

# Prophylactic cranial irradiation for patients with lung cancer



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The incidence of brain metastases in patients with lung cancer has increased as a result of improved local and systemic control and better diagnosis from advances in brain imaging. Because brain metastases are responsible for life-threatening symptoms and serious impairment of quality of life, resulting in shortened survival, prophylactic cranial irradiation has been proposed in both small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) to try to improve incidence of brain metastasis, survival, and eventually quality of life. Findings from randomised controlled trials and a meta-analysis have shown that prophylactic cranial irradiation not only reduces the incidence of brain metastases in patients with SCLC and with non-metastatic NSCLC, but also improves overall survival in patients with SCLC who respond to first-line treatment. Although prophylactic cranial irradiation is potentially associated with neurocognitive decline, this risk needs to be balanced against the potential benefit in terms of brain metastases incidence and survival. Several strategies to reduce neurotoxicity are being investigated.

## Introduction

The brain is a frequent site of metastasis in lung cancer both in small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). Because of increased control of locoregional disease and of distant metastases, the proportion of patients with brain metastases is increasing. Brain metastases are responsible for life-threatening and debilitating symptoms, serious impairment of quality of life, and shortened survival. Although there have been advances in the treatment and management of brain metastases in selected patients with NSCLC, the outcome is generally poor, with median survival of less than 6 months.<sup>1</sup>

Because the intact blood–brain barrier is poorly penetrable for most drugs, the brain is considered a sanctuary site with regard to adjuvant systemic treatments.<sup>2</sup> Therefore, prophylactic cranial irradiation can be considered as a strategy to eradicate non-detectable brain metastases. Prophylactic cranial irradiation has been shown to reduce the incidence of brain metastases in many randomised trials.<sup>3</sup> Remarkably, the effect of prophylactic cranial irradiation on survival has only been shown in patients with SCLC. In this Review, we will discuss the role of prophylactic cranial irradiation in patients with SCLC and in patients with NSCLC. We focus on the cognitive effects that can occur after prophylactic cranial irradiation and approaches for their prevention.

## Prophylactic cranial irradiation for SCLC

SCLC is characterised by a rapid doubling time (ie, the cancer doubles in size quickly) and early development of widespread metastases, particularly in the brain. Chemotherapy is the mainstay of treatment for patients with SCLC, independent of disease extent. Patients with SCLC are classically divided into two categories according to the Veterans Administration classification: those with extensive disease treated exclusively with chemotherapy, and patients with limited disease treated with chemotherapy and thoracic radiotherapy, because their disease is deemed accessible to a radical thoracic radiotherapy.<sup>4</sup> However, use of the TNM classification is

now recommended; patients with limited disease can be regarded as patients with stage I–III disease, excluding patients with tumour or nodal volume too large to be encompassed in a radiation plan.<sup>5,6</sup> In lung cancer, TNM classification was originally only used for NSCLC, whereas Veterans Administration classification was used for SCLC. Therefore, almost all studies assessing prophylactic cranial irradiation have used the Veterans Administration classification, and not the TNM classification.

Because SCLC often metastasises to the brain, brain imaging should be part of the initial assessment of all patients with SCLC. The detection of brain metastases varies according to imaging modality: in patients with newly diagnosed SCLC, brain metastases were detected in around 16 (10%) of 161 patients using CT and in up to 55 (24%) of 231 patients using MRI.<sup>7</sup> Intracranial metastases will eventually occur in more than 50% of patients with SCLC during the course of their disease.<sup>8</sup> Even with clinical complete remission after treatment for “limited disease”, about half of patients will develop brain relapse.<sup>8</sup> Prophylactic cranial irradiation was therefore introduced in the early 1980s as a treatment that could prevent the development of brain metastases for patients with SCLC. This treatment was first assessed retrospectively and then prospectively.

## Patients with limited disease or non-metastatic SCLC

The first generation of randomised trials assessing prophylactic cranial irradiation in patients with SCLC showed that the proportion of patients who developed brain metastases was lower in patients treated with prophylactic cranial irradiation than it was in patients who did not receive prophylactic cranial irradiation (0–17% vs 13–73% of 728 patients; with p values in individual trials ranging from 0.005 to 0.05 in six of nine trials, and the others being non significant).<sup>9</sup> However, these trials were done in the late 1970s and early 1980s and included very heterogeneous patient populations, which might explain the differences in the reduction of brain metastases reported. Furthermore, these studies are now of limited value because brain

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imaging techniques have evolved substantially. Other earlier studies suggested that prophylactic cranial irradiation could have an effect on survival only in patients with favourable characteristics, especially in those who have a complete response after chemotherapy. These findings led to new randomised trials assessing prophylactic cranial irradiation in patients who had a complete response.

The use of prophylactic cranial irradiation, however, remained a controversial issue until the publication of the meta-analysis of the data from these trials. Opponents argued that the published reports of randomised trials of prophylactic cranial irradiation did not show an effect on overall survival and that the late-occurring neurological effects could outweigh its possible benefits. However, one of the arguments in support of prophylactic cranial irradiation was that the development of metastases in the brain caused great morbidity and had a negative effect on quality of life for patients with SCLC.<sup>10</sup> In a study from 1982,<sup>10</sup> which measured patient quality of life using the Karnofsky performance scale, mean survival for patients with a Karnofsky score of 60 or greater was longer in those who received prophylactic cranial irradiation than in patients who received no prophylactic cranial irradiation and subsequently developed metastases to the brain (10 months vs 6 months, respectively).

Most of the randomised trials showed a significant decrease in the incidence of brain metastases in patients who had prophylactic cranial irradiation who achieved a good response to chemotherapy compared

with controls (table 1).<sup>8,11-15</sup> Furthermore, a plateau in the incidence of brain metastases was seen in the prophylactic cranial irradiation groups after 2 years in the two largest trials.<sup>8,14</sup> Thus, emergence of detectable brain metastases can be prevented and not simply delayed with prophylactic cranial irradiation in patients who have a complete response to chemotherapy.

The prevention of brain metastases can be regarded as another strong argument for the use of prophylactic cranial irradiation. However, none of these trials individually showed a significant improvement in overall survival. A meta-analysis was subsequently done by the Prophylactic Cranial Irradiation Overview Collaborative Group,<sup>16</sup> based on individual data for 987 patients with a complete response after chemotherapy who were included in seven randomised phase 3 studies. Status of thoracic complete response was based upon normalisation of chest radiographs in most trials, which is a different method from the current standard assessment with a CT scan. In this analysis, 847 (86%) of 987 patients had limited disease and 140 (14%) had extensive disease from SCLC according to now outdated staging procedures. The prophylactic cranial irradiation dose ranged from 8 Gy in one fraction to 40 Gy in 20 fractions; however, most patients in the prophylactic cranial irradiation group had a dose of 24–25 Gy (330 [63%] of 526 patients) or 30 Gy (119 [23%] of 526 patients). At 3 years, there was a 54% (SD 7) reduction in the risk of developing brain metastases in the prophylactic cranial irradiation group, corresponding to an absolute decrease of 25.3% in the cumulative

	Number of patients	PCI dose (total dose in Gy/number of fractions)	Proportion of patients who developed brain metastases			Survival*		
			No PCI group	PCI group	p value	No PCI group	PCI group	p value
Aroney et al (1983) <sup>11†</sup>	29	30/10	36%	0	0.02	NR	NR	..
Ohonoshi et al (1993) <sup>12</sup>	46	40/20	52%	22%	<0.05	15 months	21 months	NR
Arriagada et al (1995) <sup>8</sup>	300	24/8	67% at 2 years	40% at 2 years	<10 <sup>-13</sup>	21.5% at 2 years	29% at 2 years	0.14
Wagner et al (1996), ECOG/RTOG <sup>13</sup>	31	25/10	50%	20%	NS	8.8 months	15.3 months	NR
Gregor et al (1997), UKCCCR/EORTC <sup>14‡</sup>	314	Various: 8/1 to 36/18	54% at 2 years	30% at 2 years	0.00004	300 days; 11% at 3 years	305 days; 21% at 3 years	0.25
Laplanche et al (1998) <sup>15</sup>	211	Various: 24/8 to 30/10	51% at 4 years	44% at 4 years	0.14	16% at 4 years	22% at 4 years	0.25
Auperin et al (1999) <sup>16</sup> , Individual Patient Data (IPD) meta analysis§	987	Various: 8/1 to 40/20	58.6% at 3 years	33.3% at 3 years	<0.001	15.3% at 3 years	20.7% at 3 years	<0.001
Slotman et al (2007), EORTC <sup>17¶</sup>	286	Various: 20/5 to 30/10	40.4% at 1 year	14.6% at 1 year	<0.001	5.4 months; 13.3% at 1 year	6.7 months; 27.1% at 1 year	0.003
Seto et al (2014) <sup>18¶¶</sup>	163	25/10	58.0% at 1 year	32.4% at 1 year	<0.001	15.1 months	10.1 months	0.091

PCI=prophylactic cranial irradiation. NR=not reported. ECOG=Eastern Cooperative Oncology Group. RTOG=Radiation Therapy Oncology Group. UKCCCR=United Kingdom Co-ordinating Committee on Cancer Research. EORTC=European Organisation for Research and Treatment of Cancer. \*Data show median survival, survival rate, or both. †Of 172 patients analysed, only 29 patients who achieved complete response were randomised. ‡Study restricted to patients with limited disease. §Meta-analysis including patients with limited disease (86%) and extensive disease (14%) all deemed complete responders. ¶Study restricted to patients with extensive disease. ||The proportion of brain metastases only included symptomatic brain metastases.

**Table 1: Randomised trials and a meta-analysis assessing prophylactic cranial irradiation in patients with small-cell lung cancer who achieved complete or good response after first-line treatment**

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