressed regarding PCI in NSCLC include which patients are at a high risk of developing brain metastases, whether NSCLC cells are much less chemo or radiosensitive, which dose should be reached to have a therapeutic effect, if any, and which doses are compatible with an acceptable long-term brain function.

Risk of brain metastases in NSCLC patients

The brain metastasis risk depends on the initial stage and varies from 5% to 15% from stage I to III [5]. Like SCLC, brain metastases appear within the first two years of follow-up. In 75 patients with stage III, Stuschke et al. [6] described 20-30% of brain metastases as first site of failure. Ceresoli et al. described a similar rate (22%) in locally advanced NSCLC [7]. However, even this higher rate would be about a half of that described for patients with SCLC who were complete responders. Thus, if it were not possible to better define a higher risk population, about 80% of patients would receive a useless and potentially harmful treatment.

Effect of current treatment schedules in the incidence of brain metastases

With a larger use of mostly cisplatin-based chemotherapy in locally advanced lung cancer a decrease of distant metastases has been shown. However, it seems that chemotherapy is much less effective on brain metastases than on other involved sites. A relative increase of brain metastases could be related to recent improvements of local control and distant metastasis rate in locally advanced NSCLC. Improved results have been obtained by the use of higher radiation dose with conformal radiotherapy, concurrent radio-chemotherapy, accelerated hyperfractionated radiotherapy such as CHART, and cisplatin-based chemotherapy.

Effect of PCI in high risk NSCLC patients

This treatment modality has been examined in some retrospective studies and in phase III trials.

The first randomised trial [8] conducted by the Veterans Administration Lung Group included also SCLC patients, but suggested some effect in NSCLC. Another large study conducted by SWOG included 232 patients [9] and showed a preventing effect by the use of 30 Gy/10-15 fractions, but it has not been fully published. This effect was partially confirmed in other smaller trials [10, 11]. The four trials were summarised [12] and the odds ratios were estimated. In the absence of heterogeneity of results, these values were added to obtain a total odds ratio of 0.31 highly significant (p value less than 0.0001).

Brain toxicity of PCI

Potential brain toxicity of PCI has been widely described for SCLC patients, mainly in retrospective series. Indeed, the two randomised trials which evaluated prospectively potential toxicity [2, 3] did not show a significant effect of PCI up to three years of follow-up. Long-term evaluations are eagerly needed for these materials to reach more definite conclusions. These two trials used generally total doses of 24 to 36 Gy, and dose per fraction of 3 Gy or less.

Dose-effect relationship

Again, the data is coming from randomised material in SCLC patients. The PCI overview [1] suggested an effect of total PCI doses in subgroup analyses, this hypothesis has been tested by an international randomised trial PCI-01 that compared a total dose of 25 Gy with 36 Gy, the trial completed recruitment and first results are awaited for 2008.

In summary, PCI at moderate radiation doses is an effective treatment in reducing brain metastasis rate for patients at high risk of brain failure. This fact has been clearly demonstrated in SCLC patients in complete remission. Even if PCI in patients with advanced NSCLC has been used restrictively in clinical practice, almost 800 of such patients have been included in randomised trials testing the value of preventive irradiation. Despite the fact that NSCLC is generally considered more radioresistant than SCLC, the PCI effect in terms of the proportional reduction in the incidence of brain metastases is similar to that observed in SCLC patients. The available evidence clearly shows that PCI significantly decreases the risk of brain metastases in high-risk patients, even using moderate total doses of approximately 30 Gy. The next question is whether PCI in high-risk NSCLC patients would be able to improve overall survival. Because of the lower risk of brain me-

tastasis, it would be probably necessary to perform a randomised study including at least more than 1,000 patients. From several trial projects, some in Europe, only the RTOG-Intergroup US randomized trial has been launched and is including high risk NSCLC patients. The planned recruitment is above 1,000 patients and might answer the question of a potential effect on overall survival.

In conclusion, the controversy on the role of PCI on overall survival in high-risk NSCLC patients will persist in the absence of large randomised studies addressing the issue. The difficulties to launch trials on this important question, which does not receive industrial financing supports, are a matter of major concern. However, previous successful experience of PCI in patients with SCLC certainly should encourage clinicians worldwide to include patients in these new randomised trials evaluating a potential worthwhile treatment for locally advanced NSCLC disease.

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M18-04 Hot Issues in the Management of Brain Metastases, Thur, Sept 6, 10:30 - 12:00

Treatment and prevention of CNS metastases in NSCLC

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Central nervous system (CNS) failure in patients with locally advanced non-small cell lung cancer (LA-NSCLC) is a common and debilitating problem. The incidence is between 13 and 54 %.1-15,27,41 (Table 1) Review of RTOG data and other combined modality series have shown that chemotherapy significantly decreases extra-cranial failures but does not decrease the risk of CNS failures. As survival lengthens the risk of CNS metastases increases.17-19 Studies reporting the highest incidence of CNS metastases include patients treated aggressively with multimodality therapy who have a relatively long median survival. (Table 1) As treatment improves for NSCLC and survival lengthens CNS failures will increase.

Table 1: Incidence of CNS metastases

		CNS Metastases		Median Survival (Months)
Study	Stage	Overall	1st Failure Site	
Choi[30]	T1-3pN2	NA	30%	25
Stuschke[3]	T1-4pN2	54%	30%	20
Albain[2]	pN2-3 or T4	21%	15%	15
Andre[12]	cN2	22%	15%	NA
Law[10]	IIIa-b or IV	31% (53% complete resection)	16.3% (28% complete resection)	20
Ceresoli[11]	IIb,IIIa-b	NA	22%	21
Gaspar[21]	IIIa-b	17%	13%	NA
Carolan[14]	III	35%	18%	NA
Mamon[15]	IIIa	40%	34%	21
Chen[41]	III (preop therapy pCR)	55%	43%	43

There is not a standard of care for addressing CNS micro-metastases after successful therapy for LA-NSCLC. Most clinicians will perform routine physical examination with imaging of the CNS only upon development of signs or symptoms of CNS failure. The National Comprehensive Cancer Network (NCCN) guidelines for follow up of lung cancer include physical exam, chest x-ray, and thoracic CT scans at regularly defined intervals. CT or MRI screening for CNS metastases is not included. While some investigators have evaluated and endorse routine neuropsychological assessment and CT or MRI screening for early detection of brain metastases,10,16,41 others have included prophylactic cranial irradiation (PCI) as part of multimodality therapy regimens2-4,8,22 or have suggested the need for further investigation of PCI.3,9,12-15,17,20

Prospective and retrospective trials have shown that prophylactic cranial irradiation decreases the incidence or delays the onset of CNS failures in LA-NSCLC (Tables 2&3).2-7,9,22,23 Studies have not been powered to show a survival advantage nor have they evaluated the potential improvement in quality of life (QOL) or neurologic function by decreasing or delaying CNS metastases.

Neuropsychological complication rates of PCI in published data for small cell lung cancer (SCLC) and NSCLC are acceptable but data are limited .3,24,25 It is not known whether the benefits of PCI outweigh the risks. Approximately 50 % of carefully selected patients with NSCLC treated with PCI will be treated unnecessarily. Of those treated, up to 13% will still have CNS failures. Early detection of asymptomatic CNS metastases followed by intervention with aggressive therapy may improve quality of life and survival without the potential risks of PCI.

Brain metastases are more likely to be amenable to aggressive therapy with radiosurgery or surgical resection if disease is detected early, when tumor burden is low.