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.

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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.[1]

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.[2] 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.[3] 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.[4] 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.[5,6] 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.[7] Intracranial metastases will eventually occur in more than 50% of patients with SCLC during the course of their disease.[8] Even with clinical complete remission after treatment for "limited disease", about half of patients will develop brain relapse.[8] 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).[9] 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

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.[10] In a study from 1982,[10] 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).[8,11–15] 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.[8,14] 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,[16] 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)[11]†	29	30/10	36%	0	0·02	NR	NR	..
Ohonoshi et al (1993)[12]	46	40/20	52%	22%	<0·05	15 months	21 months	NR
Arriagada et al (1995)[8]	300	24/8	67% at 2 years	40% at 2 years	$<10^{-33}$	21·5% at 2 years	29% at 2 years	0·14
Wagner et al (1996), ECOG/RTOG[13]	31	25/10	50%	20%	NS	8·8 months	15·3 months	NR
Gregor et al (1997), UKCCCR/EORTC[14]‡	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)[15]	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)[16], 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[17]¶	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)[18]¶	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**

incidence of brain metastases (33·3% in the prophylactic cranial irradiation group *vs* 58·6% in the control group; pooled relative risk [RR] 0·46, 95% CI 0·36–0·57; p<0·001). Compared with the control group, overall and disease-free survival at 3 years were significantly increased in the prophylactic cranial irradiation group, respectively, by 5·4% in terms of overall survival (20·7% in the prophylactic cranial irradiation group *vs* 15·3% in the control group; p=0·01) and by 8·8% in terms of DFS (p<0·001). The magnitude of the survival benefit is similar to that achieved with the use of thoracic radiotherapy in patients with limited disease.[16,19] The researchers did an indirect comparison of four groups according to delivered dose of prophylactic cranial irradiation, which showed a significant trend towards a decrease in the risk of brain metastases with higher dose (p=0·02). Another analysis showed a lower risk of brain metastases with earlier administration (within 6 months) of prophylactic cranial irradiation after the start of treatment compared with later administration after 6 months (p=0·01). Further data analysis broken down by subgroups (age, performance status, extent of initial disease, type of induction therapy, and time between the initiation of induction therapy and randomisation) and indirect analyses (total dose of irradiation) can be found in the meta-analysis.[20]

A systematic review by Meert and colleagues[21] assessed 12 published trials (1547 patients) that randomly assigned patients to either receive prophylactic cranial irradiation or not. More trials were included in this review than in the meta-analysis based on individual data (which was restricted to patients who had a complete response),[16] because of the inclusion of trials with prophylactic cranial irradiation given at the initiation of chemotherapy, or as consolidation treatment irrespective of the response status. As expected, prophylactic cranial irradiation significantly decreased the incidence of brain metastases and improved survival in patients who had complete response after chemotherapy (incidence of brain metastases hazard ratio [HR] of 0·48, 95% CI 0·39–0·60; survival among complete responders HR of 0·82, 0·71–0·96). When all studies were included in the analysis, there was no significant difference in survival between prophylactic cranial irradiation and control groups (HR 0·94, 0·87–1·02). Meert and colleagues concluded that prophylactic cranial irradiation could only be recommended in patients achieving a complete response documented by a work-up including brain CT scan.

In a retrospective study based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program, which included 7995 patients diagnosed between 1988 and 1997, Patel and colleagues[22] reported similar results, with a significant improvement in both overall and cause-specific survival in patients treated with prophylactic cranial irradiation compared with patients who did not receive irradiation. In patients who did not have prophylactic cranial irradiation (n=7325), overall survival at 2, 5, and 10 years was 23%, 11%, and 6%, respectively, whereas in patients who had prophylactic cranial irradiation (n=670), it was 42%, 19%, and 9%, respectively (all p≤0·001).

Another retrospective study investigating the role of prophylactic cranial irradiation in patients not enrolled in prospective studies has reported similar results.[23]

Elderly patients

About 50% of patients with limited stage SCLC are older than 70 years.[24] Since randomised studies have included few patients in this age group, there is discussion about whether patients older than 70 years should have prophylactic cranial irradiation. In a SEER study that investigated the use of prophylactic cranial irradiation in 1926 patients aged 70 years or older (median age 74 years) with limited disease SCLC, 138 (7%) patients who received prophylactic cranial irradiation[25] had improved survival at both 2 years and at 5 years compared with patients who did not receive prophylactic cranial irradiation (33·3% and 11·6% *vs* 23·1% and 8·6%, respectively; p=0·028, p value for survival at 2 and 5 years combined). On multivariable analysis, prophylactic cranial irradiation was an independent predictor of survival, as were younger age, white race, female sex, tumour size less than or equal to 30 mm, lymph node status of N0 or N1, and thoracic radiotherapy. In a subgroup analysis, prophylactic cranial irradiation remained a predictor of survival in patients older than 75 years but not in patients aged 80 years or older. The researchers concluded that the benefit of prophylactic cranial irradiation on survival seems to be maintained in the elderly population. In an analysis of four trials in elderly patients with limited or extensive SCLC, prophylactic cranial irradiation was associated with a significant improvement in survival compared with no prophylactic cranial irradiation (3-year overall survival of 13·2% in patients who did not *vs* 3·1% in patients who had no prophylactic cranial irradiation, HR 0·53, 95% CI 0·36–0·78; p=0·001).[26]

However, the results from these two studies should be interpreted with some caution because there were no neurocognitive or quality of life assessments, and there are concerns about prophylactic cranial irradiation neurotoxicity related to age.

Patients with resected SCLC

Surgery can be an option in patients with very limited stage SCLC—ie, patients with stage I disease.[5,6,27,28] The use of prophylactic cranial irradiation in this population has not been assessed in randomised trials and has not been investigated sufficiently, because few patients have undergone surgery. However, several retrospective studies have investigated the risk of brain metastasis according to stage.[29–33] One team used a multimodality approach including surgery for selected patients with SCLC.[29] Of 46 patients with stage IB to IIIB SCLC, 23 had an R0 resection, none of whom developed locoregional recurrence, although nine patients developed distant

failure, of which eight were in the brain; this finding delineates the importance of the brain as a site of failure (eight [35%] of 23 R0 patients had brain failure).

Two surgical series from China have shown a lower incidence of brain metastases in patients with pathological stage I SCLC.[30,31] In the first study, the incidence of brain metastases at 3 years was 6·5% in patients with pathological stage I disease, 25·4% in patients with stage II disease, and 28·8% in patients with stage III disease.[30] In the second study, the actuarial risk of developing brain metastases at 3 years was 9·7% in patients with pathological stage I disease, 18·5% in patients with stage II disease, and 35·4% in patients with stage III disease (p=0·013).[31] On the basis of these results, the researchers concluded that prophylactic cranial irradiation could be omitted in patients with pathological stage I SCLC.[30,31]

By contrast, a recent large National Cancer Database study, investigating the effect of adjuvant treatments after surgery in more than 1500 patients with pathological T1–T2N0M0 SCLC, has reported different conclusions.[32] A multivariate analysis showed that adjuvant chemotherapy and cranial irradiation were associated with improved survival compared with no adjuvant therapy (HR 0·52, 95% CI 0·36–0·75). In a Japanese prospective study of 62 patients, the overall frequency of brain metastases was 15% (11% in patients with pathological stage I disease compared with 19% in patients with stage II or stage III disease).[33] However, patients in these studies might not have received prophylactic cranial irradiation because, according to a nationwide survey assessing the patterns of care for SCLC, less than 10% of patients in Japan undergo prophylactic cranial irradiation.[34]

Therefore, as in all patients with non-metastatic SCLC who respond to treatment, prophylactic cranial irradiation is recommended for patients with resected SCLC after adjuvant treatment.[5,6,27] There are a few small Asian studies suggesting that prophylactic cranial irradiation could be omitted in patients with pathological stage I SCLC; in such cases, surveillance with brain imaging is recommended.

Timing, dose, and fractionation

One of the challenges raised by the prophylactic cranial irradiation meta-analysis was the optimum dose of prophylactic cranial irradiation and the optimum timing.[16] In terms of timing, there was a significant trend towards a greater effect of prophylactic cranial irradiation on the incidence of brain metastases in patients randomised sooner (within 4–6 months) after the start of induction therapy than in those patients who were randomised later (p=0·01), although timing of prophylactic cranial irradiation had no significant effect on survival (p=0·39). Therefore, prophylactic cranial irradiation should be delivered early in patients who respond to induction treatment.

Few prospective studies have assessed the effects of total dose or fraction size from prophylactic cranial irradiation. In most studies, the prescribed prophylactic cranial irradiation dose has been in the range of 24–30 Gy, with fraction sizes varying between 2 and 3 Gy. Although some studies have reported results with a single fraction of 8 Gy, large fractions in prophylactic cranial irradiation should be avoided because of potential late neurotoxicity. A dose-response relation was also reported in a review that analysed data from 12 non-randomised studies and 12 randomised studies comparing brain relapse rates in patients who did or did not receive prophylactic cranial irradiation.[35] The dose-response curve was almost linear within the dose range of 20–35 Gy.

Two randomised trials have directly addressed the issue of prophylactic cranial irradiation dose.[14,36] The first was a three-arm comparison, in which two prophylactic cranial irradiation doses (24 Gy in 12 fractions and 36 Gy in 18 fractions) were compared with no prophylactic cranial irradiation.[14] The HR between the group of patients treated with a prophylactic cranial irradiation dose of 24 Gy and the no-prophylactic cranial irradiation group was 0·71 (95% CI 0·36–1·43), whereas it was 0·16 (0·07–0·36) between the group who received 36 Gy and the no prophylactic cranial irradiation group; thus, only patients who received a higher prophylactic cranial irradiation dose (36 Gy) had a significantly lower risk of developing brain metastases compared with patients who did not receive prophylactic cranial irradiation (p=0·0007). The results of the Prophylactic Cranial Irradiation Overview Collaborative Group meta-analysis also showed a dose-response relation.[16] The effect of prophylactic cranial irradiation on the incidence of brain metastases increased with the total dose when four doses (8 Gy, 24–25 Gy, 30 Gy, and 36–40 Gy) were analysed (p=0·02 for trend). Hence, the relative reduction in the risk of developing brain metastases compared with the control group was 24% in the 8 Gy group, 48% in the 24–25 Gy group, 68% in the 30 Gy group, and 73% in the 36–40 Gy group, but the effect on survival did not differ significantly according to prophylactic cranial irradiation dose (p=0·81).

The second trial to assess prophylactic cranial irradiation dose was an intergroup trial that included 720 patients with limited-stage SCLC who had achieved a complete response (ie, at least a normal chest radiograph) after induction therapy.[36] This trial compared a standard dose of 25 Gy in ten fractions with a higher dose of 36 Gy (in 18 daily fractions or in 24 twice-daily fractions). To assess neurotoxicity, quality of life and neurological assessments were done both before and after prophylactic cranial irradiation. Toxicities and treatment delivery did not differ between groups. Patients who received a higher dose of prophylactic cranial irradiation had a non-significant decrease in brain metastases compared with patients who received the standard dose (2-year incidence: 23% in the higher-dose group *vs* 29% in the standard-dose group; p=0·18). Overall survival was lower in patients in the higher-dose group than in patients in the standard-dose group (2-year overall survival: 37% *vs* 42%; HR for death 1·2, 95% CI 1·00–1·44; p=0·05).

The North Central Cancer Treatment Group retrospectively analysed prophylactic cranial irradiation-related issues from prospectively collected data from 739 patients who were included in four phase 2 or 3 randomised trials.[37] Most patients had limited SCLC (57%), 459 (62%) patients had prophylactic cranial irradiation, and 280 (38%) had no prophylactic cranial irradiation. This pooled analysis strongly supports delivery of prophylactic cranial irradiation in patients with stable disease or better, because prophylactic cranial irradiation was significantly associated with improved survival, even after adjusting for age, performance status, sex, disease stage, complete response status, and number of metastatic sites (HR 0·82, 95% CI 0·67–0·99; p=0·04). Patients who received a prophylactic cranial irradiation dose of 25 Gy seemed to have better outcome in terms of survival than those who received a dose of 30 Gy (HR 0·67, 0·49–0·94; p=0·0182). Although these results are not as robust as the ones derived from randomised trials specifically addressing the issue of prophylactic cranial irradiation dose, they support the use of prophylactic cranial irradiation and also suggest that dose fractionation is important.

A phase 2/3 Radiation Therapy Oncology Group trial (RTOG 0212) assessed the importance of fractionation in terms of efficacy, tolerance, and possible neurological sequelae by comparing conventional fractionation (36 Gy in 18 fractions) with hyperfractionated accelerated radiotherapy (36 Gy in 24 twice-daily fractions) in 264 patients with limited-stage SCLC.[38] This trial contributed 146 patients to the intergroup study that assessed the effects of total dose of prophylactic cranial irradiation (25 Gy *vs* 36 Gy) on the incidence of brain metastases.[36] Thus, there was a two-part randomisation: first within the intergroup phase 3 trial and, second, within the phase 2 trial (RTOG 0212) comparing daily and twice-daily fractionation with the 36 Gy total prophylactic cranial irradiation dose, to determine the effect of prophylactic cranial irradiation total dose and treatment schedule on incidence of chronic neurotoxicity and on quality of life. By contrast with results from a previous study,[39] the use of hyperfractionated radiotherapy did not yield a significant reduction in late neurological effects.[38]

Thus, on the basis of these trials, prophylactic cranial irradiation at a dose of 25 Gy in ten fractions is now recommended for patients with SCLC who have a good response to first-line treatment.[5,6,27,28] However, the method of response assessment has changed since these studies were published, switching from chest radiography to chest CT scan. Furthermore, the standard treatment of stage I–III SCLC has become concurrent chemotherapy and chest radiotherapy; thus, response assessment can be difficult because of inflammatory and fibrotic changes caused by radiotherapy. A complete response on a chest radiograph would be equivalent to a good or partial response on CT scan assessment. Therefore, EU guidelines recommend prophylactic cranial irradiation for all fit patients without disease progression after chemotherapy and radiotherapy to the chest,[5,28] and US guidelines recommend prophylactic cranial irradiation for patients who achieve a complete or partial response to initial therapy.[6,27]

Patients with extensive disease or metastatic SCLC

Although findings from the prophylactic cranial irradiation meta-analysis supported the use of prophylactic cranial irradiation in patients with extensive SCLC who achieved complete response,[16] the effects of prophylactic cranial irradiation in patients with partial response remained unclear. Slotman and colleagues[17] within the European Organisation for Research and Treatment of Cancer (EORTC) thus decided to do a phase 3 trial in patients with extensive SCLC who had partial or complete response to first-line treatment (table 1). Patients were randomly assigned to receive either prophylactic cranial irradiation (20–30 Gy) or no prophylactic cranial irradiation. Brain CT scan or MRI before randomisation was not required, and only symptomatic patients had to have brain imaging. Most patients in the prophylactic cranial irradiation group were treated with a short course schedule: 89 of the 143 patients in this group received 20 Gy given in five fractions; others were treated with various fractionation schedules (30 Gy in ten fractions, 30 Gy in 12 fractions, or 25 Gy in ten fractions). The primary objective of the study was to investigate whether prophylactic cranial irradiation could reduce the incidence of symptomatic brain metastases as reflected by an HR of 0·44. The results strongly favoured the use of prophylactic cranial irradiation in extensive disease: prophylactic cranial irradiation reduced the risk of symptomatic brain metastases (cumulative risk at 1 year: 14·6% in the prophylactic cranial irradiation group *vs* 40·4% in the control group; p<0·001) and improved overall survival (1-year survival: 27·1% in the prophylactic cranial irradiation group *vs* 13·3% in the control group; p=0·003). Because of the low median survival in this setting, long-term toxicity was not of major concern, thus the short course schedule (20 Gy in five fractions of 4 Gy) could be favoured. However, less hypofractionated schedules (ie, 25 Gy in ten fractions of 2·5 Gy, such as the schedule applied to non-metastatic patients) could be offered to patients with longer life expectancy. This study had major implications and contributed to the modification of the standard of treatment for patients with extensive SCLC.

However, preliminary results of a Japanese phase 3 trial are in disagreement with the findings of the EORTC study.[18] The inclusion criteria in the Japanese study were stricter than those in the EORTC study because they included patients with extensive disease, and all patients had brain MRI before randomisation and had follow-up with brain MRI every 3 months. Patients in both studies

had responded to platinum-based doublet chemotherapy. The primary endpoint of the Japanese study was overall survival, and the study investigated whether prophylactic cranial irradiation (25 Gy in ten fractions) could affect survival compared with no prophylactic cranial irradiation, as reflected by a HR of 0·45. The secondary endpoint was time to brain metastasis (assessed every 3 months by brain MRI). The planned sample size was 330 patients, but after a planned interim analysis, patient enrolment was stopped because of futility. Of the 224 patients enrolled from 2009 to 2013, 163 patients were analysed. The cumulative risk of developing brain metastases at 1 year was 32·2% in the prophylactic cranial irradiation group compared with 58·0% in the control group (p<0·001). Median survival was 10·1 months in the prophylactic cranial irradiation group compared with 15·1 months in the control group and (p=0·091). Therefore, the results of this trial confirmed that prophylactic cranial irradiation reduced the risk of developing brain metastases, whether symptomatic or asymptomatic, but did not show a benefit in terms of survival. The researchers concluded that prophylactic cranial irradiation did not confer any survival benefit for patients with extensive SCLC when absence of brain metastases was confirmed by MRI before enrolment and asymptomatic brain metastases were detected early and treated. There was a non-significant trend for longer survival in patients who did not receive prophylactic cranial irradiation compared with those who did. In the control group, about two-thirds of patients (51 of 79 patients) developed brain metastases and 41 (80%) received radiotherapy.

There are major differences between these two studies. The Japanese study required MRI before randomisation and every 3 months for surveillance, whereas the EORTC study, in accordance with EU guidelines, did no brain imaging either at baseline or during follow-up in the absence of symptoms. In a subsequent European trial of thoracic radiotherapy in which brain imaging was done before chemotherapy in about half of patients (46%), brain metastases occurred in less than 10% of patients (37 [7%] of 498 randomised patients).[40] The final results of the Japanese study are awaited.[18]

Despite these results, prophylactic cranial irradiation is still regarded as a standard of care for patients with extensive SCLC who respond to first-line chemotherapy.[5,27] The National Comprehensive Cancer Network guidelines, which were updated in 2015,[6] recommend that in patients not receiving prophylactic cranial irradiation, surveillance by brain imaging should be considered. Despite an improvement in the incidence of brain metastases, the absence of improvement in survival with prophylactic cranial irradiation in the Japanese trial prompted a change in the Japan Lung Cancer Society guidelines for the treatment of lung cancer, updated in 2014, to no longer recommend prophylactic cranial irradiation in extensive SCLC.[41]

Prophylactic cranial irradiation for NSCLC

Predictive factors of brain metastasis

NSCLC accounts for about 85% of all cases of lung cancer worldwide.[42] Therefore, even though brain metastases are less frequent in NSCLC than SCLC, treatment of patients with NSCLC and brain metastases is a major concern for patients and clinicians, as well as an economic burden for health-care systems.[43] The incidence of brain metastases in NSCLC is around 30%, ranging from 17% to 54% across studies, and the brain is the first site of recurrence in 15% to 40% of cases.[44–49] As in SCLC, brain MRI can detect smaller brain metastases than CT scan.[50] Because of advances in the management of NSCLC, the risk of developing brain metastases seems to increase as survival is prolonged. Traditionally, patients with higher tumour stage, advanced nodal status, and adenocarcinoma histology have a higher propensity for CNS dissemination.[44–49,51–63] In patients with early-stage NSCLC who have had no preoperative treatment (stage I and II), the 5-year actuarial risk of developing brain metastases is around 10% or less, and is particularly low in patients with T1N0 disease.[57,58] It should be emphasised that brain metastases represent around 30% of distant failures.[58]

In patients with more advanced (stage IIIA/N2) NSCLC who underwent surgical resection, those who had adenocarcinoma histology and preoperative chemotherapy seem to have an increased risk of developing brain metastases (>30%).[45,59,60] Whether pathological response has any effect on the pattern of recurrence is not clear: persistent nodal involvement and pathological complete response after neoadjuvant treatment have been associated with a particularly high risk of brain metastases.[59,60] Patients with superior sulcus tumours also have a particularly high risk of brain metastases after multimodality treatment.[61] Other studies have assessed the risk of brain metastases in patients with more advanced NSCLC treated with radical radiotherapy or combined chemoradiation.[46,49,62,63] The brain represented the first site of relapse in 15–18% of patients with good prognosis (recursive partitioning analysis class I and II).[62] According to another study, more than 25% of patients who had disease progression had brain metastases (71 [26%] of 268 patients with disease progression had brain failure), and time from treatment to disease progression in the brain was frequently less than 6 months.[46] As in patients with resected disease, the risk of brain metastases is higher in more advanced disease and in patients with non-squamous histology.[44,45,46,49] Other risk factors have been described, such as sex, tumour size, younger age (<60 years), prolonged survival, and more recently, genotype.[44–49,51,58,60,63]

Management of some subgroups of patients with metastatic NSCLC has changed substantially in recent years, especially in patients with adenocarcinomas that can be further subclassified by their genetic mutation profiles.[52,53] In patients with *EGFR* mutations and *ALK* rearrangements, targeted agents such as EGFR tyrosine

kinase inhibitors and ALK inhibitors have shown intracranial efficacy, justifying their use as front-line therapy in patients with these mutations.[2,52,54–56] Since patients with *EGFR* mutations could be at higher risk of brain dissemination,[2,51,64] tyrosine kinase inhibitors such as erlotinib and gefitinib could have a role in the chemoprevention of brain metastases.[56] A phase 3 study in South Korea is investigating whether prophylactic cranial irradiation could be a valid option in patients with driver mutations who are at high risk of brain metastases (NCT00955695).

Treatment of brain metastases and outcome

If the outcome of brain metastases in patients with NSCLC treated with whole-brain irradiation is considered, the disease-specific graded prognostic assessment identified patient groups for which median survival was 7 months (range 3·0–14·8 months), taking into account Karnofsky performance score, age, presence of extracranial metastases, and number of brain metastases as prognostic factors.[65] NSCLC has better prognosis than does SCLC partly because there are more treatment options. Presentation of brain metastases in NSCLC is also different from presentation in SCLC, rendering them more accessible to local treatments such as surgery or stereotactic radiotherapy, and not just whole-brain irradiation. Whole-brain irradiation is still regarded as standard treatment for multiple symptomatic brain metastases, even though a randomised trial not fully published[66] does not seem to support the use of this approach versus best supportive care.[66–68] In a subgroup of patients who have a limited number of brain metastases, management has evolved from whole-brain irradiation alone to more aggressive treatment that incorporates stereotactic radiotherapy or surgery (in case of solitary metastasis) with better results than with brain irradiation alone and median survival exceeding 12 months.[66,67]

By contrast with SCLC, chemotherapy has traditionally had a limited role in the treatment of patients with NSCLC. For asymptomatic brain metastases found by MRI screening, monitoring the cerebral response to systemic treatment before initiating local brain-directed treatment is generally accepted. Treatment is now more individualised, according to primary tumour and genotype characteristics as well as patient characteristics and size and number of brain metastases, with more emphasis on balancing treatment effectiveness against neurotoxicity. There is increasing evidence about the efficacy of tyrosine kinase inhibitors in brain metastases, especially in patients with *EGFR* mutations.[54,55,64] Because of improved survival and better local control of thoracic disease in patients with NSCLC, the risk of brain metastases has become a more challenging issue in the past 10 years, because approximately half of patients will die from progression of brain metastases. Use of prophylactic cranial irradiation has therefore been reconsidered more recently in NSCLC because of the extent brain metastases affect quality of life and survival.

Randomised trials of prophylactic cranial irradiation in patients with NSCLC

Fewer randomised trials have investigated the use of prophylactic cranial irradiation in locally advanced NSCLC than in SCLC. The first three randomised trials are quite old and heterogeneous in terms of disease (stage and histology), locoregional treatment (surgery, radiation modalities, chemotherapy), and whole-brain irradiation dose (table 2).[69–71] In these trials, incidence of brain metastases was lower in patients assigned to prophylactic cranial irradiation than in patients assigned to control (4–9% *vs* 13–27%).[69,70] Prophylactic cranial irradiation had no effect on overall survival; however, median time to development of brain metastases seemed to be longer in the prophylactic cranial irradiation group than in the control group. In the first RTOG study to assess prophylactic cranial irradiation in patients with NSCLC, prophylactic cranial irradiation did not significantly reduce the incidence of brain metastases compared with no prophylactic cranial irradiation (9% *vs* 19%; p=0·10).[71] In a subgroup analysis of patients with

	Number of patients	Stage	PCI dose (total dose in Gy/number of fractions)	Proportion of patients who developed brain metastases			Overall survival*		
				No PCI group	PCI group	p value	No PCI group	PCI group	p value
Cox et al (1981), VALG[69]	281	Inoperable	20/10	13%	6%	0·038	41·4 weeks	35·4 weeks	0·5
Umsawasdi et al (1984)[70]	97	I, II, or III	30/10	27%	4%	0·002	NR	NR	..
Russell et al (1991), RTOG[71]	187	II/III	30/10	19%	9%	0·1	21% at 2 years	13% at 2 years	0·36
Gore et al (2011), RTOG 0214[72]	340	III	30/15	18·0% at 1 year	7·7% at 1 year	0·004	24·8 months; 76·9% at 1 year	25·8 months; 75·6% at 1 year	0·86
Li et al (2015)[73]	156	IIIA/N2 resected	30/10	AR 44·2% at 3 years	AR 13·7% at 3 years	<0·001	27·4 months; 38·7% at 3 years	31·2 months; 44·5% at 3 years	0·31

PCI=prophylactic cranial irradiation. VALG=Veterans Administration Lung Group. NR=not reported. RTOG=Radiation Therapy Oncology Group. AR=actuarial rate. *Data show median survival, survival rate, or both.

Table 2: **Randomised trials assessing prophylactic cranial irradiation in patients with non-small-cell lung cancer**

resected tumours, three (25%) of 12 patients in the no prophylactic cranial irradiation group developed brain metastases compared with no patients in the prophylactic cranial irradiation group (p=0·06). It is therefore difficult to draw any conclusions from these studies; furthermore, quality of life and neurological assessments were not done for these studies.

The largest study, a randomised phase 3 trial published in 2011 (RTOG 0214), was closed prematurely because of slow accrual.[72] The trial was ambitious because it was designed to show a possible benefit of prophylactic cranial irradiation on survival (an improvement in 1-year survival of 20% in the prophylactic cranial irradiation group compared with the observation group) and 1058 patients were required. After completing locoregional treatment (surgery, radiation therapy with or without chemotherapy) for locally advanced NSCLC (stage IIIA or IIIB), patients without distant metastasis or progressive disease were randomly assigned to prophylactic cranial irradiation (30 Gy in 15 fractions) or no prophylactic cranial irradiation. 340 of 356 enrolled patients were analysed. A significant reduction in brain metastases was seen in the prophylactic cranial irradiation group at 1 year (7·7% *vs* 18·0%; p=0·004). However, 1-year overall survival did not differ between groups (75·6% *vs* 76·9%; p=0·86) and there was no significant difference between groups in 1-year disease-free survival (56·4% *vs* 51·2%; p=0·11). Median overall survival was 25·8 months in the prophylactic cranial irradiation group and 24·8 months in the control group (p=0·86). More mature results are expected, as well as subgroup analyses, focusing on subgroups at higher risk.

A recent trial from China investigated prophylactic cranial irradiation (30 Gy in ten fractions) in patients with resected stage IIIA/N2 NSCLC.[73] The primary endpoint of this trial, which aimed to recruit 254 patients, was disease-free survival with a targeted goal of a 30% reduction in recurrence in the prophylactic cranial irradiation group compared with the observation group. All patients had adjuvant chemotherapy before randomisation. This underpowered trial was closed early after the random assignment of 156 patients. Patients in the prophylactic cranial irradiation group had better median disease-free survival than patients in the control group (28·5 months *vs* 21·2 months; HR 0·67, 95% CI 0·46–0·98; p=0·037). The actuarial rate of brain metastases was 13·7% at 3 years and 20·3% at 5 years in the prophylactic cranial irradiation group compared with 44·2% and 49·9% in the control group, respectively (p<0·001). The actuarial probability of developing brain metastases as the first site of recurrence was 11·8% at 3 years and 15·6% at 5 years in the prophylactic cranial irradiation group compared with 39·2% and 45·3% in the control group, respectively. Survival did not differ between groups (5-year survival 27·4% in the prophylactic cranial irradiation group *vs* 22·8% in the control group; median survival 31·2 months *vs* 27·4 months; HR 0·81, 95% CI 0·56–1·16; p=0·310). The researchers reported no significant differences in the deterioration of quality of life and symptoms between the two groups. No information about the association with *EGFR* mutation status was provided in this study.

Although not investigating prophylactic cranial irradiation exclusively, a multicentre study by Pöttgen and colleagues[74] compared two different therapeutic strategies in patients with operable stage III NSCLC, in which one of the two groups included prophylactic cranial irradiation. In the standard group, patients underwent surgery followed by postoperative thoracic radiotherapy. In the experimental group, patients received preoperative chemotherapy followed by concurrent chemoradiotherapy before surgery and then prophylactic cranial irradiation (30 Gy in 15 fractions). At 5 years, the probability of brain metastases as first site of failure was lower in the experimental group than in the control group (7·8% *vs* 34·7%; p=0·02), and overall brain relapse was reduced comparably (9·1% *vs* 27·2%; p=0·04). Interpretation of these results is difficult because the trial did not directly address the benefit of prophylactic cranial irradiation. Patients in the experimental group also had a more aggressive locoregional treatment than patients in the control group. Another phase 2 study done by the same team assessed trimodality treatment for stage IIIA/N2 or IIIB NSCLC.[75] It included 75 patients and, after the first 28 patients were treated, the researchers decided to implement prophylactic cranial irradiation in their treatment regimen because of the high incidence of brain metastases. The introduction of prophylactic cranial irradiation reduced the rate of brain metastases as the first site of relapse from 30% at 4 years in the first 28 patients of the study who had no prophylactic cranial irradiation to 8% in those who had it (p=0·005), and that of overall brain relapse from 54% to 13% (p<0·0001). In a subgroup of patients with partial response or complete response to induction chemotherapy, introduction of prophylactic cranial irradiation also significantly reduced the rate of brain metastases as first site of relapse from 23% to 0% at 4 years (p<0·01). Studies using multimodality treatment for locally advanced NSCLC with median survival of more than 20 months have reported higher overall incidences of brain metastases (22–55%)[44,48,60,63,74,75] than reported in the RTOG 0214 trial,[72] in which most patients (225 [66%] of 340) did not have surgery.

A retrospective study in which patients with locally advanced NSCLC were treated either with induction chemotherapy followed by chemoradiation (58 patients) or upfront chemoradiation (76 patients) indirectly addressed the issue of timing of prophylactic cranial irradiation.[76] Prophylactic cranial irradiation at a dose of 30 Gy in 2 weeks was given to all patients, and 11 (8·2%) patients developed brain metastases: eight (13·8%) in the induction therapy group and three (3·9%) in the upfront chemoradiation group (p=0·03). Only three (2·2%) patients developed brain metastases as the first site of failure. Median survival was 19·3 months in patients

treated with induction therapy and 26·1 months in patients who had upfront chemoradiation. Although the results should be interpreted with caution because this was not a randomised trial, the researchers concluded that there seemed to be a significantly lower incidence of brain metastases in patients who had earlier prophylactic cranial irradiation compared with patients treated with delayed prophylactic cranial irradiation. Other confounding factors such as favourable prognostic factors or tumour and patient characteristics could explain these results, but overall the incidence of brain metastases seemed to be lower than that reported in historical series of patients with stage III NSCLC. Recently, a SEER population-based analysis of 17852 patients treated from 1988 to 1997 for stage III NSCLC for which prophylactic cranial irradiation data were available, was published. 326 patients (1·8%) had prophylactic cranial irradiation. This study suggested no overall survival benefit of prophylactic cranial irradiation (HR 1·04, 95% CI 0·93–1·16).[77]

In conclusion, on the basis of the RTOG 0214 randomised trial, patients in the control group were 2·52 times more likely to have brain metastases than those in the prophylactic cranial irradiation group,[72] and prophylactic cranial irradiation also seemed to delay onset of brain metastases. Unfortunately, because most of these trials were underpowered, no effect on overall survival could be recorded. A phase 3 trial in the Netherlands (NVALT-11/ DLCRG-02) has been completed and results are awaited. Updated results of the RTOG 0214 are warranted and a meta-analysis based on individual data to assess prophylactic cranial irradiation in patients with NSCLC is planned, giving more robust results than those of a recently published in literature based meta-analysis combining randomised and retrospective studies.[78]

In the absence of a survival benefit, prophylactic cranial irradiation is not part of standard treatment for stage III NSCLC, and cannot be recommended.[1,79] Because management of advanced NSCLC is now driven by histological cell type and genetic profile, it has changed substantially in a subgroup of patients with oncogenic driver mutations (<20% of all patients with NSCLC). For the majority of patients who do not have an identified driver mutation, management has improved but has not changed as greatly. Furthermore, these changes have had little effect on the management of early and locally advanced NSCLC. Future studies should take all these changes into account—ie, better brain imaging, possibility of treating patients with NSCLC with repeated stereotactic radiotherapy, and identification of predictive biomarkers of higher risk of brain metastases, as well as the risk of neurotoxicity. The analysis of such factors could allow us to define the population of patients with NSCLC who are at highest risk of CNS extension and who are most likely to benefit from prevention with prophylactic cranial irradiation.

Possible toxicity related to prophylactic cranial irradiation

Assessment of toxicity

Although there is strong evidence in favour of prophylactic cranial irradiation in SCLC, its indication should be considered in light of its potential contribution to neurotoxicity. Thus, some clinicians might be reluctant to propose prophylactic cranial irradiation to some patients with SCLC and accept a higher risk of cognitive decline resulting from brain metastases.[80] Additionally, as outlined in an institutional retrospective study, patients might refuse prophylactic cranial irradiation (up to 40% of patients with limited disease), mainly because of concerns about toxicity.[23] Acute toxicity is generally manageable and mostly consists of alopecia, headache, fatigue, nausea, and vomiting. Long-term sequelae such as severe memory loss, intellectual impairment, or even dementia and ataxia, as well as abnormalities on brain imaging (cerebral atrophy, ventricular dilatation, periventricular and subcortical white matter changes) started to be reported in the 1980s in several studies and attributed to prophylactic cranial irradiation. However, most of these studies were small, retrospective, and did not perform assessments at baseline; furthermore, some studies included mixed patient groups who either had whole-brain irradiation as prophylactic treatment or as treatment for brain metastases, as reviewed elsewhere.[9]

Assessment of prophylactic cranial irradiation neurological toxicity is difficult because the related symptoms can be caused by many different factors including the disease itself. Treatment variations, such as dose and fractionation scheme (fraction size ≥3 Gy), or the use of concurrent chemotherapy can contribute to neurotoxicity.[81–85] Other studies have suggested that neuropsychological impairment could be attributable to the cancer itself or to treatment given before prophylactic cranial irradiation. For instance, neuropsychological impairment was recorded at baseline before prophylactic cranial irradiation in several retrospective and prospective studies.[8,14,36,82,83] Age, effects of chronic cigarette smoking, paraneoplastic syndromes, and undiagnosed micro-metastases could also contribute to neurotoxicity or partly explain neurological symptoms.[82] Furthermore, patients might have symptoms of depression or anxiety that might interfere with neuropsychological assessments. Radiation-induced cognitive impairment can be marked by decreased attention, spatial or verbal memory, and novel problem-solving ability, with incidence and severity increasing over time. Assessment of long-term neurocognitive toxicity is therefore difficult and challenging. The importance of implementing neuro-cognitive function into prospective studies has been highlighted elsewhere.[86,87]

The best assessment of prophylactic cranial irradiation toxicity comes from long-term follow-up of randomised studies that assessed quality of life, general

health status, and neurological functions by use of validated questionnaires. Several of these trials used tests of neurological function and neurocognitive function to assess the effects of prophylactic cranial irradiation, most particularly on memory, executive function, fine motor coordination, verbal function and language skills, construction, concept formation and reasoning, perception, orientation, and attention (table 3).[8,14,88–90] Other studies have used self-reported quality of life scales. Most studies have focused on memory.

Studies in patients with SCLC

Two of the largest randomised trials assessing prophylactic cranial irradiation in patients with SCLC did not show any significant decline in neurological functions between prophylactic cranial irradiation and no prophylactic cranial irradiation groups, with a follow-up of less than 30 months.[8,14] In the study by Arriagada and colleagues,[8] there were no significant differences in terms of radiological changes on CT scan or neurological examination between the prophylactic cranial irradiation and observation groups. In the EORTC study by Gregor and colleagues,[14] cognitive impairments were reported at 6 and 12 months, but with no notable difference between prophylactic cranial irradiation and control groups. However, the baseline assessment was abnormal in 40–60% of patients in both studies. Longer-term follow-up showed a moderate decline in neurocognitive functions such as memory; however, the difference between groups was not significant.[8,91]

A third trial (Cancer and Leukemia Group B), which did not address the issue of prophylactic cranial irradiation directly, included a prospective neurocognitive assessment of all patients randomly assigned to receive irradiation and concomitant chemotherapy with or without warfarin.[85] The researchers concluded that the combination of chemotherapy and prophylactic cranial irradiation had a negative effect on cognitive functioning, confirming that chemotherapy and prophylactic cranial irradiation should not be administered concomitantly. In the prophylactic cranial irradiation intergroup trial that explored optimum dose in 720 patients with non-metastatic SCLC, clinical neurological outcomes and quality of life were assessed.[90] The EORTC health-related quality of life (HRQoL) questionnaire and its brain module were used to collect self-reported patient data. There was no significant difference between the standard-dose and higher-dose groups over 3 years in any of the 17 selected items assessing quality of life and neurological and cognitive functions. Although many patients had a mild cognitive decline over time, few patients developed severe deterioration of quality of life or neurological and cognitive functions in the 3 years following prophylactic cranial irradiation. At baseline, the unfavourable quality of life status varied according to the studied item, from 6% (communication deficit) to 62% (global health status). Overall, there was a mild deterioration across time of communication deficit, fatigue, intellectual deficit, and memory (all $p<0·005$). This study also showed the importance of age as a cofactor of neurocognitive decline.[90] Furthermore, the researchers mentioned that delivery of prophylactic cranial irradiation to patients with epilepsy who needed oral treatment could incur a greater risk because one patient died of generalised seizures after prophylactic cranial irradiation.

In both recent RTOG prophylactic cranial irradiation studies, neurocognitive functioning was assessed by use of the Mini-Mental State Examination (MMSE), which was developed to detect mild dementia, and the Hopkins Verbal Learning Test (HVLT) to assess verbal memory.[38,39,92] Other tests were used in the RTOG 0212 trial such as the Controlled Oral Word Association Test to assess language/verbal fluency, the Trail Making Test Part A for visual and spatial scanning, attention, sequencing, and speed, and the Trail Making Test Part B for executive/frontal lobe. Unfortunately, the number of patients evaluable at 12 months was too small to yield any statistically different results. Possibly, there could be better compliance with a simpler method of neurocognitive function assessment. The analysis of RTOG 0212 showed an association between higher-dose prophylactic cranial irradiation and increased chronic neurological toxicity.[38] However, higher-dose prophylactic cranial irradiation was not specifically associated with greater decline in HVLT score. Logistic regression analysis showed increasing age to be the most significant predictor of chronic neurotoxicity ($p=0·005$).

Regarding prophylactic cranial irradiation in extensive stage SCLC, quality of life was assessed in the EORTC trial.[88] The EORTC health-related QoL (HRQoL) questionnaire and its brain module were used to collect self-reported patient data. The results showed a negative but limited effect of prophylactic cranial irradiation, with a significantly decreased quality of life in terms of functioning scales in prophylactic cranial irradiation patients at 6 weeks ($p=0·018$), which tended to be not significant at 3 months and afterwards. Whether this finding can be assimilated to a subacute recovery is difficult to assert. Fatigue was also more frequent in patients in the prophylactic cranial irradiation group than in the observation group at 6 weeks and 3 months, which could partly explain some neurocognitive findings. The investigators concluded that patients should be informed about the benefits of prophylactic cranial irradiation and of its possible negative effect on quality of life to allow informed, individualised treatment choices.

Studies in patients with NSCLC

Pöttgen and colleagues[74] did a neurocognitive assessment in 11 out of 17 long-term survivors of stage IIIA NSCLC treated with or without prophylactic cranial irradiation. Although their sample size was small, the investigators

	Number of patients	Assessment schedule	Baseline assessment	Neuropsychological tests and other examinations	Control group*	Experimental group*	p values	Outcomes
No PCI (control) versus PCI (experimental)								
Arriagada et al (1995)[8]	229	Assessments made at baseline, and 6, 18, 30, and 48 months; 33 patients reassessed at 18 months; 23 patients reassessed at 30 months	Abnormalities in 59% of patients; brain CT scan normal in 83% of patients	Neuropsychological assessments made by neurologist: (1) orientation, memory, judgment, language, and praxis; (2) mood; (3) walking; (4) toxicity-related brain CT abnormalities	Neuropsychological changes at 2 years: (1) 36%; (2) 28%; (3) 11%; (4) 21%	Neuropsychological changes at 2 years: (1) 30%; (2) 19%; (3) 8%; (4) 27%	(1) 0·58; (2) 0·55; (3) 0·72; (4) 0·60	Impairment at baseline substantial but similar in the two groups; no significant differences between groups at 2 years
Gregor et al (1997), UKCCCR/ EORTC[14]	136	Assessments made at baseline, at 6 and 12 months, then yearly; 59 patients reassessed at 6 months, 32 patients at 1 year, and 9 patients at 2 years	Abnormalities in 24–42% of patients according to tests	(1) PASAT; (2) CFT; (3) AVLT learning; (4) AVLT retention; (5) HADS; (6) QoL assessment (tiredness)	Neuropsychological changes at 1 year: (1) 2/12 (17%); (2) 2/12 (17%); (3) 4/10 (40%); (4) 3/8 (38%); (5) 13%; (6) 6-month deterioration in QoL: 57%	Neuropsychological changes at 1 year: (1) 5/16 (31%); (2) 2/13 (15%); (3) 9/13 (69%); (4) 0/16; (5) 13%; (6) 6-month deterioration in QoL: 24%	(1–5) All NS; (6) NR	Impairment at baseline substantial but similar in the two groups; no evidence of major impairment attributable to PCI; deterioration in general symptoms reported more frequently in the no PCI group
Slotman et al (2009), EORTC[88]	268	QoL data collected at baseline, 6 weeks, and 3, 9, and 12 months; poor compliance: 54·5% at 3 months, 60·8% at 6 months, 46·3% at 9 months, and 48·9% at 1 year	..	EORTC-QLQ-BN20 and EORTC-QLQ-C30: (1) global health status; (2) fatigue; (3) cognitive functioning; (4) hair loss	Deterioration from baseline up to 3 months: (1) 22%; (2) 27%; (3) 10%; (4) 12%	Deterioration from baseline up to 3 months: (1) 35%; (2) 49%; (3) 22%; (4) 22%	NR	Limited effect of PCI for role, cognitive, and emotional functioning; effect on fatigue greater in PCI group than no PCI group at 3 months; adverse effect of PCI on fatigue (mostly), appetite loss, social functioning, future uncertainty, motor dysfunction, and weakness of legs at 6 weeks and/or at 3 months
Sun et al (2011), RTOG[89]	340	QoL and NCF data collected at baseline, and 3, 6, and 12 months; for NCF: 324 patients assessed at baseline, 144 at 6 months, and 97 at 1 year; for QoL: 309 patients assessed at baseline, 143 at 6 months, and 92 at 1 year	..	(1) MMSE; (2) HVLT recall; (3) HVLT delayed recall; (4) ADLS; EORTC-QLQ-C30: (5) global health status; (6) fatigue; (7) cognitive functioning	Deterioration from baseline at 3 months/ 6 months/ 1 year: (1) 21%/25%/18%; (2) 13%/5%/7%; (3) 10%/14%/5%; (4) no significant change; deterioration from baseline at 6 months/1 year: (5) 32%/34%; (6) 32%/28%; (7) 18%/25%	Deterioration from baseline at 3 months/ 6 months/1 year: (1) 36%/28%/23%; (2) 45%/19%/26%; (3) 44%/15%/32%; (4) no significant change; deterioration from baseline at 6 months/1 year: (5) 35%/22%; (6) 21%/34%; (7) 35%/41%	(1) 0·04 at 3 months, 0·6 at 1 year; (2) <0·001 at 3 months, 0·01 at 1 year; (3) <0·001 at 3 months, 0·003 at 1 year; (4) NS; (5) 0·76 at 6 months, 0·2 at 1 year; (6) 0·27 at 6 months, 0·52 at 1 year; (7) 0·02 at 6 months, 0·14 at 1 year	No significant differences in global cognitive function (MMSE) or QoL after PCI, but significant decline in memory (HVLT) at 1 year; good compliance at baseline (95%) and poor at 1 year (around 35%)
Standard-dose (25 Gy) PCI (control) versus higher-dose (36 Gy) PCI (experimental)								
Le Péchoux et al (2011)[90]	667	QoL and NCF data collected at baseline, and 6, 12, 24, and 48 months; compliance around 92% of patients at baseline, 70% at 6 months and 1 year, 60% at 2 years, and 50% at 3 years	Abnormal status/LS scale in 0–27% of patients; unfavourable QoL status varied: 6% (communication deficit) to 62% (global health status)	NCF status according to LS scale and QoL according to EORTC QLQ-C30 and QLQ-BN20; (1) LS-intellectual deficit; (2) LS-memory; (3) QoL-cognitive functioning; (4) QoL-social functioning	Abnormal status at baseline/12/24/36 months: (1) 10%/12%/20%/27%; (2) 20%/36%/36%/47%; (3) 23%/38%/41%/35%; (4) 41%/33%/32%/30%	Abnormal status at baseline/12/24/36 months: (1) 9%/20%/28%/34%; (2) 18%/34%/49%/58%; (3) 25%/41%/46%/47%; (4) 43%/33%/35%/25%	NS	Over 3 years, no significant difference in any item assessing QoL and NCF; mild deterioration across time of communication deficit, fatigue, intellectual deficit, and memory (all p<0·005); importance of age as cofactor of neurocognitive decline

The EORTC-QLQ-C30 measure consists of five functioning scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/vomiting, and pain), six single-item scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial impact), and the overall health-related quality of life (HRQoL) scale. EORTC-QLQ-BN20 BN20 is a supplemental questionnaire specifically developed for use with the previous general questionnaire (QLQ-C30) in patients with brain tumours. It assesses visual disorders, motor dysfunction, communication deficit, various disease symptoms (eg, headaches and seizures), treatment toxicities (eg, hair loss), and future uncertainty. UKCCCR=United Kingdom Co-ordinating Committee on Cancer Research. EORTC=European Organisation for Research and Treatment of Cancer. PASAT=Paced Auditory Serial Addition Test assessing auditory mental tracking. CFT=Rey-Osterrieth Complex Figure Test assessing perceptual organisation and visual memory. AVLT=Auditory Verbal Learning Test assessing memory span and verbal learning. HADS=Hospital Anxiety and Depression Scale. QoL=quality of life. NS=not significant. NR=not reported. NCF=neurocognitive functioning. MMSE=Mini-Mental Status Examination, a rapidly and easily administered test used to detect mild dementia. HVLT=Hopkins Verbal Learning Test. ADLS=Activities of Daily Living Scale. LS=Late Effects Normal Tissue (LENT)–Subjective, Objective, Management, Analytic (SOMA) scale, the result of a collaboration between the EORTC and Radiation Therapy Oncology Group (RTOG). *Data are proportion of patients (%) or n/N (%).

Table 3: **Prospective studies comparing prophylactic cranial irradiation to controls or prophylactic cranial irradiation at two different doses with neurocognitive or quality of life assessments**

reported that neurocognitive function and MRI findings did not differ between groups. The same team had previously reported on a series of 75 patients with locally advanced NSCLC treated with a trimodality therapy, of whom 47 received prophylactic cranial irradiation.[75] Neuropsychological testing showed impairments in attention and visual memory in long-term survivors independent of whether they had received prophylactic cranial irradiation. T2-weighted MRI showed white matter abnormalities of higher grade in patients who received prophylactic cranial irradiation compared with those who did not.

Two RTOG studies have assessed neurocognitive outcome with prophylactic cranial irradiation.[89,92] All patients included in the RTOG 0214 trial that assessed prophylactic cranial irradiation in patients with stage III NSCLC had a neurocognitive function assessment based on MMSE, the Activities of Daily Living Scale, and HVLT; the battery of tests was therefore simpler than that used in the RTOG 0212 trial. Quality of life was assessed with the EORTC HRQoL questionnaire (QLQ-C30) and brain module (QLQ-BN20). The researchers published their results with a median follow-up of 24 months.[72] At 1 year, there were no significant differences in global cognitive function (MMSE) or quality of life between prophylactic cranial irradiation and observational groups, but there was a significant decline in memory as measured by the HVLT in the prophylactic cranial irradiation group. Looking at neurocognitive functions over time, the researchers noted an immediate decline after prophylactic cranial irradiation on the basis of the different tests (MMSE, immediate recall [IR], delayed recall [DR]) at 3 months, followed by some degree of subacute recovery (MMSE, IR, DR) at 6 months, followed up by a chronic decline (DR) or stabilisation (MMSE, IR). An updated analysis will help to establish whether there could be some recovery with more time.[89] Another study pooled two randomised trials (RTOG 0212 and RTOG 0214) to analyse decline in tested and self-reported cognitive functioning after prophylactic cranial irradiation.[92] Patients treated with prophylactic cranial irradiation had a more than three-fold higher risk of self-reported neurocognitive decline at 6 months (odds ratio [OR] 3·60, 95% CI 2·34–6·37; p<0·0001) and 12 months (OR 3·44, 1·84–6·44; p<0·0001) compared with patients assigned to observation. Decline in HVLT recall score at 6 and 12 months was also associated with prophylactic cranial irradiation treatment but was not closely correlated with decline in self-reported cognitive functioning at the same timepoints.

Importance of baseline evaluation and compliance

In the prophylactic cranial irradiation intergroup trial in which all patients with SCLC had prophylactic cranial irradiation, most had minor or moderate complaints if any.[90] However, there was a decline over time: in the group treated with the current standard dose of 25 Gy, the proportions of patients with abnormal quality of life cognitive functioning at baseline, 6, 12, 24, and 36 months were 23%, 35%, 38%, 41%, and 35%, respectively, but 65% of patients did not complain of abnormal cognitive functioning at 3 years. For intellectual deficit assessed by the clinicians with the Late Effects Normal Tissue (LENT)-Subjective, Objective, Management, Analytic (SOMA) scale, the proportions of patients with abnormal status at baseline, 12, 24, and 36 months were 10%, 12%, 20%, and 27%, respectively. Less than 14% of the whole population had the poorest self-reported quality of life status and less than 6% had grade 3 or 4 as reported by the LENT SOMA scale. Of 720 patients with SCLC, there was one reported case of dementia (24 months in the higher dose group), and no cases of apraxia. Notably, confounding factors such as diabetes, advanced age, hypertension, and neurovascular pathologies could contribute to neurocognitive impairment. The limitation of this study, as well as other studies, is that compliance decreased over time: more than 667 (92%) of 720 patients had an initial quality of life or LENT SOMA assessment, but compliance in survivors without brain metastases decreased for the subsequent assessments, reaching 50% at 3 years, considering only patients with sufficient follow-up and not known to be dead or to have brain metastases. In the pooled RTOG 0212 and 0214 analysis focusing on neurocognitive functioning, completion of the self-reported neurocognitive functioning or HVLT at 1 year was around 35%, whether patients had or had not received prophylactic cranial irradiation.[92]

Brain imaging abnormalities

Brain imaging abnormalities (cerebral atrophy, ventricular dilatation, periventricular and subcortical white matter changes) are common and seem to progress over time after brain irradiation.[93,94] Radiation injury seems to be related to a steady rate of white matter damage over time, as indicated by progressive accumulation of white matter changes. However, whether radiation-induced white matter injury correlates with any change in neurocognitive symptoms is not clear, because it varies across studies probably because of the range of imaging modalities used as well as other factors that can induce white matter changes such as diabetes, hypertension, and older age.[90,93–97] In the intergroup study in patients with SCLC, patients were followed up with yearly brain CT scans or MRI. As expected, the percentage of abnormalities was higher in the MRI group because it is known to be more sensitive. Most observed abnormalities were deemed minor to moderate changes.[90] We await with interest the results of an ongoing phase 3 study on prophylactic cranial irradiation in patients with SCLC, which has implemented functional and structural MRI abnormalities as secondary endpoints (NCT01780675).

Because of this risk of potential neurotoxicity, Lee and colleagues[98] proposed a decision analysis model to assess the survival benefit associated with prophylactic cranial irradiation, penalised by its possible neurotoxicity.

The investigators concluded that prophylactic cranial irradiation offered a better quality-adjusted life expectancy over no prophylactic cranial irradiation with moderate or low neurotoxicity.

Future directions

Current areas of active research that hold great potential to reduce the risk of neurocognitive decline after whole-brain irradiation include hippocampal-sparing radiotherapy (figure) and the use of neuroprotective agents.[99–103] Neurocognitive toxicity from whole-brain irradiation might be related to damage to neural progenitor cells in the subventricular zone and hippocampus and the induction of inflammation in the brain. The cause of radiation injury to the brain is likely to be multifactorial, but data suggest that injury to neural progenitor cells and inflammation has a role.[103–105] Reducing radiation dose to the hippocampus during whole-brain irradiation could then reduce or prevent neurocognitive impairment, considering that brain metastases in the hippocampal region seem rare (about 5%).[100,101] A small phase 2 RTOG trial has shown that whole-brain irradiation for brain metastases with the hippocampal-sparing technique was associated with the preservation of memory and quality of life compared with historical series.[102] The mean relative decline in HVLT-Revised (HVLT-R) distant recall score from baseline to 4 months was 7% compared with 30% in historical series. These findings have generated several studies assessing prophylactic cranial irradiation with or without hippocampal sparing. In most of these trials, neurocognitive function is the primary endpoint. There are ongoing phase 3 trials in patients with SCLC in the Netherlands and Belgium (NCT01797159), Spain (NCT01780675), and in North America led by NRG Oncology (formerly RTOG; NCT02635009). The studies in Spain and North America are assessing hippocampal volume on MRI as a potential predictor of cognitive decline. A phase 3 trial is planned in Germany to investigate the effect of hippocampal-sparing prophylactic cranial irradiation on survival status in patients with locally advanced adenocarcinoma (NCT02341170). Clinicians are invited to support the existing trials by accruing patients to them.

Preclinical studies suggest a potential role of exercise in attenuating cognitive impairments by increasing hippocampal neurogenesis.[99] Erythropoietin, lithium, melatonin, and memantine have been described as potential neuroprotectants.[106–109] Preclinical studies of peroxisome proliferator-activated receptor agonists and renin-angiotensin system blockers, clinically approved and well-tolerated agents used in the treatment of type 2 diabetes, hyperlipidaemia, and hypertension, have suggested that these drugs could prevent or ameliorate radiation-induced cognitive impairment independent of changes in neurogenesis.[105] Two potential neuroprotectants have been investigated in phase 3 trials.

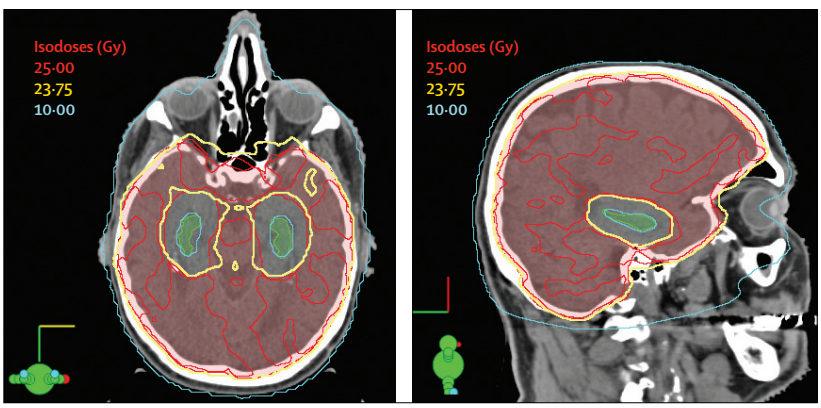

Figure: **Isodose distribution of prophylactic cranial irradiation with avoidance of the hippocampus**
The maximum mean dose to the right and the left PRV (planning organ at risk volume, being the hippocampus as defined on MRI plus an isotropic margin of 5 mm) of the hippocampus is 10 Gy in ten fractions. The rest of the brain receives a mean dose of 25 Gy in ten fractions. Axial (A) and sagittal (B) views.

The first, memantine, was assessed in a trial (RTOG 0614) that included 508 eligible patients treated with whole-brain irradiation for brain metastases, of whom 149 were evaluable.[110] 335 (70%) of the population had lung cancer and 80 patients were asymptomatic or had minor symptoms before whole-brain irradiation. Compared with placebo, the use of memantine during and after whole-brain irradiation resulted in better cognitive function over time, specifically delaying time to cognitive decline and reducing decline in memory, executive function, and processing speed. However, decline in HVLT-R distant recall score did not differ between the memantine and placebo groups. Because memantine was very well tolerated, the investigators concluded that its use during whole-brain irradiation should be considered.

The second, donepezil, was assessed in a 24-week, placebo-controlled, phase 3 trial in 198 patients who had whole-brain irradiation or partial brain irradiation for brain metastases or primary tumours in the past 6 months.[111] 15 (8%) patients included in the analysis had prophylactic cranial irradiation; a subgroup analysis was not done. The researchers concluded that neurotransmitter regulators, like the reversible acetylcholinesterase inhibitor donepezil, could have a role in treating cognitive impairment associated with brain cancer and its treatments. However, treatment with donepezil did not significantly improve cognitive function. Donepezil seemed more effective in patients with greater pretreatment cognitive impairment. An ongoing phase 1/2 study is investigating the effects and safety of lithium in patients with SCLC, because this drug might help to prevent or lessen memory problems caused by prophylactic cranial irradiation (NCT01553916).

Conclusion

Randomised trials have shown that neurocognitive functions seem to be moderately altered after prophylactic cranial irradiation compared with no prophylactic

Search strategy and selection criteria

We identified data for this Review by searching PubMed and references from relevant articles. We used the search terms "prophylactic cranial irradiation", "PCI", "lung cancer", "small cell lung cancer", "non small cell lung cancer", "radiotherapy", "quality-of-life", and "neurocognitive function". We included only articles published in English before Dec 31, 2015. We searched the ClinicalTrials.gov database for the term "prophylactic cranial irradiation" for trials of this intervention in lung cancer.

cranial irradiation. The use of concomitant chemotherapy with prophylactic cranial irradiation, as well as large dose per fraction, results in a significant increase in neurotoxicity.[84–85] Such neurological and intellectual impairment is a subject of concern to clinicians. Several strategies to reduce neurotoxicity are being investigated, and efforts to identify high-risk patients should be pursued. This risk has to be weighed against the benefits of prophylactic cranial irradiation in terms of reduced incidence of brain metastases and increased survival in SCLC. Patients have to be informed of the potential harm of prophylactic cranial irradiation, which is generally moderate. The risk of neurotoxicity seems to be higher in elderly patients, and in patients with vascular risk factors. There is currently no really effective second-line treatment in SCLC and survival after brain failure is poor because brain metastases are often small and disseminated, and therefore less accessible to local treatments, such as stereotactic radiotherapy. Evidence from randomised controlled trials and a meta-analysis strongly suggests improved survival with prophylactic cranial irradiation in patients with SCLC; therefore, prophylactic cranial irradiation is recommended by most guidelines as part of standard treatment. The use of prophylactic cranial irradiation continues to be investigated in high-risk patients with NSCLC. Prophylactic cranial irradiation should be reconsidered if long-term survival increased dramatically or if neurotoxicity appeared more frequent and more severe.[98] Thus, long-term follow-up of patients included in prospective studies is needed.

Contributors

CLP did the literature search, and wrote and edited the manuscript. AS, BJS, and EMG contributed to the writing and editing of the manuscript. DDR and JB contributed to the literature search, and to the writing and editing of the manuscript. DDR provided the figure.

Declaration of interests

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