Technetium-99m MIBI imaging in diagnosis of pelvic and abdominal masses in patients with suspected gynaecological malignancy

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Abstract

BACKGROUND: The aim of this study was to determine the diagnostic value of 99mTc MIBI planar dynamic scintigraphy in the diagnosis of gynaecological malignancies and to determine if it has a greater diagnostic accuracy than conventional ultrasound technique (US).

MATERIAL AND METHODS: A prospective trial was performed to assess the accuracy of 99mTc MIBI scintigraphy and ultrasound in 93 female patients (mean age 50, SD 16; range 17–82 years). Three readers assessed all the imaging independently and this was compared with histological examination in 89 cases and by clinical follow-up and correlative imaging for a minimum of 6 months in 4 patients.

RESULTS: There were 37 patients with cancer of gynaecological origin. There were in addition 56 benign lesions within the pelvis. 99mTc MIBI identified correctly 29 of the 37 malignant tumours localised within the pelvis and also correctly identified 21 of 23 metastases within the abdomen. Conventional US identified correctly 35 of the 37 tumours in the pelvis and 16 sites of metastases within the abdomen. The sensitivity and specificity of tumour detection within the pelvis for 99mTc MIBI were as follows: 78% and 70%; and for metastases within the abdomen 91% and 90%. The results of ultrasound for tumour detection within the pelvis: the sensitivity and specificity were 95% and 79% and for abdominal metastases 70% and 97%. Analysis of the index area under a receiver operator characteristic (ROC) curve in scintigraphy did not show a significant difference between both techniques in the diagnosis of pelvic lesions. There was however a significant increase in the sensitivity of scintigraphy 99mTc MIBI over US in metastases detection within the abdomen.

CONCLUSIONS: 99mTc MIBI cannot be recommended for the imaging of pelvic cancer alone, but it may be helpful in the identification of intra-abdominal spread of ovarian carcinoma and appears to offer significant advantages over ultrasound.

Key words: gynaecological malignancies, 99mTc MIBI, dynamic scintigraphy

Introduction

Ovarian cancer is the leading cause of death from gynaecological malignancy in Europe and the United States. The lifetime risk of ovarian cancer in the US population is about 1.4%. The risk is increased in women who have a strong family history of the disease [1]. The survival of patients with endometrial carcinoma, the second most common gynaecological malignancy is good
and is related to their surgical stage and substage of disease [2]. The prognosis for ovarian cancer however remains poor despite advances in molecular biology, surgical oncology and chemotherapy. The exception is the excellent survival rates for stage I diseases and this provides the rationale for efforts to screen for early-stage of cancers. However, there are doubts about the feasibility of screening related to the natural history of the disease, and the performance of the available diagnostic tests, such as ultrasound examination (including using endovaginal and transabdominal methods) and blood markers such as CA-125 [3, 4].

The majority of patients present with advanced disease. Maximum cytoreductive surgery (aggressive surgery to remove virtually all gross tumour) followed by chemotherapy for ovarian cancer and combined therapy, employing external-beam pelvic irradiation and total hysterectomy, is used in endometrial cancer [2]. Such an approach results in a high incidence of initial clinical remission in both cancers and can prolong survival to 2 or 3 years. However, relapse and death due to ovarian cancer often occur in spite of additional therapy. Further operations may be needed for secondary cytoreduction or palliation Bowel obstruction, recurrent ascites, and pleural effusion are often terminal events. Identification of recurrent disease can be even more problematical than finding the primary tumour as previous surgery can obscure changes on both ultrasound and CT [5–7]. In addition the metastases may be very small and be present only as peritoneal plaques of seeds of tumour without a mass being present.

In endometrial carcinoma tumour recurrence is the most common in women with advanced stage disease or those with high-risk features in their primary tumour. Late recurrence is uncommon and virtually all failures are clinically evident within 3 years of original diagnosis [2]. One half of patients whose tumours recur are symptomatic [1, 2].

Functional imaging may be able to identify the presence of gynaecological malignancy when anatomical methods have proved less than ideal. Early work has concentrated on the use of radiolabelled antibodies. This has however produced mixed results [8–10] and the cost of this method and low accuracy makes the widespread use of immunoscintigraphy unlikely.

Methods depending on metabolic uptake of tumours, for example 99mTc MIBI in breast cancer, have often proved to be very useful when anatomical imaging has failed [11]. Initially it was thought that such an approach would not be possible in ovarian cancer because of the marked physiological 99mTc MIBI excretion into the bowel. Previous studies in breast have shown that the optimal imaging of tumours with 99mTc MIBI is often within 5–10 minutes of the injection of the tracer [12, 13]. Excretion into the bowel appears to occur after this time and therefore it may be possible to image the carcinoma of the ovary if imaging of the pelvis and abdomen was performed in the first 10 minutes post injection of the tracer and before there is substantial gut activity. 99mTc MIBI imaging has been shown to be effective in the diagnosis of different tumours and has become well established for the diagnosis of breast cancer [14–16] and therefore it was decided that it may be worth looking at early imaging with this agent in gynaecological cancers.

The aim of this study is therefore to determine if early dynamic imaging of the abdomen and pelvis with 99mTc MIBI is able to accurately detect malignancy in patients with clinical suspicions of primary pelvic or recurrent abdominal gynaecological malignancy.

Material and methods

Patients

There were 93 female patients enrolled in this prospective study (mean age 50, SD 12, range 17–82 years), from Warsaw (central Poland). Each patient had a physical examination by a specialist gynaecologist and endovaginal and transabdominal ultrasound examination as routine before radionuclide study. Both these examinations were used to select those patients with suspected gynaecological cancer. The study was approved by the Scientific Committee of the Medical Academy of Warsaw, Poland, also individual patient consent was obtained.

Sonography

Patients with pelvic masses suspected of malignancy were imaged using a standard endovaginal 7.0 MHz transducer probe Sonoline SL (Siemens, Erlangen, Germany). All patients had additionally conventional abdominal ultrasound using a 3.5 MHz probe Sonoline SL (Siemens, Erlangen, Germany), and standard protocols to assess any abnormalities within the abdomen. Each lesion found in the abdomen or pelvis was measured and described. All pathological lesions were evaluated using colour Doppler and spectral Doppler technique. In each case the resistive index (RI) of blood flow wave was used to determine malignant or non-malignant tumours. RI less then 0.4 was considered as suspicious.

99mTc MIBI imaging

The examinations were performed in fasting patients. In each case 5 min before 99mTc MIBI injection each patient was injected with Glucagon 1 mg i.m. (Lilly; USA). The Glucagon was used to stop bowel activity of 99mTc MIBI and to avoid the problem of non-specific uptake of gut, thereby improving the quality of the images. Radionuclide imaging was performed 2–3 minutes after intravenous injection of 740 MBq 99mTc MIBI (Łódź; Poland) into arm vein. Planar images were performed using a 128 × 128 matrix and 20% windows around a 140 keV photopeak, on a single-head gamma camera, connected into an Icon computer system Di-acam (Siemens, Erlangen, Germany). A high resolution, low energy collimator was used in each case. The anterior pelvic and lower abdominal view was obtained with the patient supine and both arms held above the head. Each image was acquired for a minimum of 300,000 counts.

Image reading

Three independent specialists in Nuclear Medicine reported all the 99mTc MIBI images blinded to the clinical presentation and results of any other imaging modality. Uni- or multi-focal accumulation of 99mTc MIBI within pelvis and abdomen greater than surrounding tissue, except physiological localisation (in the early phase of examination: blood pool in liver, spleen kidney heart and the uterus of women in reproductive age) was defined as a positive result. Diffuse low homogeneous uptake in both pelvis and abdomen was considered normal. When there was a disagreement in the report, the majority decision was taken as the correct
read. Five grades of certainty were used to quantify the results in a semi-quantitative way. These were as follows; grade 1 definitely benign or normal, grade 2 probably benign or normal, grade 3 equivocal, grade 4 probably cancer and grade 5 definitely cancer.

Confirmation of pathology
Surgical exploration and biopsy to confirm the final diagnosis was performed in 89 patients. Tissue was obtained from all sites of clinical suspicion for histopathological examination to confirm a final diagnosis. All pathological specimens obtained were reported by a histopathologist with a special interest in gynaecological malignancy (JK). In 4 cases women were assessed by clinical follow-up and correlative imaging for a minimum of 6 months.

Data analysis
Images were interpreted as true positive when cancer was confirmed by the histopathology, and the images had been scored as probably or definitely cancer (grade 4 and 5). False negative result was when cancer was present but the images had been reported definitely or probably benign or normal or as equivocal (grades 1–3). The examination was interpreted as true negative when cancer was excluded by histology and the images was scored as definitely or probably normal or benign (grades 1 and 2). A false positive result was defined when the images were reported as probably or definitely cancer or equivocal (grades 3–5) but there were no malignant tumour.

A receiver operator characteristic (ROC) curve for scintigraphy and for US were composed using the same grading score obtained with either modality separately for detection of cancer, separately for pelvis and abdomen. Each point of the ROC curve was evaluated to assess the false positive and true positive rates for grade 5, then studies reported as grades 4 and 5 together and finally grades 5 + 4 + 3. To compare both techniques areas under ROC curves were calculated using the trapezoidal rule of measurement. The significance of difference between areas of under each ROC was assessed using Willcoxon’s statistics [17–19].

Results
It was confirmed that 37 patients had evidence of cancer. Histopathology identified 22 patients with ovarian carcinoma, including one case of malignant fibrothecoma and one borderline ovarian tumour (17 cases were primary and 5 had recurrent disease) (Table 1). There were 14 patients with confirmed endometrial carcinoma and one case of endometrial carcinosarcoma. In those patients there were 13 primary tumours and 2 recurrences (Table 2).

\[99mTc\] MIBI identified correctly 27 of 37 malignant tumours occurring within the pelvis (Fig. 1A and Fig. 2A) and also correctly identified 21 of 23 metastases within the abdomen. Conventional US with Doppler technique correctly diagnosed 35 of 37 malignant tumours occurring in the pelvis (Fig. 1B, C, 2B) and 16 of 23 metastases occurring within the abdomen. However, \[99mTc\] MIBI had uptake in 17/56 of the benign masses in the pelvis including 4 leymyomatous tumours of the uterus, 3 cases of dermoid cysts, 2 inflammatory tumours, one case of piceal cyst and one benign cystadenoma tumour (Fig. 3A, B). There were also 6 other benign lesions including simple cysts and serosal cysts. There were 12 false positive results within the pelvis using ultrasound.

Within the abdomen there were 7 patients with false positive uptake of \[99mTc\] MIBI. Two of them had cancer within the pelvis but...
Figure 1. A. $^{99m}$Tc MIBI true positive study of 65-year-old lady. Focal late uptake of tracer within both ovaries (not shown), early focal and diffuse rapid abdominal accumulation within paraaortic lymph nodes, omental involvement, massive ascites. B. and C. US (endovaginal), solid tumour with mixture echogenic pattern involving both ovaries with RI = 0.38 on Doppler examination. D. US (abdominal) massive ascites, no tumour mass within abdomen. Pelvic true positive, abdomen false negative study. Histology — ovarian carcinoma (FIGO IIIc).

Figure 2. A. $^{99m}$Tc MIBI study of 47-year-old patient with focal and diffuse whole abdominal and pelvis uptake, ascites, solid cystic lesion within left ovary. True positive study of pelvis and abdomen. B. US (endovaginal), solid tumour and ascites within pelvis, peripheral angiogenesis with RI = 0.40. C. US (abdominal) no abnormal mass, no lymph nodes involvement. Pelvic true positive, abdomen false negative.
Leszek Królicki et al., Gynaecological malignancy, 99mTc MIBI scintigraphy imaging in diagnosis of pelvic and abdominal masses ...

Table 2. Details of all patients with endometrial carcinoma (15 subjects) including patient with carcinosarcoma: age, clinical information, primary or recurrent seeking, final histology of cancer and FIGO stage (International Federation of Gynaecology and Obstetrics staging)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Clinical</th>
<th>Primary/recurrence</th>
<th>Histology</th>
<th>FIGO</th>
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<tr>
<td>1</td>
<td>70</td>
<td>Uterine tumour</td>
<td>P</td>
<td>Endometrial carcinoma G1</td>
<td>Ic</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>Uterine tumour</td>
<td>P</td>
<td>Endometrial carcinoma G1</td>
<td>Ic</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
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<td>P</td>
<td>Endometrial carcinoma G1</td>
<td>Ib</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
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<td>P</td>
<td>Endometrial carcinoma G2</td>
<td>IIb</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>Uterine tumour</td>
<td>P</td>
<td>Endometrial carcinoma G2</td>
<td>Ila</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>Uterine tumour</td>
<td>P</td>
<td>Endometrial carcinoma G2</td>
<td>Ila</td>
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<tr>
<td>7</td>
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<tr>
<td>8</td>
<td>58</td>
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</tr>
<tr>
<td>9</td>
<td>39</td>
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<td>P</td>
<td>Endometrial carcinoma G2</td>
<td>Ila</td>
</tr>
<tr>
<td>10</td>
<td>52</td>
<td>Uterine tumour</td>
<td>P</td>
<td>Endometrial carcinoma G2</td>
<td>Ila</td>
</tr>
<tr>
<td>11</td>
<td>61</td>
<td>Uterine tumour</td>
<td>R</td>
<td>Endometrial carcinoma G3</td>
<td>IIIC</td>
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<tr>
<td>12</td>
<td>62</td>
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<tr>
<td>13</td>
<td>50</td>
<td>Uterine tumour</td>
<td>P</td>
<td>Endometrial carcinoma G3</td>
<td>Ila</td>
</tr>
<tr>
<td>14</td>
<td>61</td>
<td>Uterine tumour</td>
<td>P</td>
<td>Endometrial carcinoma G3</td>
<td>Ila</td>
</tr>
<tr>
<td>15</td>
<td>76</td>
<td>Uterine tumour</td>
<td>P</td>
<td>Carcinosarcoma</td>
<td>IIC</td>
</tr>
</tbody>
</table>

no metastases were found within the abdomen. One patient with huge leymomymata expanded into the abdomen was also misreported as positive. In 4 other examinations there were incorrect interpretations due to increased bowel activity of 99mTc MIBI despite the glucagon.

Metastatic disease of the abdomen on ultrasound was recognised mainly by the presence of ascites (Fig. 1D) and not by direct visualisation of a tumour mass (Fig. 2C). In contrast to 99mTc MIBI uptake of the tracer was noted in most patients with abdominal metastases.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for tumour detection within the pelvis for the 99mTc MIBI were as follows: 78%, 70%, 63% and 83%, and for abdominal metastases within the abdomen 91%, 90%, 75% and 97%. The sensitivity, specificity, PPV and NPV for US results within the pelvis were 95%, 79%, 74% and 96% and for abdominal metastases 70%, 97%, 89% and 91%. (Table 3, 4).

An evaluation of the area under ROC curves for 99mTc MIBI and US of pelvic masses provides results as follows: 0.81 and 0.91, it was not significant. However for abdominal metastases an
of the use of 99mTc Furifosmin (an agent not unlike MIBI) in the detection of recurrent ovarian cancer but with a poor result [25].

Radiological imaging such as ultrasound, either endo-vaginal or trans-abdominal and other techniques such as CT or MRI, have often been unable to clearly identify metastatic ovarian cancer [3, 6, 26, 27]. The purpose of the invasive “second-look operation” is to completely explore the abdominal cavity; if disease is present, additional therapy should be routinely recommended. Therefore any imaging technique which indicates presence and extent of disease within the abdomen is helpful to avoid a “second look operation” which has a high rate of morbidity over 19% [28]. Currently “second-look” operations are routinely recommended only for women participating in clinical trials to evaluate patients who have completed a programme of chemotherapy and by clinical examination and by diagnostic imaging studies are free of evidence of persistent cancer [28]. Therefore while the results of this study cannot recommend the use of 99mTc MIBI in identifying primary intrapelvic disease it may be possible to use 99mTc MIBI to identify the presence of metastatic disease within the abdomen. This was confirmed using ROC area under the curve analysis. Further work must be concentrated in using this technique within the abdomen to decide if there is sufficient accuracy using 99mTc MIBI alone or in combination with other techniques to prevent the need for diagnostic “second look” surgery.

In conclusion 99mTc MIBI is able to identify gynaecological malignancies in the pelvis and abdomen using dynamic early imaging; however the relatively poorer sensitivity and specificity compared to standard US in the pelvis means that this technique is best applied in the search for intra-abdominal metastases.

**Discussion**

The results of our study show that the sensitivity and specificity of 99mTc MIBI is not as high in the identification of pelvic malignancies as conventional US with Doppler technique. There was false positive activity in a range of benign pelvic tumours, which wereavid for 99mTc MIBI. Also there were some false positives due to increased uterine blood pool in young patients. This might be a weakness of this technique as it depended on early imaging to identify tumour before abdominal and pelvic cancer was obscured by physiological gut activity but unfortunately whilst activity in blood pool activity in the uterus is at its peak. This may be avoided by timing the scan to occur at the point in the first phase of the menstrual cycle. Though we have no evidence to support this, the use of a glucagon injection before the study to stop bowel activity appears to be very useful. With early dynamic imaging up to 5 minutes in most of the cases there was only uterine activity seen but with no gut activity. There was also some abnormal uptake in benign tumours, a phenomenon seen in other cancers such as breast [14]. This is probably related to the increased vasculature of the tumours and this problem may be worsened by the use of early dynamic imaging.

Other scintigraphic techniques used in ovarian cancer include antibodies such as 99mTc H170 [10, 20, 21]. The sensitivity of antibodies appears worse or at best similar to 99mTc MIBI but with a high range of specificity, from as low as 30% [20] to 90% using the same class of antibodies Mab-170 [21]. Also other reports using other class of antibodies and radiotracers like In111 indicated immunoscintigraphy as a powerful tool to assess regional extent of tumour detected with higher sensitivity than computed tomography [8, 9, 22]. However it is unclear whether the use of non-human protein with its accompanying risks justifies the use of immunoscintigraphy for such a small gain in overall accuracy.

PET techniques have been used in ovarian cancer but the excretion of 18FDG in the urine means that pelvic images are often difficult to read [23, 24]. The high cost of 18FDG PET has prevented more extensive use of this technique. There has been a single case of the use of 99mTc Furifosmin (an agent not unlike MIBI) in the detection of recurrent ovarian cancer but with a poor result [25].

**Table 3. Number of subjects using 99mTc MIBI and US technique identified gynaecological malignancy**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>99mTc MIBI Pelvis</th>
<th>Abdomen</th>
<th>US with Doppler technique Pelvis</th>
<th>Abdomen</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP</td>
<td>29</td>
<td>21</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>TN</td>
<td>39</td>
<td>63</td>
<td>44</td>
<td>68</td>
</tr>
<tr>
<td>FP</td>
<td>17</td>
<td>7</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>FN</td>
<td>8</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

TP — true positive results, TN — true negative results, FP — false positive results and FN — false negative results, PPV — positive predictive value, NPV — negative predictive value

**Table 4. Overall diagnostic accuracy of 99mTc MIBI and US in detection of gynaecological malignancy within pelvis and metastases within abdomen, all in %**

<table>
<thead>
<tr>
<th>Subjects</th>
<th>99mTc MIBI Pelvis</th>
<th>Abdomen</th>
<th>US with Doppler technique Pelvis</th>
<th>Abdomen</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>78</td>
<td>91</td>
<td>95</td>
<td>70</td>
</tr>
<tr>
<td>Specificity</td>
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<td>79</td>
<td>97</td>
</tr>
<tr>
<td>PPV</td>
<td>63</td>
<td>75</td>
<td>74</td>
<td>89</td>
</tr>
<tr>
<td>NPV</td>
<td>83</td>
<td>97</td>
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<td>91</td>
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</table>

PPV — positive predictive value, NPV — negative predictive value

**References**