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Original

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 ^{99m}Tc 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 ^{99m}Tc 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. ^{99m}Tc 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 ^{99m}Tc 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 ^{99m}Tc MIBI over US in metastases detection within the abdomen.

CONCLUSIONS: ^{99m}Tc 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, ^{99m}Tc MIBI, dynamic scintigraphy

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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 ^{99m}Tc 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 ^{99m}Tc MIBI excretion into the bowel. Previous studies in breast have shown that the optimal imaging of tumours with ^{99m}Tc 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. ^{99m}Tc 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 ^{99m}Tc 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.

^{99m}Tc MIBI imaging

The examinations were performed in fasting patients. In each case 5 min before ^{99m}Tc MIBI injection each patient was injected with Glucagon 1 mg *i.m.* (Lilly; USA). The Glucagon was used to stop bowel activity of ^{99m}Tc 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 ^{99m}Tc MIBI (Łódź; Poland) into arm vein. Planar images were performed using a 128 $\times$ 128 matrix and 20% windows around a 140 keV photopeak, on a single-headed gamma camera, connected into an Icon computer system Diacam (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 ^{99m}Tc MIBI images blinded to the clinical presentation and results of any other imaging modality. Uni- or multi-focal accumulation of ^{99m}Tc 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 5 and 4 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).

^{99m}Tc 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, ^{99m}Tc MIBI had uptake in 17/56 of the benign masses in the pelvis including 4 leyomyomatous 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 ^{99m}Tc MIBI. Two of them had cancer within the pelvis but

Table 1. Details of all patients with ovarian cancer (22 subjects) including patients with malignant fibrothecoma and ovarian borderline seeking: age, clinical information, primary or recurrent seeking, final histology of cancer and FIGO stage (International Federation of Gynaecology and Obstetrics staging)

Patient	Age	Clinical	Primary/recurrence	Histology	FIGO
1	72	Ovarian tumour	P	Serous adenocarcinoma	IIIc
2	60	Ascites, ovarian tumour	P	Serous adenocarcinoma	IV
3	82	Ovarian tumour	P	Serous adenocarcinoma	IV
4	47	Ovarian tumour, previously breast carcinoma	P	Mucinous adenocarcinoma	Ib
5	67	Ovarian tumour	P	Mucinous adenocarcinoma	IIIb
6	47	Ovarian tumour	P	Serous adenocarcinoma	IIIc
7	59	Ovarian tumour	P	Mucinous adenocarcinoma	IIIc
8	45	Recurrent ovarian cancer	R	Mucinous adenocarcinoma	IIIc
9	54	Recurrent ovarian cancer	R	Serous adenocarcinoma	IIIc
10	43	Ascites, ovarian tumour.	P	Serous adenocarcinoma	IIIc
11	62	Pelvic tumour	P	Serous adenocarcinoma	IIIc
12	54	Ovarian tumour	P	Serous adenocarcinoma	IIIc
13	65	Abdominal tumour	P	Mucinous adenocarcinoma	IIIc
14	64	Ascites, ovarian tumour.	P	Serous adenocarcinoma	IIIc
15	73	Pelvic tumour	P	Serous adenocarcinoma	IIIc
16	59	Ovarian tumour	P	Serous adenocarcinoma	IIIc
17	52	Bilateral ovarian tumour	P	Mesonephroid adenocarcinoma	IIIc
18	66	Ovarian tumour	P	Mucinous adenocarcinoma	IIIc
19	47	Recurrent ovarian cancer	R	Mucinous adenocarcinoma	IIIc
20	46	Recurrent ovarian cancer	R	Mucinous adenocarcinoma	IIIc
21	72	Recurrent ovarian cancer	R	Malignant fibrothecoma	Ia
22	42	Ovarian tumour	P	Borderline ovarian carcinoma	Ib

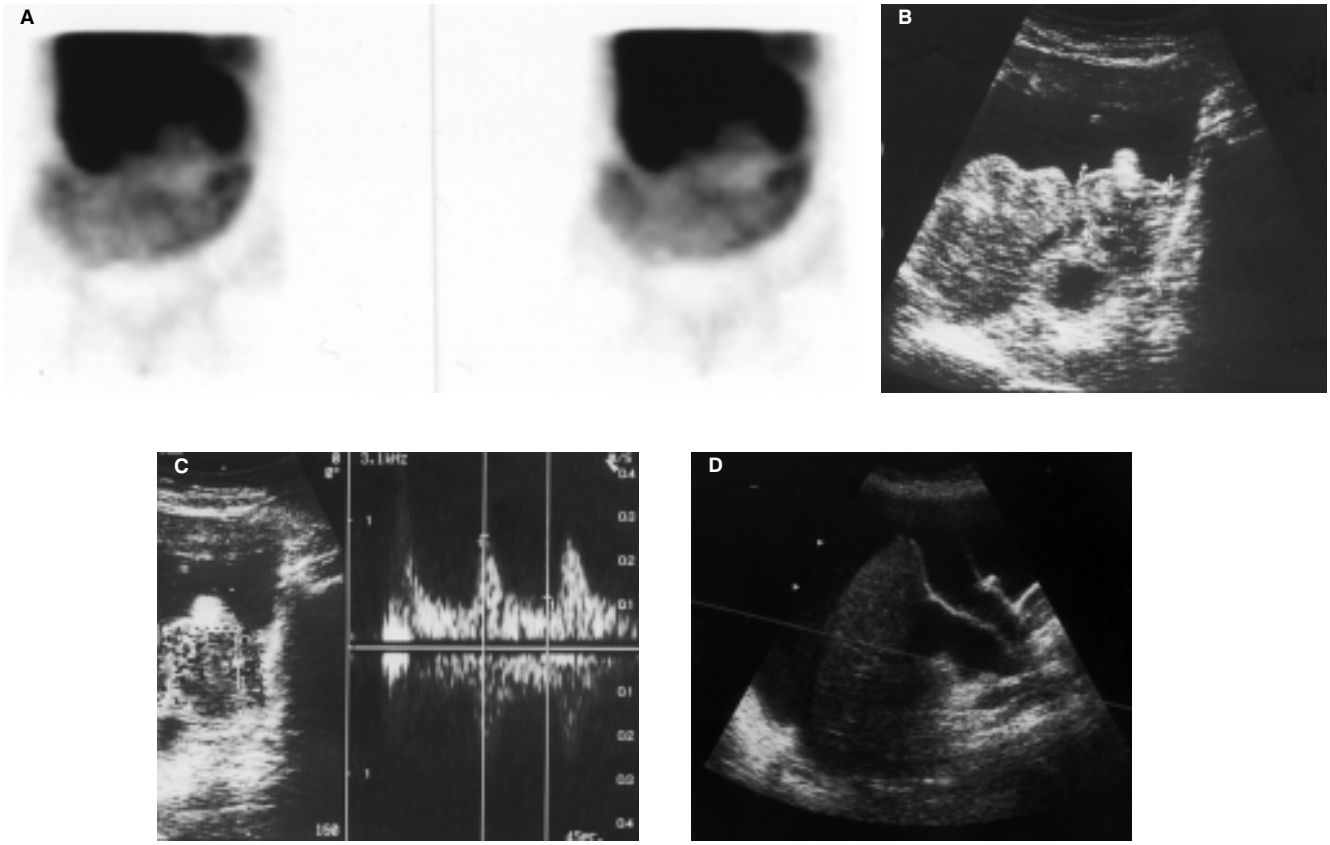


Figure 1. A. ^{99m}Tc MIBI true positive study of 65-year-old lady. Focal late uptake of tracer within both ovaries (not shown), early focal and diffuse rapid abdominal accumulation within pariaortic lymph nodes, omental involvement, massive ascites; **B.** and **C.** US (endovaginal), solid tumour with 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).

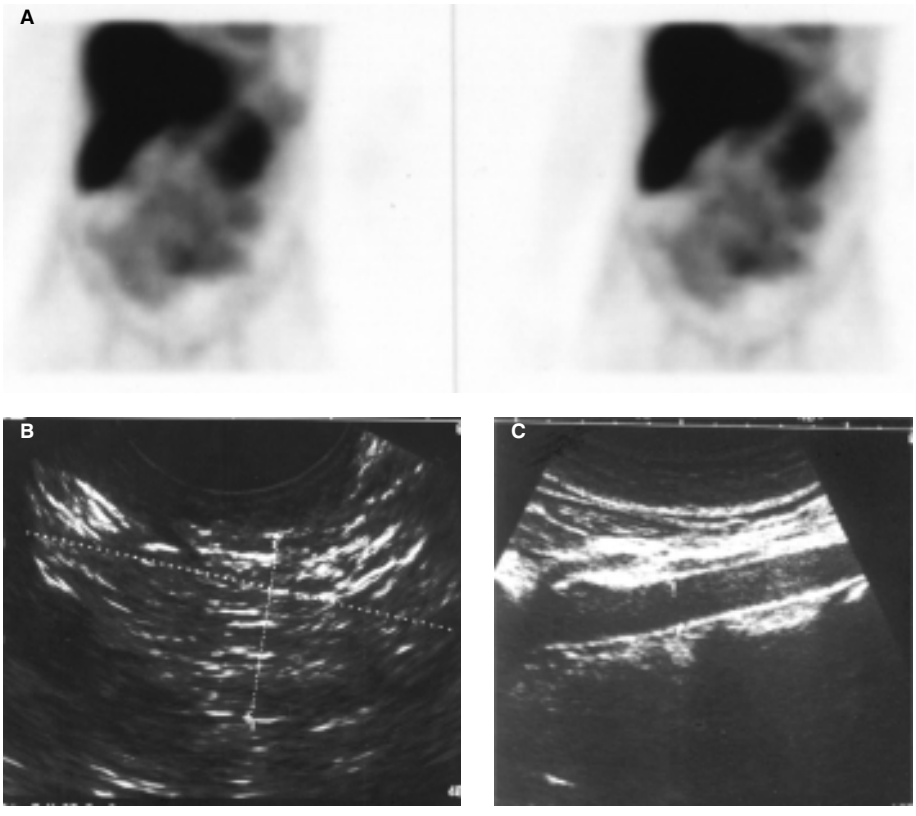
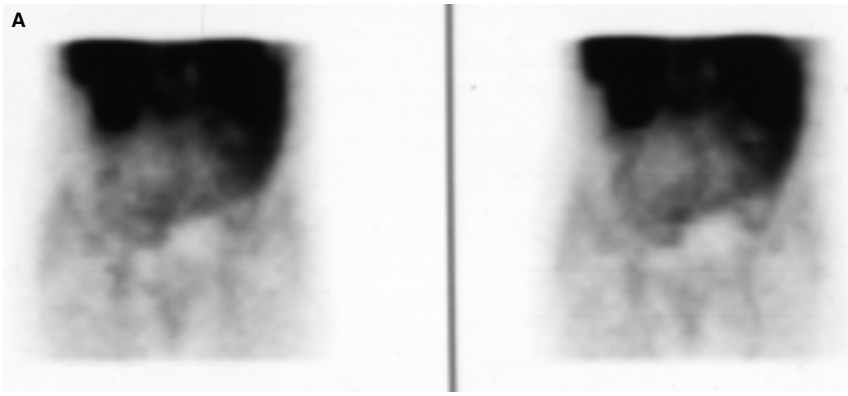


Figure 2. A. ^{99m}Tc MIBI study of 47-year-old patient with focal and diffuse whole abdominal and pelvis uptake, ascites, solid cytic lesion within left ovary. True positive study of pelvis and abdomen; **B.** US (endovaginal)), solid tumour and ascites within pelvis, peripheral angiogenesis with RI = 0.40; **C.** US (abdominal) no abnormal mass, no lymph nodes involvement. Pelvic true positive, abdomen false negative.



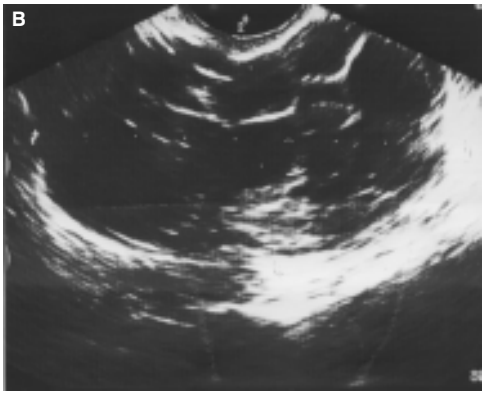


Figure 3. A. ^{99m}Tc MIBI focal uptake of tracer in 42-year-old patient within upper part of the pelvis, solid — cystic lesion within left and right ovary. Focal abdominal accumulation of radiotracer within omenetal nodes. Pelvis and abdominal false positive; **B.** Mix solid and cystic tumour involving left and right ovary, with RI = 0.4–0.42 on Doppler examination, equivocal result of US. No abdominal deposits. Pelvic false positive and abdominal true negative. Histology — benign cystadenofibroma bilaterale.

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)

Patient	Age	Clinical	Primary/recurrence	Histology	FIGO
1	70	Uterine tumour	P	Endometrial carcinoma G1	Ic
2	57	Uterine tumour	P	Endometrial carcinoma G1	Ic
3	75	Uterine tumour	P	Endometrial carcinoma G1	Ib
4	53	Uterine tumour	P	Endometrial carcinoma G2	IIb
5	65	Uterine tumour	P	Endometrial carcinoma G2	IIa
6	59	Uterine tumour	P	Endometrial carcinoma G2	IIa
7	77	Uterine tumour	P	Endometrial carcinoma G2	IIIc
8	58	Uterine tumour	P	Endometrial carcinoma G2	IIa
9	39	Uterine tumour	P	Endometrial carcinoma G2	IIa
10	52	Uterine tumour	P	Endometrial carcinoma G2	IIa
11	61	Uterine tumour	R	Endometrial carcinoma G3	IIIc
12	62	Uterine tumour	R	Endometrial carcinoma G3	IIIc
13	50	Uterine tumour	P	Endometrial carcinoma G3	IIa
14	61	Uterine tumour	P	Endometrial carcinoma G3	IIIc
15	76	Uterine tumour	P	Carcinosarcoma	III

no metastases were found within the abdomen. One patient with huge leyomyomata expanded into the abdomen was also misreported as positive. In 4 other examinations there were incorrect interpretations due to increased bowel activity of ^{99m}Tc 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 ^{99m}Tc 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 ^{99m}Tc 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 ^{99m}Tc MIBI and US of pelvic masses provides results as follows: 0.81 and 0.91, it was not significant. However for abdominal metastases an

Table 3. Number of subjects using ^{99m}Tc MIBI and US technique identified gynaecological malignancy

Subjects	^{99m}Tc MIBI		US with Doppler technique	
	Pelvis	Abdomen	Pelvis	Abdomen
TP	29	21	35	16
TN	39	63	44	68
FP	17	7	12	2
FN	8	2	2	7

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 ^{99m}Tc MIBI and US in detection of gynaecological malignancy within pelvis and metastases within abdomen, all in %

Subjects	^{99m}Tc MIBI		US with Doppler technique	
	Pelvis	Abdomen	Pelvis	Abdomen
Sensitivity	78	91	95	70
Specificity	70	90	79	97
PPV	63	75	74	89
NPV	83	97	96	91

PPV — positive predictive value, NPV — negative predictive value

area under ROC for ^{99m}Tc MIBI was 0.96 compared to US 0.88, a significant difference with 80% of probability between scintigraphy and US was found using a one-sided test of significance with $p = 0.05$.

Discussion

The results of our study show that the sensitivity and specificity of ^{99m}Tc 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 were avid for ^{99m}Tc 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 ^{99m}Tc H170 [10, 20, 21]. The sensitivity of antibodies appears worse or at best similar to ^{99m}Tc 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 In^{111} 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 ^{18}FDG in the urine means that pelvic images are often difficult to read [23, 24]. The high cost of ^{18}FDG PET has prevented more extensive use of this technique. There has been a single case of the use of ^{99m}Tc 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 ^{99m}Tc MIBI in identifying primary intrapelvic disease it may be possible to use ^{99m}Tc 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 ^{99m}Tc MIBI alone or in combination with other techniques to prevent the need for diagnostic "second look" surgery.

In conclusion ^{99m}Tc 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.

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