Justification for power calculations

Lung Cancer

-Only 20-40% of patients referred via the 2 week wait pathway with suspected lung cancer are found to have the disease (NCRN audit data). CT scanning forms part of the pre-diagnostic work up for the vast majority of these patients. Furthermore as few as 40% of lung cancers are currently diagnosed via the two-week pathway, the rest via internal hospital referrals mainly after CT scanning (network audit data) . Practically WB-MRI is highly unlikely to be cost effective employed as a pre-diagnosis test given the high prevalence of normality and the current miscellaneous referral pathways

-For each hypothetical 500 patients diagnosed with non small cell lung cancer, 65% (325) have intra thoracic disease only on their pre-diagnostic work up CT scan and are potential candidates for primary surgery

-According to NICE guidelines (2005), patients potentially eligible for surgery should undergo PET or PET/CT, plus any other relevant investigations (such as CT head or X-Rays) depending on symptoms suggestive of metastatic spread.

-Of the theoretical 325 patients potentially eligible for surgery, around 25% (1,2, LCN audit data) (ie around 81 patients) will have distant metastatic disease undiagnosed by standard CT. Of these PET-CT will detect just over 50% (1, 2)-undiagnosed distal metastasis after normal PET-CT accounts for a significant proportion of futile thoractomies after surgical resection (2).

-Review of the literature (3-15) suggests WB- MRI may have superior sensitivity for brain and bone metastasis over conventional imaging, including PET/CT. Differences in diagnostic accuracy for other sites of disease (eg adrenal, liver, lung) are less defined

Metastasis site	PET & PET/CT sensitivity	PET & PET/CT specificity	WB-MRI sensitivity	WB-MRI specificity
brain	30*	100	70*	95+
liver/adrenal	86	56	similar to PET	similar to PET
bone	75**	90+	85***	94

*Average sensitivity for brain mets (8-10). Sensitivities as high as 88% for WB-MRI have been reported (13)

**Average sensitivity on literature review(14)

***(8)

-The premise of the study power is to detect a higher diagnostic rate for extra thoracic disease (specifically brain and bone metastasis) with WB-MRI in comparison to conventional imaging paradigms. To power on equivalence or non-inferiority would be would be well beyond pragmatic recruitment and funding

-Based on recent meta-analysis data (14) considering 1874 patients, the overall prevalence of brain metastasis at presentation in NSCLC is 13% (6% to 32%) and bone 20% (8-34%). Around 20% have metastasis at multiple sites (1, 8, 16, 17).

-Prevalence assumptions

(i) Conservative estimate of the prevalence of brain metastasis at presentation is 10%

(ii) 20% of these patients are already identified as having metastatic disease via detection of co-existing extra cranial disease on pre-diagnosis CT (eg liver, adrenal)

(iii) A further 10% of patients will have disease at more than one site on CT (and therefore more likely detected by PET CT than if isolated to the brain)

Overall 12% (n=40) of the hypothetical 325 patients with potentially operable disease will have isolated brain metastasis and 5% (n=16) have bone metastasis. The remaining 8% (of the total 25% with undiagnosed extra-thoracic metastatic disease) will have metastasis at other organ sites (eg lung, liver adrenal)

Sample size calculation

Comparison of WB-MRI to PET & PET/CT accuracy - both against reference standard

- paired study design - all tests on all patients
- Sample size method: Julious et al 1999 J Biopharm Statistics 9 p241 Table 3
- Power study to show difference in sensitivity, as fewer patients with metastasis than without. Study powered like this should also be suitable for difference in specificity
- 80% power type II error, type I error 5% ($p<0.05$)
- Assume ratio of marginal cells of 2 x 2 table comparing WB-MRI to PET: $s/t = 9$
- Assume sum of marginal cells as proportion of total with disease: $s+t/N=0.238$
- A sample size of 50 patients with occult metastasis is needed, from a population of 25% prevalence of metastasis. Thus a total sample size of 200 (50 times 4) is required.

200 patients where no metastasis at lung cancer diagnosis and potential surgical candidates will be required to detect at difference of 24% in sensitivity of WB-MRI for metastatic disease (79%) compared to conventional staging (55%) given site specific disease prevalence as described above. We will allow for 20% drop out or death at 1 year (based on survival statistics for surgical candidates with initially suspected limited disease)

Power to address secondary outcomes

Reduction in average number of test per patient

Assumptions
-On average patients with potentially operable disease undergo and additional 1.5 tests prior to definite staging, including PET/CT lymph node sampling etc (UCH audit data)
-WB-MRI will detect at additional 24% of patients with extrathoracic metastasis compared to PET CT (see main power calculation)
-Assume a more conservative 20% reduction in patients requiring more than 1 test by WB-MRI compared to conventional pathways
- a 20% reduction in the average number of tests patients undergo would be clinically advantageous
- treating test number as a continuous variables and assuming a sd of 0.3 for the difference between test number (conventional pathway vs. WB-MRI)
-Sample size method: Julious et al 1999 J Biopharm Statistics 9 p241 Table 1, 80% power α =0.05
-a sample of **90** patients is required to detect a reduction of 20% in average test number using WB-MRI compared to conventional pathways.

Colon Cancer

-The detection of metastatic disease during colon cancer staging has significant therapeutic implications, although subsequent patient pathways are variable. For example the patient may become a candidate for chemotherapy, or surgical metastectomy (notably liver or lung). Conversely detection of additional sites of metastatic disease may preclude patients from metastectomy or change the surgical approach etc. To power on any one of these specific patient pathways (or the extra tests they generate) would be well beyond pragmatic recruitment and funding. For example only around 10-15% of colorectal cancer patients in our network undergo surgical metastectomy, an insufficient substrate to power a cohort study of this kind. Indeed a recent survey of UK practice indicates the rate of metastectomy is on average just **2.7%** of patients undergoing surgery for colon cancer (18)

- The cleanest approach is therefore to power on change in detection rate of metastatic disease after diagnosis and collect data on specific changes in patient management and test utility as a secondary outcomes

-There is a limited literature investigating the use of whole body MRI in staging colorectal cancer (19)

-Conversely there is a well-established literature for detection of liver disease-by far the most common site for colorectal liver metastasis

-of patients with newly diagnosed colon cancer cases, around 25% will have detectable liver metastases at the time of the initial diagnosis although a further 40–50% of patients will eventually develop metastases after resection of the primary, peaking at 1.5 years of follow up (suggesting many metastatic deposits are occult during staging investigations) (20)

-The highest level of evidence currently available is a recent meta analysis of imaging for the detection of hepatic metastasis from colorectal cancer (21), updated in Sep 2010 (22)

-Based on older studies, sensitivity of helical thin collimation CT was estimated at 65% versus 75% for 1.5T MRI. Smaller paired studies also provide evidence of MRI having 10-40% increase in sensitivity per lesion . Recent meta-analysis of studies performed post 2004 (using current iterations of high technology imaging platforms now ubiquitous throughout the NHS) show CT sensitivity has improved to **74.9%** and MRI to **84.9%** (22)

-The premise of the study power is to detect a higher diagnostic rate for extra nodal metastatic disease (notably liver) using WB-MRI in comparison to conventional imaging paradigms. To power on equivalence or non-inferiority would be would be well beyond pragmatic recruitment and funding

-prevalence assumption- prevalence of metastatic disease detected using conventional investigations =30% (20), local cancer network audit data)

-The sample size calculation requires making some assumptions about the correlation between the two methods in lesion detection. Different estimates of the ratio of the marginal cells (MRI+CT- vs MRI-CT+) is expressed as the s/t ratio (J Biopharm Stats 9 p241). Note that per patient analysis will be more correlated due to clustering of multiple lesions within each patient

- correlation between the 2 methods can be estimated from Hagspeil (23), Strotzer(24) and Lencioni(25).

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-s/t ratio) for the least correlated models (Hagspeil)(23) are (s/t=2 or infinity), Strotzer (s/t=3 or infinity) (24)and Lencioni (s/t=3.25 or infinity).(25) For the largest sample size it is reasonable to assume an estimate of s/t=3 or above per patient.

Sample size calculation

- paired study design - all tests on all patients
- Sample size method: Julious et al 1999 J Biopharm Statistics 9 p241 Table 3
- Power study to show difference in sensitivity, as fewer patients with metastasis than without. Study powered like this should also be suitable for difference in specificity
- 80% power type II error, type I error 5% ($p<0.05$)
- s/t=6
- s+t/N = 0.14
- A sample size of 116 patients with metastasis is needed, from a population of 40% prevalence of metastasis. Thus a total sample size of 290 (116 times 2.5) is required.

290 patients will be required to detect at difference of 10% in sensitivity of WB-MRI for metastatic disease (85%) compared to conventional staging (75%) given the disease prevalence as described above. Allowing for 10% death or drop out at 1 years, 322 patients will be recruited.

Power to address secondary outcomes

Number of tests prior to definitive staging

Assumptions

-38% of colon cancer is situated in the rectum and is currently staged with 2 tests (CT and MRI)
-around 50% of colorectal patients with isolated liver metastasis at presentation undergo at least 1 additional staging scan to assess suitability for liver resection (UCH audit data)
-based on the above, on average patients with colorectal cancer undergo 1.5 tests in addition to staging CT scan prior to definite treatment (including local MRI staging of rectal cancer), and 46 patients out of every 100 have more than 1 test during staging
-By providing a "one stop shop" for local and distant staging, for every 100 colorectal cancer patients, WB-MRI has the potential to reduce additional tests in 46 patients (46%) (assuming equivalent accuracy of WB-MRI to conventional pathways)
- Sample size method: Julious et al 1999 J Biopharm Statistics 9 p241 Table 3, 80% power α =0.05

-s+t)/N=46/100=0.46

-s/t=40/6=6.66

37 patients would be required to detect a reduction in test number in 46% of patients

Reduction in average number of test per patient

Assumptions

-as outlined above, on average patients with colorectal cancer undergo 1.5 tests in addition to staging CT scan prior to definite treatment (including local staging of rectal cancer).
-a 20% reduction in the average number of tests patients undergo would be clinically advantageous.
-treating test number as a continuous variables and assuming a sd of 0.6 for the difference between test number (conventional pathway vs. WB-MRI)

-Sample size method: Julious et al 1999 J Biopharm Statistics 9 p241 Table 1, 80% power α =0.05
-a sample of **90** patients is required to detect a reduction of 20% in average test number using WB-MRI compared to conventional pathways.

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