Brain imaging in lung cancer staging:

A real-world, multi-centre study of prevalence of brain metastases, impact on treatment and re-modelling of the NICE health economic analysis

Authors: Christopher Brockelsby[1], Ross Maconachie[2], Neal Navani[3], Ruth Prendecki[3], Victoria Randles[4], Jenny King[1], Babar Dildar[1], Xiang Lee[5], Thapas Nagarajan[5], Matthew Rice[6], Haider Al-Najjar[6], Abby Atkins[7], Ram Sundar[7], Louise Brown[8], Sumat Sharma[9], Emma O'Dowd[10], Elinor Crisp[10], Muhammad Tufail[11], Claire Vella[11], Seamus Grundy[12] & Matthew Evison[1]

[1]*Lung Cancer and Thoracic Surgery Directorate, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Southmoor Road, Manchester, M23 9LT.*

2 NICE Centre for Guidelines, National Institute for Health and Care Excellence.

3 Lungs for Living Research Centre, UCL Respiratory, University College London, and Department of Thoracic Medicine, University College London Hospital, London, United Kingdom

 4. Mid-Cheshire Hospitals NHS Foundation Trust, Leighton Hospital Middlewich Rd, Crewe CW1 4QJ

5. East Cheshire NHS Trust, Macclesfield District General Hospital Victoria Road Macclesfield, Cheshire, SK10 3BL

6. Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Oxford Road, Manchester M13 9WL

7. Royal Albert Edward Infirmary, Wrightington, Wigan & Leigh NHS Foundation Trust, Wigan Lane, Wigan WN1 2NN

8. The Pennine Acute Hospitals NHS Trust, North Manchester General Hospital, Manchester M8 5RB.

9. University Hospitals of Derby and Burton NHS Foundation Trust, Uttoxeter Rd, Derby DE22 3NE

10. Nottingham University Hospitals NHS Trust, Nottingham City Hospital Hucknall Road, Nottingham NG5 1PB

11. Glenfield Hospital, University Hospitals of Leicester NHS Trust, Groby Road, Leicester LE3 9QP

12. Salford Royal Hospital, Stott Lane, Salford, M6 8HD

Corresponding Author: Dr Christopher Brockelsby christopher.brockelsby@mft.nhs.uk

Highlights:

Non-small cell lung cancer

Brain imaging

Economic analysis

Magnetic resonance imaging

Diagnostic imaging

Abstract

Introduction: In 2019, the National Institute for Health and Care Excellence (NICE) updated their recommendations with respect to brain imaging in the staging of non-small cell lung cancer (NSCLC) based on an analytic cost-effectiveness model using published data and modelling assumptions from committee experts. In this study, we aimed to re-run this model using real-world multi-centre UK data.

Materials and Methods: Retrospective data was collected on consecutive patients with radically treatable clinical stage II and III lung cancer from eleven acute NHS Trusts during the calendar year 01/01/2018 to 31/12/2018. Following a written application to the NICE lung cancer guideline committee, we were granted access to the NG122 brain imaging economic model for the purpose of updating the input parameters in line with the real-world findings from this study.

Results: A total of 444 patients had data for analysis. The combined prevalence of occult brain metastases was 6.2% (10/165) in stage II and 6% (17/283) in stage III, compared to 9.5% and 9.3% used in the NICE economic model. 30% of patients with clinical stage III NSCLC and occult BMs on pre-treatment imaging went to complete the planned curative intent treatment of extracranial disease, 60% completed SRS to the brain and 30% completed WBRT. This compares to 0%, 10% and 0% in the NICE assumptions. The health economic analysis concluded that brain imaging was no longer cost-effective in stage II disease (ICERs £50,023-£115,785) whilst brain imaging remained cost-effective for stage III patients (ICERs 17,000-£22,173), with MRI being the most cost-effective strategy.

Conclusion: This re-running of the NICE health economic model with real-world data strongly supports the NICE guideline recommendation for brain imaging prior to curative-intent treatment in stage III lung cancer but questions the cost-effectiveness of CT brain imaging prior to curative-intent treatment in stage II lung cancer.

Introduction

The role of brain imaging to detect asymptomatic brain metastases (BMs) prior to curative-intent treatment in patients with lung cancer continues to be an area of debate across the international lung cancer community [1]. The detection of asymptomatic BMs may change the type of treatment from curative-intent to palliative-intent treatment and may necessitate specific BM treatment to achieve the best patient outcomes. These changes may have significant impacts on healthcare costs. Furthermore, for the individual patient, detection of asymptomatic BMs could preclude driving. However, there is much disparity between international guidelines on the provision of routine brain imaging in lung cancer staging. In 2019, the National Institute for Health and Care Excellence (NICE) updated their recommendations in this area of lung cancer diagnosis and management [2]. For patients with clinical stage III non-small cell lung cancer (NSCLC) lung cancer, NICE recommend a contrast-enhanced MR brain is performed and for patients with clinical stage II NSCLC a contrast-enhanced computed tomography (CT) scan of the brain is performed, followed by an MR brain scan if suggestive of BMs. NICE recommend patients with stage I lung cancer do not undergo routine brain imaging prior to curative-intent treatment. These recommendations were underpinned by a decision analytic cost-effectiveness model across stage I, II, and III NSCLC sub-groups. The principal differences between the model's inputs for these different subgroups were the assumed prevalence of brain metastases (BM) and the committee's assumptions about what treatments they would receive given a positive result (Table 1). The prevalence of brain metastases used in the model was taken from a

retrospective single-centre United Kingdom (UK) study that examined the proportion of patients presenting with brain metastases in the 12 months following surgical resection and which also estimated how many of these patients would have visible brain metastases on pre-operative brain imaging using a reverse volume doubling time calculation [3]. Treatment decisions used in the modelling for patients identified to have brain metastases were based on the assumptions of the NICE guideline committee. The accuracy of this model is, therefore, highly dependent upon the accuracy of the prevalence estimations and the assumptions made on the impact on treatment when asymptomatic brain metastases are identified. In this study, we aimed to perform a multi-centre analysis of real-world prevalence of asymptomatic brain metastases and the real-world impact on treatment decisions. This data could then be re-run through the NICE health economic analysis tool to see if the same conclusions would be made and add further evidence to this topic.

Material and Methods:

Real-world data. Eleven acute care NHS trusts from across the UK contributed to this retrospective real-world multi-centre dataset (MCD) [4]. Data was collected on consecutive patients with clinical stage II and III lung cancer and deemed suitable for curative intent treatment without any symptoms of brain metastases presenting to each trust during the calendar year 01/01/2018 to 31/12/2018. Patients were split into two cohorts: those that underwent pre-treatment brain imaging and those that did not. For those that underwent pre-treatment brain imaging the following data points were collected: 8th edition TNM stage, histological sub-typing, the presence/absence of brain metastases on pre-treatment brain imaging, number of brain metastases if present (categorised as '1-3' or '>4'), the planned treatment prior to the brain imaging, treatment given following the brain imaging and any specific brain metastasis treatment provided including surgical resection, stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT). For those that did not undergo brain imaging prior to treatment, data was recorded on whether the patient presented with brain metastases in the 6-months following treatment. The study did not require NHS REC review [5].

NICE Economic model. Following a written application to the NICE lung cancer guideline committee, we were granted access to the NG122 brain imaging economic model for the purpose of updating the input parameters with the real-world findings from this study. A full description of the NICE economic model is available in NICE NG122 (Evidence Review B pp.88-162). Briefly, the model separately considers stage I, II and IIIA patients who are indicated for radical treatment and assesses the relative

cost-effectiveness of three management strategies; straight to radical treatment, brain imaging with MRI or brain imaging with CT followed by confirmatory MRI. Patients who are positive for 1-3 and 4+ brain metastases (the True Positives) are assigned treatment probabilities that reflect the more advanced nature of their disease. Patients whose brain metastases are undetected proceed to their planned radical treatment. Patients whose brain metastases are detected by the early imaging can gain QALYs through brain metastasis-specific treatments and the NHS realise some cost savings through reductions in surgeries and courses of radical radiotherapy. The incremental costs and benefits of newer targeted and immunotherapies for loco-regional and advanced disease were not included in the model although the guideline committee considered this limitation minor. A fuller discussion is available in the NICE guideline but it should be noted that evidence that is specific enough to accurately model the distal pathway is limited and NHS-discounted treatment costs for newer therapies are seldom in the public domain. In line with the NICE economic model, we removed any patients that were diagnosed with small cell lung cancer from our dataset. Those patients in the non-imaged cohort who did not go on to have radical treatment despite MDT decision were also excluded from analysis. For the prevalence of brain metastases parameter, we used different definitions to provide a broad assessment of cost-effectiveness. This included a 'pre-treatment image-detected prevalence' using only the cohort of patients that completed brain imaging prior to treatment, a 'post-treatment prevalence' using only the cohort of patients that did not undergo pre-treatment brain imaging and a 'pooled prevalence', which pooled the pre and post imaging prevalence data together in meta-analyses for each stage. A random effects model was used for the stage II data because of statistical heterogeneity between the two estimates. To acknowledge that not all brain metastases identified during the 6 months following treatment would have been detected on pre-treatment brain imaging, the 'post-treatment prevalence' was divided by the pooled sensitivity of MR brain imaging to detect metastases used in the NICE economic model. No patients with a positive pre-treatment brain scan were assumed to be false positive, which is consistent with the 100% specificity data for both CT and MRI used in the NICE model. It has been previously demonstrated that the prevalence of brain

metastases is higher in adenocarcinoma sub-type of NSCLC [6]. Therefore, and in line with the NICE model, a sub-group analysis of patients with adenocarcinoma was completed using the lung cancer tumour subtyping data in those patients in the pre-treatment brain imaging cohort. To estimate the prevalence in the post-treatment cohort we used the same relative-risk based equations used in the NICE model; 52% of the cohort having adenocarcinoma histology [7] with a relative risk of 1.97 for BM vs. non-adenocarcinoma patients [3]. For the lung cancer and brain metastases treatment parameters we used the data from the patients that underwent brain imaging prior to treatment and were found to have asymptomatic brain metastases. Using the planned treatment, actual treatment, and brain-specific treatment we could update the proportion of patients in whom the treatment plan changed due to the presence of brain metastases and the type of any brain-specific treatment completed within the economic model and document any differences with the assumptions made by the NICE guideline committee.

Results

A total of 624 patients were submitted for analysis from the 11 contributing trusts. 38 patients were excluded due to a diagnosis of small cell lung cancer and a further 142 patients were excluded as they did not complete radical treatment (Figures 1 & 2). A total of 444 patients had data for analysis in line with the NICE economic model. Patients with clinical stage II lung cancer accounted for 36% (161/444) whilst 64% (283/444) had clinical stage III disease. In the 161 patients with stage II lung cancer, 29% (47/161) underwent pre-treatment brain imaging and 71% (114/161) did not. In the 283 patients with stage III lung cancer 68% (193/283) underwent pre-treatment brain imaging and 32% (90/283) did not. The prevalence of patients with adenocarcinoma in the pre-imaged cohort was 57% (27/47) in stage II and 41% (80/193) in stage III disease.

In stage II lung cancer, the pre-treatment image-detected prevalence of asymptomatic brain metastases was 2.1% (1/47). The post-treatment prevalence of brain metastases was 7.9% (9/114). Therefore, the combined prevalence of occult brain metastases in stage II lung cancer in this study is

6.2% (10/161). This compares to a prevalence of 9.5% (CI: 5.3% -14.8%) used in the NICE economic model. In stage III lung cancer, the pre-treatment image-detected prevalence of asymptomatic brain metastases was 5.2% (10/193). The post-treatment prevalence of brain metastases was 7.8% (7/90). Therefore, the combined prevalence of occult brain metastases in stage III lung cancer in this study is 6% (17/283). This compares to a prevalence of 9.3% (CI: 4.6% - 15.5%) used in the NICE economic model.

There were several differences noted in the assumptions made by the NICE guideline committee on the impact of a positive brain scan on treatment provided (Table 2). In stage II lung cancer 100% (1/1) of patients found to have 1-3 brain metastases on pre-treatment brain imaging continued to have curative intent treatment with surgical resection, compared to 75% assumed in the NICE model. In the 10 patients with stage III NSCLC that underwent pre-treatment brain imaging and were found to have asymptomatic brain metastases, 100% (10/10) had 1-3 metastases. In the ten patients with 1-3 metastases 30% (3/10) continued to have the planned curative-intent treatment of thoracic disease despite the identification of brain metastases compared to the 0% assumed in the NICE model. 70% of patients with stage III disease had their treatment plan changed from curative to palliative based on the identification of brain metastases on imaging. Table 3 presents the planned treatment prior to brain imaging and the actual treatment provided after the identification of asymptomatic BMs. Furthermore, in the same 10 patients with stage III NSCLC found to have 1-3 brain metastases on pre-treatment brain imaging, 60% (6/10) completed SRS to the brain metastases and 30% (3/10) completed WBRT, compared to 10% and 0% used in the NICE model. All patients who underwent WBRT had a diagnosis of adenocarcinoma. The decision regarding WBRT was at the discretion of the neuro-oncology Multidisciplinary team.For these patients the treatment intent was changed from curative to palliative. Finally, we observed that no patients had 4+ BM after their scan whereas the NICE committee had assumed this figure would be 10%. The NICE committee assumed all patients with 4+ BM would switch away from radical treatment.

The health economic analysis was re-run with the input parameters detailed above. Brain imaging was no longer cost-effective in stage II disease across every prevalence input used. Using the most accurate prevalence data (pre-treatment imaging cohort) the incremental cost-effectiveness for CT brain imaging versus no imaging was £115,785 (Table 4). This remains above the NICE cost-effectiveness threshold when the pooled prevalence is used at £50,023. Brain imaging remained cost-effective for stage III patients with ICERs for CT brain imaging versus no imaging of £20,337 using the pre-treatment imaging prevalence and £17,000 using the pooled prevalence. There was some uncertainty over whether MRI or CT+/-MRI is the most cost-effective strategy with ICERs of £27,045 and £22,173 for MR imaging versus CT imaging for the same two prevalence inputs.

Discussion

Key findings – prevalence of brain metastases. This is a large multi-centre study of 444 patients to investigate the prevalence of brain metastases in patients with clinical stage II & III NSCLC. An accurate estimate of this prevalence is required to analyse the cost-effectiveness of undergoing brain imaging prior to curative intent treatment. The current NICE recommendations are based on an estimated prevalence of unsuspected brain metastases of 9.5% in stage II lung cancer and 9.3% in stage III which in turn were based on a retrospective study of 161 and 123 patients with stage II & III lung cancer respectively. O'Dowd et al. evaluated the prevalence of brain metastases in the 12 months following surgical resection and used a reverse volume doubling time calculation to estimate how many of these

metastases would have been identified on pre-operative imaging. One concern is that this methodology may overestimate the prevalence of detectable brain metastases at the point of diagnosis. This concern is supported by the finding of a higher prevalence of brain metastases within our post-treatment cohort compared to metastases detected on pre-treatment imaging in our study (7.9% vs 2.1% in stage II, 7.8% vs 5.2% in stage III). The most accurate assessment of the prevalence of unsuspected brain metastases is through pre-treatment brain imaging results and this study has provided information on 47 patients and 193 patients undergoing brain imaging before treatment in clinical stage II & III lung cancer respectively. In this cohort of patients, the prevalence of unsuspected brain metastases was significantly lower than that used in the NICE economic model (2.1% vs 9.5% stage II, 5.2% versus 9.3% stage III).

Key findings – cost-effectiveness of pre-treatment brain imaging. NICE typically recommends interventions that achieve an ICER below £20-30,000/QALY gained versus the next best alternative. When using a range of prevalence rates identified across this study, brain imaging prior to curative intent treatment was no longer cost-effective in stage II disease. In particular, when using the prevalence from the pre-treatment brain imaging cohort (likely to be the most accurate assessment of prevalence as described above) the cost-effectiveness is exceptionally poor at >£100,000 per QALY for both CT and MR scanning. The new data on prevalence and treatment probabilities from this study suggest that there is no plausible prevalence at which imaging stage II patients becomes cost-effective. This is principally due to the new data implying that 100% of patients with a positive brain scan still get radical treatment. The upfront imaging costs are therefore no longer offset by the reduction in treatment costs. This was, however, only based on one patient so we have undertaken some scenario analyses on treatment probabilities for True Positive patients with 1-3 BM who were otherwise thought to have stage II disease. As discussed in NG122 Appendix B, the greater weight of "net benefit" is gained through cost-savings from radical treatments avoided rather than QALY gains for converting False Negatives to True Positives. It is therefore not surprising that the limited MCD data on treatment probabilities for stage II patients affect the cost-effectiveness in this way. In scenario analyses with

alternate plausible treatment decisions (Table 5), imaging stage II patients remained cost-effective with MRI.

For stage III patients, this study has provided a large cohort of patients including 193 patients with pre-treatment brain imaging data which confirms that brain imaging prior to curative intent treatment is a cost-effective strategy and strongly supports the recommendations made by NICE. This study has suggested the prevalence of unsuspected brain metastases may be lower and there are differences in treatment decisions when brain metastases are identified in comparison to the NICE economic model. This includes a higher proportion of patients continuing to have curative intent treatment and a higher proportion having SRS to the brain metastases. Despite this, brain imaging remains cost-effective. In most of the scenarios we ran, MRI is the most cost-effective strategy, but it is no longer cost-saving as predicted by the NICE model. The small difference between the modalities is driven by a combination of the relatively modest difference in sensitivity, the small number of positive patients to which the sensitivity statistics are being applied and the relatively modest ability for early detection to generate large gains in QALYs for positive patients. Another reason for the higher ICERs produced by our re-analysis is that we observed no patients with 4+ BM. Although these patients only constituted 10% of the positives in the NICE analysis, they contributed relatively more net benefit because none of them were assumed to receive radical treatment.

Furthermore, this real-world data highlights that there is inequity in adherence to the current NICE recommendations, with 32% of stage III patients not receiving pre-treatment imaging. This further supports NICE guidelines to help achieve equity of care across the UK.

Key findings – Review of excluded patients and impact on economic analysis. We reviewed the data from the 142 patients who were excluded to understand whether any of them would likely have been eligible to receive brain imaging as part of their work up, were it available. Of the 142 patients, 1 was stage I and 67 were stage IIIB+ and therefore not relevant to the NICE recommendations. 49 patients were stage II/III but received BSC only, likely because of lack of fitness

for radical (or any other) treatment and they are therefore unlikely to be relevant to the NICE recommendations either. The remaining 25 patients (5 stage II and 20 stage III) had palliative treatment. These patients are conceivably relevant to the decision problem if radical treatment were planned but then their condition deteriorated during work-up.

We do not think a sensitivity analysis to examine the effect of adding this final group of patients is necessary for several reasons:-

- Although these palliative patients were stage II/III, it is not clear if any of them originally had a radical treatment plan. The most likely reasons that these patients did not receive radical treatment is that they declined it or were not fit enough for it, which would exclude them from the analysis.

- 20/25 patients were stage III and imaging is comfortably cost-effective in this cohort so even the extreme sensitivity analysis of giving all these patients imaging and assuming 0% had brain metastases would not make a qualitative difference to the model's conclusions for the stage III group at large.

- Similarly, only 5 patients were stage II so would not greatly influence the analysis for this group."

Study Limitations. Although this represents a large multi-centre cohort of patients, larger than that used to inform the prevalence data in the NICE economic model, the prevalence of brain metastases is low. Therefore, treatment decision data, which are the primary driver of cost-effectiveness in the model, are based on only one stage II and 10 stage III patients in the pre-treatment brain imaging cohort. The scenario analyses show that if prevalence data are higher and radical treatment proportions lower than those suggested by our study pre-treatment imaging dataset, brain imaging may continue to be cost-effective in patients with stage II disease. It would require very large datasets

of patients with stage II lung cancer undergoing brain imaging with accompanying data on the impact on treatment from any positive scans to provide further confidence to these conclusions.

Conclusions. This study strongly supports the NICE guideline recommendation for brain imaging prior to curative-intent treatment in stage III lung cancer. However, this study questions the cost-effectiveness of brain imaging prior to curative-intent treatment in stage II lung cancer which warrants further consideration and exploration. This would require confirmation of the prevalence of BMs in clinical stage II NSCLC and the impact of treatment decisions following a positive scan in a very large cohort of patients undergoing pre-treatment brain-imaging to collect the required information on the small proportion with brain metastases. A national registry may be required to provide the most accurate answer to this important question in lung cancer staging.

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Table 1: Summary of the NICE assumptions on prevalence of asymptomatic brain metastases and impact on treatment decisions from a positive brain scan – defined by the expert NICE guideline committee

	Stage II	Stage III

	1-3 brain mets	≥4 brain mets	1-3 brain mets	>4 brain mets
Overall Cancer treatment				
% still having curative intent therapy	75%	0%	0%	0%
% of curative intent treatments that are surgery	20%	0%	0%	0%
% switching to palliative therapy	25%	100%	100%	100%
Brain metastases treatment				
% treated with SRS for BMs	75%	0%	10%	0%
% treated with brain resection	10%	0%	0%	0%
% treated with WBRT	10%	92.5%	0%	92.5%

SRS – stereotactic radiosurgery, BMs – brain metastases, WBRT – whole-brain radiotherapy

Table 2: Comparison of outcomes from the multi-centre data (MCD) pre-treatment cohort versus NICE Guideline economic modelling assumptions

	Stage II

	1-3 mets MCD (n=1)	1-3 mets NICE	≥4 mets MCD (n=0)	≥4 mets NICE
Overall Cancer treatment				
% still having curative intent therapy	100%	75%	-	0%
% of curative intent treatments that are surgery	100%	20%	-	0%
% switching to palliative therapy	0%	25%	-	100%
Brain metastases treatment				
% treated with SRS for BMs	100%	75%	-	0%
% treated with brain resection	0%	10%	-	0%
% treated with WBRT	0%	10%	-	92.5%
Stage III				
	1-3 mets MCD (n=10)	1-3 mets NICE	≥4 mets MCD (n=0)	≥4 mets NICE
Overall Cancer treatment				
% still having curative intent therapy	30%	0%	0%	0%
% of curative intent treatments that are surgery	0%	0%	0%	0%
% switching to palliative therapy	70%	100%	0%	100%
Brain metastases treatment				
% treated with SRS for BMs	60%	10%	0%	0%
% treated with brain resection	0%	0%	0%	0%
% treated with WBRT	30%	0%	0%	92.5%

SRS – stereotactic radiosurgery, BMs – brain metastases, WBRT – whole-brain radiotherapy

Table 3: Planned treatment versus actual treatment in patients with stage III lung cancer found to have brain metastases on pre-treatment brain imaging

Patient	Number of metastases	Planned treatment	Actual Treatment
1	1-3	Surgical Resection	Palliative SACT
2	1-3	Surgical Resection	Palliative SACT
3	1-3	Chemoradiotherapy	Continued with radical treatment
4	1-3	Chemoradiotherapy	Continued with radical treatment
5	1-3	Chemoradiotherapy	Continued with radical treatment
6	1-3	Chemoradiotherapy	Palliative SACT
7	1-3	Chemoradiotherapy	Palliative SACT
8	1-3	Chemoradiotherapy	Palliative SACT
9	1-3	Radical Radiotherapy	Palliative SACT
10	1-3	Radical Radiotherapy	Palliative SACT

SACT – systemic anti-cancer therapy

Table 4: Re-working of the NICE economic analysis based on the real-world data from this study.

Cohort	Prevalence of BM on MRI	CT ICER vs. no imaging	MRI ICER vs. CT	Most cost effective
Stage II pre- treatment imaging	2.1%	£115,785	£140,991	No Imaging
Stage II pre-treatment imaging (adenocarcinoma)	3.7%	£60,555	£67,850	No Imaging
Stage II post-treatment imaging	7.9%	£64,776	£66,512	No Imaging
Stage II post-treatment imaging (adenocarcinoma*)	10.3%	Extendedly dominated	£44,233	No Imaging
Stage II pooled (adenocarcinoma*)	6.3%	£50,023	£52,472	No Imaging
Stage II pooled prevalence	4.8%	£69,130	£76,142	No Imaging
Stage III pre-treatment imaging	5.2%	£20,337	£27,045	MRI
Stage III pre-treatment imaging (adenocarcinoma)	10.1%	Extendedly dominated	£10,221	MRI
Stage III post-treatment imaging	7.8%	£10,146	£12,164	MRI
Stage III post-treatment imaging (adenocarcinoma*)	10.2%	Extendedly dominated	£10,165	MRI
Stage III pooled (adenocarcinoma*)	7.6%	£13,596	£15,014	MRI
Stage III pooled prevalence	5.8%	£17,000	£22,173	MRI

*adenocarcinoma patient prevalence estimated rather than reported in post imaging and pooled cohorts

Table 5: Selected Scenario Analyses for the stage II patients based on the post-imaging prevalence data and alternate assumptions about treatment decision.

Cohort	Prevalence of BM on MRI	CT ICER vs. no imaging	MRI ICER vs. CT	Most cost effective
Stage II post-treatment imaging cohort (Tx decision=NICE)	7.9%	£34,961	£36,549	No Imaging
Stage II post-treatment imaging adenocarcinoma (Tx decision=NICE)	10.3%	ext. dom.	£25,911	MRI
Stage II post-treatment imaging cohort (Tx decision=50% radical)	7.9%	£26,270	£27,850	MRI
Stage II post-treatment imaging cohort (Tx decision=MCD Stage III)	7.9%	£19,551	£21,131	MRI