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Prophylactic cranial irradiation in non-small cell lung cancer

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introduction

Brain metastases are a common complication in lung cancer. In radically-treated patients the risk of CNS failure ranges from 13% to 54% [1–10]. These patients have also a 15–30% (9–12) risk of failing first in the brain. The risk of CNS metastases has been related to histology, to the stage of the disease at diagnosis, to the length of survival, to the gender of the patient, with females having a higher risk of brain failure [9–14].

In a large meta-analysis, prophylactic cranial irradiation (PCI) has been shown to improve overall survival in patients with limited disease small cell lung cancer who achieved complete response after combined chemotherapy and radiotherapy [15]. PCI has also demonstrated, in selected series, to reduce or delay the incidence of CNS failure in non small cell lung cancer patients after primary therapy [2–4, 8], but its impact on overall and disease free survival is uncertain, and it is a matter of debate if these patients may benefit from prophylactic cranial irradiation or early detection and aggressive treatment of brain metastases.

factors affecting the risk of brain metastases

histology

The incidence of CNS metastases is higher with adenocarcinoma and large cell carcinoma than with squamous cell carcinoma in some series [12–14]. Consequently some studies evaluating prophylactic PCI in non small cell lung cancer patients have included only patients with non squamous histology. This correlation has not been confirmed in other series, also a trend toward increased incidence of CNS failure in patients with adenocarcinoma has been observed (Table 1).

duration of survival

Many combined modality series have shown that chemotherapy decreases significantly extracranial failures, but not decreases the risk of CNS relapse. A review of RTOG data [13] has shown that in patients treated with radiotherapy or chemotherapy and radiotherapy for locally advanced non small cell lung cancer, longer survival is associated with an increased incidence of brain metastases. Recursive partitioning analysis (RPA) of RTOG studies [16] showed that patients included in the two RPA groups with the longest survival had the highest incidence of brain metastases (18% vs. 9%, $P = 0.0004$). RPA classes I and II included patients with good performance status (Karnofsky 80 to 100) and no pleural effusion. Several series [1, 4, 9, 11] have recently reported excellent median survival rates for locally advanced non small cell lung cancer treated with multimodality therapy (chemotherapy, radiation ± surgery). These studies have also reported the brain as the most frequent site of initial failure; in fact as survival lengthens, the risk of brain metastases increases (Table 2).

age

Young age (less than 60 or 70 years) has been associated in some series with a higher risk of brain metastases [18]. Why younger age may represent a risk for CNS failure might be related to microenvironmental factors related to a better brain vascularization, but better performance status and consequently better survival rates in younger patients can play a role.

stage

In some series T4 was associated with a higher risk of brain metastases than N2-N3 disease [11]. The T status however has not unanimously been reported as a predictive factor. The N2 status was identified as a factor predictive of brain metastases in the two studies in which it was assessed [9, 19]. In the studies by Jacobs et al. [18] the Cox regression model showed that the risk of brain metastases was significantly higher in the presence of hilar (RR = 4,26) and homolateral mediastinal lymph nodes (RR = 5,49) than in the absence of lymphatic involvement. Ceresoli and coworkers [11] described a trend for a higher of brain metastases in case of clinical bulky (>2 cm) mediastinal nodes ($P = 0.09$).

In conclusion, young patients with a good performance status, adenocarcinoma histology, T4 and/or N2-3 stage, treated with multimodality therapy, have the higher risk of developing brain metastases during the course of the disease. Table 3 summarizes the studies on patient and disease related factors predictive of brain metastases.

treatment of CNS metastases

Early detection of CNS metastases allows for intervention before debilitating neurological symptoms. Improved neuroradiological imaging techniques can help in earlier detection of metastases. Yokoi and coworkers evaluated the

potential benefit of postoperative evaluation of the brain with MRI or CT to detect metastases in patients with stage I–IIIb non small cell lung cancer [20]. In 76% of the patients diagnosed with CNS metastases, the disease was detected before development of neurological symptoms. Additionally, when tumor burden in the brain is low, disease is more likely to be amenable to aggressive therapy with surgical resection or radiosurgery ± whole brain irradiation. Better patient selection and aggressive therapy has resulted in improved outcomes for patients with CNS metastases. Studies with the most favourable results have included patients with good prognostic factors (young age, primary disease controlled, good performance status, prolonged interval between primary treatment and CNS relapse, no metastases in other sites, <3 brain metastases, surgical resection or radiosurgery followed by whole brain irradiation. Also in this favourable group median survival ranges from 10 to 12 months [21].

Table 1. Incidence of brain metastases according to histology

Author	N. pts.	Squamous	Non-squamous
Robnett, 2001	150	13%	23%
Bajard, 2004	305	16%	39%
Carolan, 2004	83		HR 2,7

Table 2. Incidence of brain metastases in patients treated with multimodality therapy

Author	Stage	Overall	First failure site	Median survival
Stuschke	T1-4 pN2	54%	30%	20 mos
Choi	T1-3 pN2	NA	30%	25 mos
Albain	pN2-3 or T4	21%	15%	15 mos
André	cN2	22%	15%	NA
Law	IIIa-b or IV	31%	16%	20 mos
Ceresoli	IIb, IIIa-b	NA	22%	21 mos

Table 3. Studies on factors predictive of brain metastases

Author	Stage	N.Pts	Age (years)	T status	N status	Stage	Adenocarcinoma
Bajard	I–IIIb	305	<62	T4	N2N3	ND	+
Ceresoli	III	112	<60	ND	bulky	−	ND
Robnett	II–III	150	−	ND	ND	IIIb	+
André	III N2	267	ND	−	ND	ND	+
Jacobs	II–III	78	−	−	N1 N2	ND	ND

ND: not determined, + : predictive value; − : no predictive value

prophylactic cranial irradiation (PCI)

The rationale behind PCI is to control or eradicate undetectable micrometastases before they become clinically significant without inducing severe adverse effects. Four prospective randomised trials have evaluated PCI for patients with non small cell lung cancer [6, 22, 57]. There are significant problems with all four trials that should be considered when interpreting their results. All except one are relatively small and none of them was powered to reliably identify what might be considered a clinically relevant survival benefit. Furthermore they are heterogeneous in patient selection, thoracic treatment and PCI dose (Table 4).

Three of these four trials did show a significant reduction in the incidence of brain failure after PCI. Two trials reported no significant difference in overall survival between the PCI and control arms. The SWOG trial showed a significant reduction of median survival; unlike the other trials in the SWOG study PCI was given concurrently with thoracic irradiation, and it may be that the subsequent uncreased toxicity contributed to shorter survival in the PCI arm.

Several nonrandomized multimodality studies [2–4, 8] have demonstrated the potential benefit for PCI in locally advanced non small cell lung cancer patients (Table 5).

conclusions

The data presented suggest that PCI may reduce the incidence of brain metastases, but it is unclear that this reduction does lead to a survival advantage. It is reasonable to assume that a reduction in the incidence of brain metastases in patients receiving PCI might improve quality of life even in the absence of a survival advantage, but data on the long term effect of PCI on cognitive function and quality of life are lacking. There is enough evidence to suggest a large randomised controlled trial

Table 4. Randomized controlled trials of PCI vs. observation in non small cell lung cancer treated with radical intent

Study	Patients	PCI dose	Incidence of brain metastases (PCI vs. no PCI)	Median survival in months (PCI vs. no PCI)
RTOG, 1991	187 adenocarcinoma confined to the chest	30 Gy/10 fx	9% vs. 19 % p = 0,10	8,4 vs 8,1 p = 0,36
SWOG, 1998	254 stage III not operable NSCLC	37,5 Gy/15 fx or 30 Gy/10 fx	1% vs. 11% p = 0.003	8,0 vs. 11,0 p = 0,004
Umsawasdi, 1984	97 NSCLC stage I/II (13%) stage III (87%)	30 Gy/10 fx	4% vs. 23% p = 0,02	NA
VALG, 1981	281, males, inoperable NSCLC	20 Gy/10 fx	6% vs. 13% p = 0,03	8,2 vs. 9,7 p = 0,5

Table 5. Non randomized controlled trials of PCI vs. observation in non small cell lung cancer treated with radical intent

Study	PCI dose	Primary Tx	No PCI	PCI	Overall survival	Median survival (Months)
Albain, 1995	36 Gy/18 fx	Trimodality (NSCLC)	16% (16/100)	8% (2/26)	37% (2 ys)	15
Strauss, 1992	30 Gy/15 fx	Trimodality (non squam)	12% (5/41)	0 (0/13)	58% (1 yr)	15.5
Stuschke, 1999	30 Gy/15 fx	Trimodality (NSCLC)	54% (15/28)	13% (6/47)	31% (3 ys)	20
Skarin, 1989	NA	Trimodality (NSCLC)	26% (7/27)	14% (1/7)	31% (3 ys)	32

would be justified. RTOG 0214 is a randomised controlled trial that is currently open. It aims to recruit more than 1000 patients who have completed definitive therapy for locally advanced NSCLC and randomise them between PCI or observation. Unlike previous trials detailed toxicity and quality of life data will be collected. This trial may be large enough to demonstrate a survival benefit with PCI. Outside of clinical trials there is insufficient evidence to support the use of PCI in the management of patients with non small cell lung cancer treated with curative intent.

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