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Brain metastases following radical surgical treatment of non-small cell lung cancer: Is preoperative brain imaging important?

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ABSTRACT

Objectives: There is a lack of good quality evidence or a clear consensus of opinion internationally regarding who should receive preoperative imaging of the brain prior to radical treatment for non-small cell lung cancer (NSCLC). We aimed to establish the proportion of patients who developed brain metastases following curative surgery and to estimate how many could have been detected by preoperative magnetic resonance imaging (MR).
Methods: We performed a retrospective analysis of 646 patients who underwent surgery for lung cancer with curative intent at a regional thoracic surgical centre in the United Kingdom. We identified those who developed brain metastases in the postoperative period and, by using volume doubling times, estimated the size of the metastasis at the time of surgery. We then determined the proportion of metastases that would have been seen on preoperative MR brain at detection thresholds of 2 and 5 mm diameter.
Results: There was a 6.3% incidence of postoperative brain metastases, with the majority occurring within 12 months of surgery. Those who developed metastases were more likely to have adenocarcinoma and the majority had early stage malignancy (73% stage I or stage II).

We estimate that 71% of those who developed cerebral metastases might have been detected had they undergone MR brain as part of their staging (4.4% of all patients).
Conclusion: Based on our findings we suggest that, in addition to standard staging investigations, patients have brain imaging (MR or equivalent) prior to curative surgery in NSCLC regardless of preoperative stage.

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1. Introduction

American College of Chest Physicians (ACCP) guidelines recommend magnetic resonance imaging (MR) of the brain in those with clinical stage III or IV disease even if neurologically asymptomatic [1], whilst National Institute for Health and Care Excellence (NICE) and British Thoracic Society (BTS) guidelines recommend consideration of MR or contrast-enhanced CT of the head in patients selected for treatment with curative intent, particularly in stage III disease [2,3]. The level of evidence to support these recommendations is low, owing to there being no large study to definitively support this guidance or a clear consensus of opinion. The widespread use of integrated positron emission tomography–computed tomography (PET–CT) preoperatively, which often includes head CT, may also detect a proportion of brain metastases. Thus the potential gain from more sensitive brain imaging such as MR or contrast-enhanced CT of the brain is uncertain.

In this study our aim was to establish the proportion of patients who developed brain metastases following curative surgery, all of whom were staged with preoperative PET–CT, and to estimate how many could have been detected by preoperative MR.

2. Materials and methods

2.1. Study population

We performed a retrospective study of all patients who underwent surgery for lung cancer with curative intent at Nottingham

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University Hospitals (NUH), a regional thoracic surgical centre, between 2006 and 2011. All patients had a preoperative PET–CT from vertex to mid-thigh. CT was performed without contrast and CT parameters used for attenuation correction. The FDG dose was 400 MBq and dose to scan time was 1 h. We used electronic patient records and radiological imaging to identify those who developed brain metastases in the postoperative period and also accessed radiology and patient records at the referring district general hospital to ensure that we obtained complete follow-up data on each patient.

2.2.. Covariate definitions

Stage and histological sub-type were obtained from patient records and pathological reports. Procedure types were coded as segmentectomy/wedge resection, lobectomy/bilobectomy, pneumonectomy/sleeve pneumonectomy, sleeve resection +/− lobectomy, video-assisted thoracoscopic (VATS) resection/lobectomy or any resection with chest wall resection. All CT, MR and PET–CT images were imported to the NUH picture archiving and communication system (PACS). They were independently reviewed by a consultant radiologist to ensure that there was no visible cerebral metastasis on the preoperative PET–CT and to confirm the presence of postoperative metastases. The maximum diameter of the largest metastasis was measured for each patient and the number of metastatic deposits on the diagnostic scan recorded as 1, 2 or multiple (if there were greater than two separate deposits). Patient records were then reviewed to look at subsequent management and date of death (if applicable) was obtained. Follow-up data and death records were last updated on 30th September 2012 to ensure that we had at least 12 months complete follow-up on each patient. We chose 12 months as we felt that it was reasonable to expect a brain metastasis to have been potentially visible pre-operatively if it was detected within this time frame.

2.3. Determination of preoperative detectability

We wanted to determine if the brain metastasis might have been visible on a preoperative MR brain. To do this we estimated how large a metastasis would have been at the time of surgery. This was calculated by using the measurements of the largest metastasis and the time from the date of surgery. A paper by Yoo et al. [4] looked at metastatic brain tumour growth rates in NSCLC and found a volume doubling time of 58.48 days. We calculated the change in diameter of lesions over time using this volume doubling time (rounded to 60 days), assuming the metastases were spherical. We plotted the change in diameter over time of 2 mm and 5 mm diameter lesions. These represent the detection limits for optimally performed MR and a more generous "real world" threshold respectively. We then plotted the maximum tumour diameter measured on the diagnostic scan against the number of days after surgery that the imaging was performed. We used the date of surgery as time 0. The lesions that fell above the detection limit curves were classified as likely visible had a preoperative MR been performed and reported optimally or in "real world".

2.4. Statistical analysis

All statistical analyses were performed using Stata/MP, version 12 (StataCorp LP) software.

3. Results

3.1. Study population

We identified 891 patients who underwent surgery with curative intent over this time period. We excluded 159 who had resection of a solitary secondary lung deposit, 3 who were diagnosed with a brain metastasis in the pre-operative period, 1 who did not undergo curative resection as extensive pleural disease was found at the time of the procedure and 1 with incomplete follow-up data. A further 20 duplicate records were excluded and we also excluded 61 patients who had non-lung histology, small cell lung cancer (SCLC), carcinoid or benign disease (Fig. 1). This left a population of 646 patients in total. All had pre-operative PET–CT confirming no distant metastases.

Patients were more likely to be male (59%) and to have squamous cell carcinoma (51%) in our surgical population. Median age at the time of surgery was 69 years (interquartile range (IQR) 63.7–74.6 years) and the most common procedure type performed was lobectomy/bilobectomy (57%). Seventy patients (11%) died within 6 months of surgery. Of these, 3 were diagnosed with brain metastases and the others died of surgical complications, other metastatic complications or co-morbid conditions.

3.2. Brain metastases patient demographics

Overall 41 (6.3%) patients developed brain metastases during the follow-up period. All of these patients were neurologically asymptomatic at the time of their surgery. Twelve were diagnosed with brain metastases within 6 months of surgery (1.9%) and 16 (2.5%) were diagnosed within 6–12 months. Demographics of those who developed brain metastases compared to those who did not is summarised in Table 1. Those with cerebral metastases were more likely to have adenocarcinoma sub-type (56%). Four per cent with stage I disease developed brain metastases (16/361), which rose to 8% of those with stage II disease (13/161) and 9% of those with stage III disease (11/123).

Eighteen patients (44%) had solitary metastases, 6 (15%) had 2 deposits visible and 17 (41%) had multiple metastases at the time of diagnosis. Ninety per cent (37) who developed brain metastases died during the study period, with a median survival of 100 days following diagnosis of the metastasis (IQR 29–160 days).

3.3. Detection by MRI brain

We excluded three patients who developed metastases at over 2 years post-surgery from this portion of the analysis as we felt that these could not reasonably have been detected with a pre-surgery MR brain. Fig. 2 shows the plot of the remaining 38 patients with curves to show both 2 mm and 5 mm detection thresholds.

Using a 5 mm detection threshold 29 (71%) of brain metastases should have been of at least 5 mm maximum diameter at time 0. Using a 2 mm detection threshold 34 (83%) would have been at least 2 mm in maximum diameter at time 0. These would be potentially detectable had MR brain been performed as part of the staging process. This means that 4.4% (29/646) of our patients who underwent surgery would have had their brain metastases detected by preoperative MR and this might have been as high as 5.3% (34/646) with optimal MR detection limits.

4. Discussion

In our large series of 646 patients we have shown a 6.3% incidence of post-operative brain metastases, with the majority (4.4%) occurring within 12 months of surgical resection. Those who subsequently developed metastases were more likely to have had an

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