Incidence of symptomatic brain metastasis following radical radiotherapy for non-small cell lung cancer: is there a role for prophylactic cranial irradiation?

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Objective: Brain metastases following radical radiotherapy for non-small cell lung cancer (NSCLC) are a recognised phenomenon; however, the incidence of symptomatic brain metastasis is currently unknown. The aim of the study was to identify the number of patients, staged in accordance with National Institute for Health and Clinical Excellence (NICE) guidance, who developed symptomatic brain metastasis following radical radiotherapy. There are two aims: to evaluate NICE guidance; and to provide vital information on the likely benefit of prophylactic cranial irradiation (PCI) in reducing neurological symptoms from brain metastasis.

Methods: A retrospective review of 455 patients with NSCLC who had undergone radical radiotherapy in 2009 and 2010 was performed. Computer-based systems were used to identify patient and tumour demographics, the staging procedures performed and whether brain imaging had identified brain metastasis in the follow-up period.

Results: The total number of patients with brain metastasis within 6 months was 3.7%. The proportion of brain metastasis within 6 months in Stage I, II and III NSCLC throughout both years was 2.8%, 1.0% and 5.7%, respectively. Within the follow-up period (median 16 months, range 6–30 months), the total number of patients who developed symptomatic brain metastasis was 7.9%.

Conclusion: Patients staged in accordance with NICE guidance, of whom only 7.7% underwent brain staging, have a minimal incidence of brain metastasis following radical radiotherapy. The number of patients developing symptoms from brain metastasis following radical radiotherapy may be less than the morbidity caused by PCI.

Advances in knowledge: This finding supports the NICE guidance and brings into question the potential benefit of PCI.

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Brain metastases occur in 20% of patients with non-small cell lung cancer (NSCLC) and have a profound impact on quality of life [1]. The median survival is less than 3 months [2–5]. Although they are more common in higher stages and in adenocarcinoma, brain metastases can occur in any stage and in any tumour type [6–8].

Staging with CT of the chest/abdomen/pelvis and positron emission tomography (PET)/CT is performed prior to radical treatment to rule out systemic metastatic disease [5]. However, staging the brain is not routine in the UK. This is likely to be the result of the National Institute for Health and Clinical Excellence (NICE) guidelines from 2005, which suggested that staging in this setting is optional. A recent update in April 2011 has maintained the same guidance. NICE suggests that staging the brain prior to radical treatment should be left to the discretion of the clinician: “Consider MRI or CT of the head in patients selected for treatment with curative intent, especially in stage III disease” [9]. These guidelines conflict with National Comprehensive Cancer Network guidelines, which recommend staging the brain

in any patient being worked up for radical treatment of NSCLC Stage IB or higher [10]. Because of these conflicting guidelines, the UK thoracic community is undecided on whether or not to stage the brain routinely prior to radical treatment.

Radical treatment has evolved significantly over the last 10 years, and these changes in treatment make it increasingly important to identify brain metastasis prior to radical treatment. These changes include:

1. The increasing toxicity of treatment with the implementation of multimodality treatment and dose escalation [11, 12]. These changes have improved the median survival of patients to between 22.3 and 23.6 months [13, 14]. This lengthy, toxic, expensive treatment is entirely appropriate when we aim to achieve these median survival figures. However, in patients with aggressive, large or multiple brain metastases, the median survival is 2.7 months; with this limited life expectancy, multimodality treatment becomes entirely inappropriate [15]. As the toxicity of radical treatment increases, the clinical and economic benefit of delivering radical toxic treatment to patients without ruling out non-radically treatable brain metastasis becomes more questionable.

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2. There is a wider availability and increasing use of radical approaches to patients with solitary or a limited number of brain metastases; these include surgical resection or stereotactic radiosurgery to the brain. 5-year survival following resection is reported to be 10–20% [16, 17], and following synchronous primary NSCLC and brain metastasis treated with radical thoracic treatment and stereotactic irradiation of the brain lesion(s) is reported to be as high as 21% [18]. With the option of radical treatment to solitary or limited brain metastases, it is important to identify these patients so appropriate treatment can be instigated with the hope of improving overall survival.

For these reasons, throughout the UK thoracic oncology community, the question remains whether staging the brain should be obligatory rather than optional.

There is also increasing interest in the use of prophylactic cranial irradiation (PCI) in NSCLC. PCI is the delivery of prophylactic irradiation to the whole brain with two potential benefits. First is the potential for PCI to improve overall survival. This is achieved by reducing risk of brain metastases and as a result the associated mortality. An overall survival benefit has been demonstrated in selected patients with both limited and extensive stage small cell lung cancer [19, 20]. The other potential benefit of PCI is a reduction in the significant morbidity of brain metastases, which includes neurological symptoms, neurocognitive impairment, reduction in performance status and steroid-induced myopathies. However, this must be measured against the toxicities of PCI. In the short term these include headache, fatigue, alopecia, nausea, vomiting and insomnia [21], and in the longer term the most concerning side-effects are neurocognitive decline and decreased quality of life [22–24].

A recent study demonstrated that the use of PCI in locally advanced NSCLC reduced the 1-year brain metastasis rate from 18.0% to 7.7% [25]. The end point was overall survival; however, because of poor accrual there was insufficient power to determine any overall survival benefit. In this study, asymptomatic patients were scanned routinely as survival was the primary end point. There is no information regarding symptomatic patients; therefore, no conclusions can be reached regarding the potential of PCI to reduce brain metastasis-related morbidity.

Possibly as a result of increased aggressive treatments to cranial metastasis, the cause of death in the majority of patients with brain metastases is extracranial disease [26]. This may suggest that survival is not the best end point in studies looking at therapeutic interventions, but a decrease in brain metastasis-related morbidity may be more appropriate [27]. The toxicity of PCI is well documented; to compare this with the morbidity of brain metastases it is vital to quantify the incidence of symptomatic brain metastases after radical treatment. Asymptomatic brain metastases in patients being worked up for radical radiotherapy have been widely reported at between 4.8% and 14% [28–31]; however, there are no reports looking at the incidence of symptomatic brain metastases following radical treatment.

We planned to identify the number of patients who received radical radiotherapy in the West of Scotland

who subsequently presented with symptomatic brain metastasis within 6 months of radical treatment. The two aims of this study were to offer guidance both locally and nationally on whether NICE guidance is adequate and to provide further evidence to inform the decision regarding the potential benefit of PCI.

Methods and materials

We performed a retrospective review of all patients who had undergone radical radiotherapy for NSCLC during 2009 and 2010 in The Beatson West of Scotland Cancer Centre, Glasgow, UK. Over this period of time, the local guidelines were identical to the current NICE guidelines. Imaging of the brain prior to radical treatment was not routine and only occasionally undertaken at the discretion of the oncologist. In our centre there are 12 radiation oncologists treating lung cancer; therefore, it is difficult to define criteria for staging the brain. Anecdotally, brain scans were performed if patients complained of headaches or other neurological symptoms; however, within this study it is impossible to define the indication for brain imaging. Patients treated with radical radiotherapy who had presented with synchronous, radically treatable brain metastases were excluded. As a result, only patients with negative brain staging or no brain staging were included. PCI is not offered at our centre.

Patients were included if they had received a 2-Gy equivalent dose of ≥ 60 Gy in 30 fractions as part of sole or multimodality treatment for NSCLC. Patients receiving radiotherapy for recurrent disease were excluded. If the patient had two primary tumours, the tumour with the highest stage was noted. The Beatson West of Scotland Cancer Centre is the tertiary referral centre for four main National Health Service (NHS) trusts. Only patients who had undergone initial staging within one of these four trusts were included.

The ARIA® Oncology Information System v. 8.6 (Varian Medical Systems, Palo Alto, CA) was used to identify patients and note the start date of treatment and the total dose delivered. The four NHS trusts that refer to The Beatson West of Scotland Cancer Centre have three separate electronic systems where pathology and radiology reports are stored. These include the SCI Store (SCI NHS National Services Scotland, Edinburgh, UK) for Lanarkshire and for Forth Valley; Clinical Portal (eHealth Clinical Portal, Scottish Centre for Telehealth, Aberdeen, UK) for Greater Glasgow and Clyde; and Electronic Results Reporting (e-Health Department, NHS Ayrshire & Arran, Ayr, UK) for Ayrshire and Arran.

The primary end point was the development of symptomatic brain metastases within 182 days (6 months) from the start of treatment. 6 months was selected as a cut-off as this is a short enough period of time that the brain metastasis would probably have been visible at staging prior to treatment. In our centre, following radical radiotherapy, patients only undergo brain imaging if there are neurological symptoms. As a result, all patients with brain imaging demonstrating brain metastasis within this time frame will have been symptomatic. These were identified using the above electronic systems. In addition, the following factors

Table 1. Patient and tumour demographics

Characteristics	Patients, n (%)
Total	455 (100)
Pathology	
Adenocarcinoma	81 (18)
Squamous	214 (47)
Unclassified	94 (21)
No pathology	62 (14)
Other	4 (1)
Stage	
I	144 (32)
IA	83 (18)
IB	61 (13)
II	99 (22)
IIA	56 (12)
IIB	43 (10)
III	210 (46)
IIIA	164 (36)
IIIB	46 (10)
IV	2 (0)

were noted: any brain imaging within 2 months (80 days) prior to radical treatment, tumour stage, tumour pathology and whether a PET/CT had been performed. The secondary end point was the presence of brain metastases up to the date of data analysis; therefore, these results were also noted.

Those who had developed brain metastasis had their imaging reviewed to ascertain whether the patient would have been appropriate for more radical treatment to the brain. According to our local guidelines, radical brain radiosurgery can be considered when fewer than three lesions measuring <3 cm are present. We noted the number of patients who would have been eligible for radical treatment on the basis of brain imaging and described whether patients went on to receive radiosurgery. In those who did not, the rationale for not performing radiosurgery was described.

Results

The retrospective review of all radically treated patients identified 455 eligible patients. Patient and tumour characteristics are illustrated in Table 1. Staging prior to radical treatment is illustrated in Table 2.

The total percentage of patients with symptomatic brain metastasis within 6 months was 3.7%. The

Table 2. Additional staging investigations performed prior to radical radiotherapy

Characteristic	Patients, n (%)
Total number	455 (100)
PET/CT	
Yes	410 (90)
No	45 (10)
Brain imaging	
Yes	35 (7.7)
No	420 (92.3)

PET, positron emission tomography.

proportion of brain metastases within 6 months in Stage I, II and III NSCLC throughout both years was 2.8%, 1.0% and 5.7%, respectively. Figure 1 demonstrates the number of brain metastases in each stage.

Only 35 (7.7%) patients underwent brain staging prior to radical radiotherapy. Of the remaining 420 patients, only 3.6% developed brain brain metastases within 6 months of radical radiotherapy.

Of the 17 patients who developed brain metastases within 6 months, 7 were <3 cm and <3 in number, which is our current local guidance for stereotactic radiosurgery to the brain. Despite this, only two patients went on to receive radiosurgery. There were a number of reasons why the remaining five patients did not receive radiosurgery: two patients deteriorated from a neurological perspective too quickly to be suitable; one patient had systemic disease requiring systemic treatment, one patient had low performance status owing to progressive systemic disease; and one patient died of a chest infection prior to undergoing radiosurgery (Figure 2).

The median follow-up was 16 months (range 6–30 months). The total percentage of patients who had developed symptomatic brain metastases within the follow-up period available was 7.9%. In the group who had not undergone staging of the brain, the total percentage of symptomatic brain metastases within this follow-up period was 7.4%.

Discussion

It is an anticipated finding that the number of brain metastases identified in our study is less than in previously published papers staging asymptomatic patients. We have quantified a different group—patients who have symptoms from their brain metastasis prior to

Figure 1. Number of patients developing symptomatic brain metastases.

Figure 2. Patients developing brain metastases within 6 months and subsequent treatment.

problematic local or systemic disease. This is the first study quantifying the group of patients who have symptomatic brain metastasis within 6 months of aggressive radical treatment.

There are obvious limitations to a retrospective, cancer centre-based study. Although electronic systems are reliable for imaging results, if patients had moved outside their presenting area following radical treatment, or if they had presented with symptoms but imaging was not felt to be appropriate because of performance status or comorbidities, they will not have been identified. This introduces the potential for a small underestimation of the number of symptomatic brain metastases. Another problem of a cancer centre-based study is that information on toxicities, clinical outcomes and cause of death is not available. This would have contributed important outcome data and could have led to more significant, potentially management altering, data. This raises the continued need for adequate data collection within the NHS.

The NICE guidelines were followed during this time frame with a CT of the brain occasionally being performed at the discretion of the clinician. Ideally, the rate of brain imaging in asymptomatic patients could have been assessed. However, those with synchronous brain metastasis at presentation were excluded from the study and those with multiple metastases would not have been identified as they would not have proceeded to radical treatment. As a result, it is not possible to assess the rate of imaging in asymptomatic patients, although we have reported the number of patients in our series who underwent brain imaging prior to radical radiotherapy and it is low at 7.7%. The low rate of symptomatic brain metastases in our group, staged according to NICE guidelines, indicates that current guidelines are appropriate.

This result brings into question the requirement for PCI. This is the first study with a large cohort of patients looking at the rate of symptomatic brain metastasis within 6 months of radical treatment. With such a low rate of symptomatic brain metastasis it is difficult to advocate PCI, with the toxicity involved. In the aforementioned Phase III clinical trial of PCI, 340 patients were randomised between observation and PCI. They demonstrated a reduction in brain metastasis; however, data on whether these patients were symptomatic or asymptomatic were not provided. It is likely that a large

number of these patients had asymptomatic brain metastasis as they were routinely scanned. It is difficult to justify the significant morbidity in patients who do not develop neurological symptoms from their brain metastasis or in those who have local or systemic relapse prior to any neurological symptoms as a result of brain metastasis. Although there may be criticism that our primary end point was brain metastasis at 6 months, as this may not be long enough to identify a potential benefit for PCI, there is a 16-month median follow-up (range 6–30 months) in the group as a whole. As there is good evidence that only a small number of brain metastases occur more than 12 months after initial treatment [32], the fact that only 7.9% of patients had symptomatic brain metastasis with our 16-month median follow-up is concerning to those advocating PCI.

A further observation is that a significant proportion of those suitable for radiosurgery did not undergo the procedure, owing to progressive systemic disease. This would suggest that systemic disease can cause symptoms prior to asymptomatic brain metastases, further confirming the requirement to assess the number of symptomatic metastases rather than asymptomatic brain metastasis to measure the benefit of PCI.

We would conclude that our current practice, of staging the brain in high-risk cases only, is sufficient to identify the majority of patients who will have symptomatic brain metastasis within 6 months. In addition, the low rate of symptomatic brain metastasis found in our study brings into question the necessity for PCI. Finally, although there is a suggestion in the literature that identifying brain metastasis earlier provides a better prognosis [33], this is currently unproven. Until this is studied further in a prospective trial, there is no robust rationale for routine brain imaging in NSCLC patients undergoing work-up for radical treatment.

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