Staging cancer of the uterus: A national audit of MRI accuracy

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AIM: To report the results of a nationwide audit of the accuracy of magnetic resonance imaging (MRI) staging in uterine body cancer when staging myometrial invasion, cervical extension, and lymph node spread.

MATERIALS AND METHODS: All UK radiology departments were invited to participate using a web-based tool for submitting anonymized data for a 12 month period. MRI staging was compared with histopathological staging using target accuracies of 85, 86, and 70\% respectively.

RESULTS: Of the departments performing MRI staging of endometrial cancer, 37/87 departments contributed. Targets for MRI staging were achieved for two of the three standards nationally with diagnostic accuracy for depth of myometrial invasion, 82\%; for cervical extension, 90\%; and for pelvic nodal involvement, 94\%; the latter two being well above the targets. However, only 13/37 (35\%) of individual centres met the target for assessing depth of myometrial invasion, 31/36 (86\%) for cervical extension and 31/34 (91\%) for pelvic nodal involvement. Statistical analysis demonstrated no significant difference for the use of intra-venous contrast medium, but did show some evidence of increasing accuracy in assessment of depth of myometrial invasion with increasing caseload.

CONCLUSION: Overall performance in the UK was good, with only the target for assessment of depth of myometrial invasion not being met. Inter-departmental variation was seen. One factor that may improve performance in assessment of myometrial invasion is a higher caseload. No other clear factor to improve performance were identified.

Introduction

Uterine cancer is relatively common, with the commonest type — endometrial cancer — the fourth commonest malignancy in women. The incidence is rising: in 2000 in the UK there were approximately 6000 new cases, in 2007 there were 7536, with 1741 deaths in 2008.\cite{1} Clinical staging is unreliable and surgical staging was recommended by International Federation of Gynecology and Obstetrics (FIGO) in 1988, when a detailed classification system was published.\cite{2} This has recently been updated.\cite{3} At presentation 80\% of endometrial cancers are stage I.\cite{4} The most important prognostic factor is the degree of myometrial invasion.\cite{5} In the absence of deep myometrial invasion, the reported lymph node metastatic rate is only 3\% of cases, whereas when there is deep myometrial invasion, lymph node metastatic rates have been reported in as many as 46\%.\cite{4} Accurate prediction of more extensive disease may, as a result, affect the type of surgery planned. The 1988 FIGO guidelines\cite{2} include lymphadenectomy as a component of the surgical staging system, but in 2000, FIGO suggested it only be performed in...
high-risk cases. However, due to the associated morbidity and uncertainty as to benefit, many centres in the UK no longer perform lymphadenectomy routinely in high-risk cases, but restrict lymphadenectomy to patient with clearly involved nodes. At present therefore, due in part to differing surgical practices with respect to lymphadenectomy, indications for MRI of the uterus are not firmly established. The place of imaging remains controversial and practice varies across the UK and elsewhere. One commonly held view is that patients with early-stage disease do not require any imaging other than ultrasound prior to surgery, whilst others believe all patients require imaging. Many now consider it the reference standard that all patients with histological high-grade tumours should undergo MRI preoperatively. Centres undertaking lymphadenectomy at the time of hysterectomy may scan all patients with biopsy-proven endometrial carcinoma, whatever the grade, to identify patients with deep myometrial invasion or cervical involvement to identify appropriate patients. The Royal College of Radiologists’ (RCR) guidelines “Making the Best Use of Clinical Radiology Services,” 6th edition (MBURG) and “Recommendations for Cross-Sectional imaging in Cancer Management,” both advocate its use, as do both the American College of Radiologists (ACR) guidelines and the European Society of Urogenital Imaging guidelines.4,5 The recently published European guidelines list indications for MRI as including: “high-grade, serous or clear cell adenocarcinomas; suspicion of disease greater than stage 1B; screening for lymphadenopathy; medical contraindication for surgical staging; suspected inability of curtailage.”6,7 However, there is no consensus as to the best technique.

The aim of the present national audit, undertaken by the RCR Clinical Radiology Audit Committee (CRAC), was to assess the use and accuracy of MRI in women with uterine cancer as currently performed in the UK for benchmarking purposes and, by distribution of results, hopefully promotion of good practice. No attempt was made to assess its efficacy in terms of disease management, but instead elected to determine whether the depth of myometrial invasion was being assessed accurately with MRI as this directly affects patient management.

As there is no nationally agreed guideline for which grade or stage of tumour should be assessed with MRI; no agreed sequences to be used; or defined expected accuracy rates, the standards we used were based on a review of the current literature in 2007. Published papers are often based on the work of specialist centres with high throughput and do not necessarily reflect what is achievable in smaller, non-specialist centres. It was hoped that this audit would determine whether all centres could achieve the standards suggested by the ACR, namely that MRI with contrast enhancement can be between 85 and 91% accurate in assessing the depth of myometrial invasion, with accuracy of cervical extension ranging from 86 to 95%.8,9 As the ACR did not discuss the accuracy of lymphadenopathy assessment, work by Rockall et al.10 and Manfredi et al.11 was used to set the lymphadenopathy standard; they reported accuracy rates between 72 and 90%.10,11

Materials and methods

In 2008 all radiology departments in the UK were initially contacted to determine whether they undertook MRI as part of the assessment of uterine malignancy. Departments responding in the negative were not further contacted. Participants were asked, with the aid of their pathology department and gynaecological multidisciplinary team (MDT) co-ordinator, to identify all patients with a diagnosis of uterine malignancy during a recent 12 month period. The exact dates were not stipulated as it was appreciated that departments may collect their data in different ways, for example, they may use the financial year or the calendar year. The surgical stage was to be established using the pathology report and case notes as necessary. The imaging record was to be reviewed to identify whether they had MRI evaluation prior to surgery. Patients were excluded if they had had neoadjuvant chemotherapy prior to hysterectomy, or if endometrial cancer was picked up incidentally at hysterectomy for other indications. For the purposes of assessing the accuracy of the imaging findings, the histopathology findings were taken as the reference standard.

Individual anonymized patient data were submitted using an online Snap Survey Software, Version 9, data collection tool. The data were then collated centrally. Participants were also asked to complete an online questionnaire detailing their departmental policy for uterine cancer imaging, including MRI sequences used and data on the number of cases managed locally with uterine cancer.

In 2009, after the design and commencement of the data collection period for this audit, the FIGO staging classification was revised.5 Stage I tumours are confined to the body of the uterus and are subdivided depending on their extent. Under the old FIGO classification there were three subdivisions: confined to the endometrium (1A), invading through one half or less of the myometrium (1B), invading more than one half of the myometrium (1C). Under the new classification this has been reduced to two categories with 1A now “no or less than half of the myometrium” and 1B now “invasion equal to or more than half the myometrium”. Stage IIa was previously subdivided into IIA endocervical involvement and IIB cervical stromal invasion. Now only cervical stromal involvement is classed as stage II with endocervical involvement considered stage I. Stage III incorporates tumours with local and/or regional spread and stage IV, either bladder or bowel invasion or distant metastases. IIC is now subdivided depending on the extent of nodal involvement.

Part of the data collected was categorized using the FIGO categories under the old system. However, it was felt that it would be more clinically useful to present the results using the current new categories. As data collected included the parameters used to determine FIGO stage, all cases were reclassified by the authors under the new staging system. With the change in classification myometrial involvement is now classified as either less or more than 50%; therefore,
the results were analysed as to whether deep invasion was correctly predicted. With regard to the cervix, only cervical stromal data were analysed. Endocervical involvement data were collected but not analysed as it no longer affects staging under the revised classification.

The audit targets used for this study were (1) 85% accuracy of MRI for predicting myometrial involvement; (2) 86% accuracy for determining cervical extension; and (3) 70% accuracy for predicting lymph node involvement.

**Statistical analysis**

Data were analysed using STATA v11.0 (Stata Corporation, College Station, TX, USA). Diagnostic accuracy was calculated as the percentage of cases where histology and MRI were concordant. Concordant cases were (a) those in which myometrial involvement on histology and MRI were both \(<50\)% or \(>50\)%; (b) those in which histological staging and MRI both reported cervical involvement, (c) those in which lymph node involvement was reported by histology and on MRI, respectively. Missing responses and “don’t know” were excluded from the analysis. The percentage (with an exact binomial confidence interval) of concordant cases was calculated for each indicator to assess national performance against the audit standards. Sensitivities and specificities were also calculated for each of the three indicators.

Fisher’s exact test was used to test for associations between intravenous contrast medium use and the sensitivity and specificity for each indicator. The tests were repeated in subgroups defined by stage (IA, IB, II, or III/IV) and by caseload (less than 20, and 20 or more patients seen). Fisher’s exact test was also used to test for associations between these sensitivities and specificities and stage (treated as a four-level categorical variable, classified IA, IB, II, or III/IV).

Logistic regression models were used to test for associations between intravenous contrast medium use and the sensitivity and specificity for each indicator and caseload (treated as a continuous variable). Where statistically associations were seen fitted values from the model were plotted and compared with observed sensitivities and specificities (with exact binomial confidence intervals) in workload groups (<10, 10–19, 20–29, 30–39, 40–49, and \(\geq 50\) patients). Further logistic regression models were used to adjust for stage and to provide a joint test of associations between sensitivity and specificity and caseload (with and without adjustment for stage). In models testing the joint associations the outcome variable was the (log) odds of agreement with the histological diagnosis and caseload (and stage, if included) as predictor variables. Including histological diagnosis as a predictor variable allows caseload-specific sensitivity to differ from specificity. Analogous logistic regression models were used to provide joint tests of differences in sensitivity and specificity with intravenous contrast medium use.

The percentage of concordant cases for each indicator was compared among rather than between participating departments. Funnel plots were used to analyse these data to identify predominant common causes or special causes for variation. The upper and lower control limits enclose a region in which 99.7% of departmental results are expected to lie. For continuous variables this corresponds to the mean \(\pm\) three times the standard deviation. However, for a percentage the 99.7% control limits are appropriately asymmetrical.

**Results**

All RCR listed radiology departments were contacted. Eighty-seven responded stating that they undertook MRI staging of uterine cancer; 54 responded stating that they did not, and 92 did not respond but were re-invited to respond. Thirty of the 87 departments (34%) provided departmental data and 37 of 87 departments (43%) provided staging data. This response rate is similar to previous national audits conducted by the RCR Clinical Radiology Audit Committee.

**Departmental data**

The responding departments were felt to be representative of UK departments in that the proportion of teaching hospitals to other hospitals differed by only one percentage point when comparing respondents (England only) to English NHS trusts in general. Endometrial cancer caseloads varied from eight to 85. Departmental referral policies varied: 18 departments perform MRI in all cases of endometrial cancer, seven in high-grade cancers only, and in the other five there was a range of policies. MRI protocols also varied with 24/30 (80%) departments using a mix of standard plus personal preference sequences. From reviewing the submitted data, 21/37 (57%) departments always used intravenous contrast medium and 12/37 (32%) never used it. Only 12/30 (40%) departments used a standard definition of lymph node abnormality, but this varied greatly from \(>6\) mm short axis diameter to \(>10\) mm short axis diameter, with others using abnormal signal and morphology also. The number of endometrial staging cases per department, per year varied from one to 68, with 13/37 (35%) departments doing less than 10 cases and 23/37 (62%) no more than 20 cases in the 12 month period reviewed (Table 1).

During the 12 month period evaluated, eight of 30 (27%) departments reviewed MRI images performed elsewhere when cases were referred for surgery. Departmental performance in terms of concordance between MRI and pathology findings for depth of myometrial invasion, cervical stromal invasion, and pelvic node involvement were compared using funnel plots (Fig 1). Only two departments showed special cause variation. One department was above the upper control limit (UCL) for the assessment of the presence of deep

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<tr>
<td>Frequency</td>
<td>14</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>1</td>
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myometrial invasion and the other was below the lower control limit (LCL) for the assessment of cervical stromal invasion. On further discussion with the audit leads in these departments, a cause for this variation could not be identified. None of the remaining departments differed from each other by an order of magnitude greater than that assignable to chance alone: common cause variation predominates throughout. However, the control limits at the lower end of the caseload volume scale were wide, and it was noted that although within the control limits, the proportion of departments below the national departmental mean of 79% for myometrial involvement (Fig 1a) was greater with lower caseloads.

The relationship between caseload and accuracy was further analysed using logistic regression models. Fig 2 shows the sensitivities and specificities of assessment of myometrial invasion in caseload bands (<10, 10–19, 20–29, 30–39, 40–49, and ≥50 patients) plotted against the mean caseload in each band together with fitted values from simple univariable logistic regression models. There was evidence that the sensitivity ($p = 0.036$, likelihood ratio test) and the specificity ($p = 0.016$) increased with increasing caseload. A joint test of the association with sensitivity and specificity was highly statistically significant ($p = 0.002$). Adjusting for stage had little material impact on the magnitude of the associations, although the $p$-value for the association between caseload and sensitivity was no longer formally statistically significant ($p = 0.061$).

There was evidence that the sensitivity of assessment of cervical stromal invasion ($p = 0.0499$) increased with...
increasing caseload. However, this association did not remain statistically significant after adjustment for stage ($p = 0.075$). The effects of caseload on the sensitivity and specificity of pelvic nodal involvement assessment and on the sensitivity of cervical stromal involvement were not statistically significant.

**Individual patient staging data**

Seven hundred and seventy-five sets of individual patient staging data were received of which 713 (92%) were performed within the institution, 8% of scans had been performed elsewhere but were referred for surgery. Intravenous contrast medium was given in 566/775 (73%) cases. The breakdown by FIGO staging category is depicted in **Table 2**. In total, unequivocal detail was received on all three parameters in 452 of 775 cases. Assessment of the accuracy of the MRI report required histological data and, therefore, for example, when lymphadenectomy was not performed it was not possible to determine the accuracy of the MRI assessment of lymph nodes in that instance.

Overall concordance between MRI and histopathology findings was 81.9% (95% CI 79, 84.6%) for depth of myometrial invasion, 89.7% (95% CI 87.3, 91.8%) for cervical extension, and 94% (95% CI 91.4, 96%) for pelvic nodal involvement. Thus, nationally, the standard for depth of myometrial invasion (85%) was not met, but the standards for assessment of cervical extension (86%) and pelvic nodal involvement (70%) were. **Table 3** illustrates the accuracy of the imaging staging of the three parameters together with sensitivities and specificities. The specificity was over 95% for assessment of cervical stromal invasion and pelvic nodal involvement and 88% for assessment of depth of myometrial invasion. Conversely, the sensitivity was highest for assessment of depth of myometrial invasion and markedly lower for assessment of cervical stromal invasion. With regard to the per patient accuracy, for the 452 cases where both radiological and histological data were available on all three parameters, in 337 cases there was complete concordance, i.e., in 75% of patients the findings at MRI for all three parameters were compatible with the histopathology findings.

There was no evidence that use of intravenous contrast medium was associated with differences in the sensitivity or specificity of assessment of cervical stromal invasion or of depth of myometrial invasion. There was some evidence that the use of intravenous contrast medium in assessing pelvic nodal involvement was beneficial. The specificity was 97% (317/327) when intravenous contrast medium was used and only 93% (102/110) when it was not; a difference of borderline statistical significance ($p = 0.09$). The difference in sensitivities also favoured the use of intravenous contrast medium [15/22 (68%) vs. 3/6 (50%)] although numbers here are small. Combining these two results (using a logistic regression model in which the risk of a correct diagnosis depends on whether intravenous contrast medium is used and on the true outcome) gives a $p$-value of 0.044.
In this audit of UK practice, overall concordance of MRI and histopathology findings was 82% for depth of myometrial invasion, 90% for cervical extension, and 94% for pelvic nodal involvement when individual patient data were analysed. When the performance of individual departments was considered 13/37 (35%) met the national target for assessing depth of myometrial invasion, 31/36 (86%) for cervical extension and 31/34 (91%) for pelvic nodal involvement. The funnel plots (Fig 1) indicate that there is hardly any special cause variation with almost all departments lying within the control limits. However, due to the small numbers of examinations performed in many departments, these control limits are wide and further analysis of the effect of caseload suggested that improved accuracy in assessment of myometrial invasion (Fig 2) and, to a lesser degree, cervical stromal invasion in departments may be associated with increasing caseload. The margins are small, but for departments concerned about their accuracy in assessing the depth of myometrial invasion, it may be appropriate for them to consider increasing their exposure to this examination type by double reporting within the centre or with another centre. Data on double reporting was not collected as part of the present audit, it is not known which, if any, centres currently undertake this. However, smaller centres did report that their patients were often transferred to a larger centre for further management and the MRI studies were re-reported there as part of the MDT process.

When looking for other reasons for varying performance, one of the main variations in practice between departments noted was the use of intravenous contrast medium. Opinion in the literature is mixed with regard to the use of intravenous contrast medium.4,5,7–9,11–16 However, a meta-analysis published in 1999 stated it was beneficial17 and the 2005 ACR guidelines9 recommend its use. In the RCR publication, “Recommendations for Cross-Sectional imaging in Cancer Management”5 it states “Data suggests that overall no significant statistical difference exists between T2W and contrast-enhanced sequences in predicting myometrial invasion.” However, these recommendations do also state that: “it is agreed that the two sequences are necessary to optimize accuracy and ease interpretation”. Several authors have reported the benefits of dynamic contrast-enhanced imaging sequences.4,7,11,14,16 A review paper in 2006 suggests dynamic sequences may be beneficial as a problem-solving tool in difficult cases such as coexistent benign uterine disease or in restless patients, as the sequences are shorter.14 The recently published European guidelines suggest “a single enhanced acquisition at optimal image orientation”.9 Therefore, there is no agreed ideal set of imaging sequences for evaluating endometrial cancer, and as a result, departments have devised their own protocols depending on experience, equipment, and personal preferences. From the data collected for this audit, it would appear that 57% of departments always use intravenous contrast medium, and 32% of departments never use intravenous contrast medium in endometrial cancer staging examinations. When collecting data for this audit standard post contrast and dynamic contrast imaging were not differentiated. However, analysis of the collected results showed only a borderline improvement in sensitivity with intravenous contrast medium usage in pelvic nodal assessment and no benefit in the assessment of cervical stromal or deep myometrial invasion.

With regard to stage of disease, accuracy has been reported to increase with increasing stage of disease, i.e., stage III/IV disease.19 However, the present data do not demonstrate this.

Do we need to revise the standards?

The present audit was initially planned in 2007, and the standards applied were based on the literature at that

### Table 4
Accuracy in assessment of other aspects of disease spread.

<table>
<thead>
<tr>
<th>Involvement of:</th>
<th>No. of cases at histopathology</th>
<th>No. of cases correctly identified at MRI</th>
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<tbody>
<tr>
<td>Serosa</td>
<td>65</td>
<td>18 (28%)</td>
</tr>
<tr>
<td>Vagina</td>
<td>4</td>
<td>1 (25%)</td>
</tr>
<tr>
<td>Para-aortic nodes</td>
<td>3</td>
<td>2 (67%)</td>
</tr>
<tr>
<td>Bladder</td>
<td>2</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bowel</td>
<td>2</td>
<td>1 (50%)</td>
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MRI, magnetic resonance imaging.

(likelihood ratio test). On further adjustment for stage (in categories) and caseload (treated as continuous), the association remained statistically significant ($p = 0.033$). Given the borderline nature of this result and the fact that a number of different statistical models have been fitted this result should be interpreted cautiously.

There was strong evidence that the specificity of assessment of cervical stromal invasion ($p = 0.001$) and that of pelvic nodal involvement ($p < 0.001$) differed by stage, with the highest specificity for stage IA. A similar trend for the specificity of assessment of deep myometrial invasion was apparent, but this was not statistically significant. No compelling evidence was found that the sensitivities of the three aspects differed by stage.

Data were also collected on periaortic node involvement, vaginal involvement, bladder involvement, and bowel involvement (Table 4). Due to the small number of positive cases, these aspects of tumour spread were not further analysed.

**Discussion**

In this audit of UK practice, overall concordance of MRI and histopathology findings was 82% for depth of myometrial invasion, 90% for cervical extension, and 94% for pelvic nodal involvement when individual patient data were analysed. When the performance of individual departments was considered 13/37 (35%) met the national target for assessing depth of myometrial invasion, 31/36 (86%) for cervical extension and 31/34 (91%) for pelvic nodal involvement. The funnel plots (Fig 1) indicate that there is hardly any special cause variation with almost all departments lying within the control limits. However, due to the small numbers of examinations performed in many departments, these control limits are wide and further analysis of the effect of caseload suggested that improved accuracy in assessment of myometrial invasion (Fig 2) and, to a lesser degree, cervical stromal invasion in departments may be associated with increasing caseload. The margins are small, but for departments concerned about their accuracy in assessing the depth of myometrial invasion, it may be appropriate for them to consider increasing their exposure to this examination type by double reporting within the centre or with another centre. Data on double reporting was not collected as part of the present audit, it is not known which, if any, centres currently undertake this. However, smaller centres did report that their patients were often transferred to a larger centre for further management and the MRI studies were re-reported there as part of the MDT process.

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**Do we need to revise the standards?**

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Recent papers from the UK, Portugal, Spain, and South Korea have reported lower accuracy rates in assessing myometrial invasion. Sanjuan et al. reported a rate of 58% despite the use of dynamic enhanced sequences and a throughput of 72 patients in 2 years. Specialist centres have reported high levels of accuracy using thin-section high-resolution sequences, and attention to detail, such as the use of smooth muscle relaxants. Nationally, greater accuracy could perhaps be achieved by a standardized approach to cancer imaging. The present target of 85% was achieved by some centres. However, in the light of recent published literature, a target of 80% would appear to be more appropriate.

Cervical stromal invasion

One of the reasons for the overall high rate for cervical extension concordance in comparison to the target is that the reported accuracy rates in the literature are for both endocervical and stromal invasion as the papers were published prior to the revision of the FIGO staging criteria in 2009. Many of the non-concordant reported cases were due to failure to detect endocervical invasion, which no longer affects staging. Excluding these cases raises the accuracy rates, for example, from 80 to 98% in the paper by Cunha et al. Therefore, it would seem appropriate that this target is raised.

Lymph nodes

Few papers have reported accuracy rates in lymph node assessment. A review of lymph node metastases detection in all cancer types by Klerkx et al. in 2010 reported an 84% sensitivity and 82% specificity when contrast-enhanced sequences were combined with the use of multiple malignancy criteria. The study by Rockall et al. showed that accuracy rates are dependent on the definition of abnormal lymph node size with an increased number of false-positive results when a criteria of >8 mm was used as opposed to >10 mm, resulting in a drop in accuracy from 88 to 72% due to an increase in the number of false-positive results.

In conclusion, many centres now use MRI findings as a preoperative staging method to enable treatment planning, rather than the surgical staging originally advocated by FIGO. Early-stage disease may be treated laparoscopically at local hospitals, and more advanced cases referred to a specialist gynaecological unit. Accurate staging allows optimisation of surgical treatment with tailoring of the resection to the individual patient, reducing lymphadenectomy rates in particular, which is important when reported complication rates are close to 20%. Preoperative imaging staging is carried out at many departments within the UK, some within local hospitals and others attached to specialized gynaecological oncology units. The aim of the present audit was to collect information on current practice to determine how accurate MRI staging of uterine cancer was within the UK; as with previous RCR audits, assess whether there were any identifiable factors that affected accuracy; and also provide information to individual centres on their performance both in relation to the targets set from the literature and in relation to their peers for benchmarking purposes. Overall, when all results were pooled, performance in the UK was good, with only the target for assessment of depth of myometrial invasion not being met. However, inter-departmental variation was seen, with only 35% of departments achieving the myometrial invasion target. One factor that may improve performance in assessment of myometrial invasion is a higher caseload.

No other clear factors to improve performance were identified but consideration of nationally rationalizing MRI protocols and reporting templates, e.g., those to be proposed by the RCR NCIN project may be appropriate. The results of the present study do not support the 2006 RCR recommendations that including an intravenous contrast-enhanced sequence optimises accuracy. The seventh edition of the RCR imaging referral guidelines, ‘Making the Best Use of Clinical Radiology Services’ (in press), will not make this recommendation. The responses to the departmental questionnaire do highlight the wide variation in practice with regard to the routine or selective use of MRI in staging of endometrial cancer. This may reflect its greater usefulness in certain cases, such as high-grade disease, and in a resource-limited healthcare system, this too is worth consideration when new guidelines are being developed.

Based on the data collected in this audit, for future audits the minimum achievable standards of MRI accuracy could be set at 80% for predicting myometrial involvement; 90% for determining cervical extension; and 85% for predicting lymph node involvement.

Acknowledgements

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References


