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Authors: Schmidt S, Meuli RA, Achtari C, Prior JO

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Peritoneal carcinomatosis in primary ovarian cancer staging: Comparison between MDCT, MRI and ^{18}F-FDG PET/CT

Sabine Schmidt, MD[1], Reto A. Meuli, MD[1], Chahin Achtari, MD[2], John O. Prior, MD, PhD[3]

[1] Department of Diagnostic and Interventional Radiology, Lausanne University Hospital, Rue du Bugnon 46, 1011 Lausanne, Switzerland

[2] Department of Obstetrics and Gynecology, Lausanne University Hospital, Rue du Bugnon 46, 1011 Lausanne, Switzerland

[3] Department of Nuclear Medicine, Lausanne University Hospital, Rue du Bugnon 46, 1011 Lausanne, Switzerland

Abstract

Purpose

To compare MDCT, MRI and FDG-PET/CT imaging for the detection of peritoneal carcinomatosis (PC) in ovarian cancer

Methods

Fifteen women with ovarian cancer and suspected PC underwent MDCT, MRI and FDG-PET/CT, shortly before surgery. According to the peritoneal cancer index nine abdominopelvic regions were defined. We applied lesion size scores on MDCT- and MR and measured FDG-PET/CT standard uptake. We blindly read MDCT-, MR- and PET/CT before joint review and comparison with histopathology. Receiver operating characteristics (ROC) analysis was performed.

Results

Ten women had PC (67%). Altogether, 135 abdominopelvic sites were compared. Sensitivity for MDCT, MRI and FDG-PET/CT was 96%, 98%, and 95%, and specificity was 92 %, 84% and 96%, respectively. Corresponding ROC-area was 0.94, 0.90 and 0.96, respectively, without any significant differences between them (p=0.12). FDG-PET/CT detected supradiaphragmatic disease in 3 (20%) women not seen by MDCT or MRI.

Conclusion

Although MRI had the highest sensitivity and FDG-PET/CT the highest specificity, no significant differences existed between the three techniques. Thus, MDCT, as fastest, most economical and most widely available modality, is the examination of choice, if a stand-alone technique is required. If inconclusive, PET/CT or MRI may offer additional

insights. Whole-body FDG-PET/CT may be more accurate for supradiaphragmatic metastatic extension.

Key words: ovarian cancer, peritoneal carcinomatosis, MRI, MDCT, ^{18}F-FDG PET/CT

INTRODUCTION

Ovarian cancer is the fifth most common malignancy in women and the most lethal among all gynaecological diseases[1]. Approximately 70% malignant ovarian tumours are detected at an advanced stage only, which means that, at the time of initial diagnosis, abdominopelvic dissemination has already occurred[1-6]. The most indicative imaging findings of malignancy in ovarian cancer are peritoneal fluid, lymphadenopathies and peritoneal carcinomatosis (PC)[7-9].

Patients' management in ovarian cancer depends on the results of initial staging., traditionally performed by laparotomy with simultaneous therapeutical "debulking" in case of PC. However, certain sites of the abdominal cavity are difficult to fully explore by surgery[1,5]. Furthermore, sampling errors may occur, leading to false negative results and/or understaging in up to 30% of cases [4]. Today, most clinicians would prefer a non-invasive staging in order to decide on neoadjuvant chemotherapy, if indicated, which permits downstaging prior to the surgical intervention.

Technical advances in multidetector computed tomography (MDCT), magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography combined with computed tomography (PET/CT) have enabled non-invasive staging, but which of these three techniques achieves the best patient management?

Several trials have already evaluated these imaging modalities for the initial detection of PC associated with ovarian cancer; however they were done either not in comparison with each other[10], or using old technical equipment for image acquisition and processing[2,3,8,11-15]. Thus, we decided to undertake a re-evaluation using modern image equipment. Our principal goal was to find out if the diagnostic value of these three

modalities, either taken separately or altogether, would enable clinicians to non-invasively decide on the following neoadjuvant chemotherapy. Using surgical exploration with histopathology as gold standard we prospectively compared MDCT, MRI and ^{18}F-FDG PET/CT in ovarian cancer patients, in whom PC was suspected.

METHODS

Patients

After approval by our ethical committee we prospectively studied 17 women, consecutively addressed for primary ovarian cancer staging. In all women concomitant PC was suspected and debulking surgery was planned. Before imaging each woman gave written informed consent.

Inclusion criteria were suspected ovarian cancer based on physical examination including an increased level of serum cancer antigen 125 (>35 U/mL) and/or sonographic findings of an ovarian mass with/without ascites. Exclusion criteria were known allergic reaction to iodinated contrast medium or gadolinium, renal failure (creatinine clearance <40ml/min) and known contraindications to MRI.

We had to exclude two patients. In one the final diagnosis was hepatobiliary cancer and in the second previous diagnostic laparoscopy lead to false positive SUV uptake on ^{18}F-FDG PET/CT. Thus, 15 women, all without surgery prior to imaging, finally constituted our study group (mean age 65, range 31-89).

Technical imaging parameters

Shortly before surgery all 15 women underwent MDCT, MRI and ^{18}F-FDG PET/CT. In 12 women the three techniques were performed the same day, in 1 patient with a delay

of 1 day between FDG-PET/CT and MDCT/MRI, in 1 patient of 4 days, and in 1 of 2 weeks. Thus, the mean interval was 1±4 days and the range 0-14 days.

MDCT

MDCT was performed on a 64-row machine (Light Speed, VDT, 64 Pro, General Electric Healthcare, Milwaukee, Wisconsin, USA). After administration of a rectal enema with 1L of water we acquired axial slices (120 kV, 300mA, 0.8 sec/rotation, pitch 1.375 2mm/2mm) from diaphragm to symphysis during portal venous phase at 70 seconds after intravenous (i.v.) iodine contrast medium injection (Iohexol®, 300mgI/ml, 3ml/sec, volume in millilitres = body weight +30ml), followed by multiplanar reconstructions with 30% overlap.

MRI

MR data were acquired on a 3.0 Tesla (T) MR scanner (TRIO or VERIO, Siemens Healthcare, Erlangen, Germany) with a maximum gradient strength of 45 mT/m. To include the whole abdomen in our examination protocol we combined two 6-channel phased-array body coils anteriorly and two 3-channel spine clusters posteriorly. After fasting for 6h prior to MRI and being administrated a rectal enema with 1L of water all patients were i.v. injected an antiperistaltic agent (20 mg scopolaminbutylbromide (Buscopan®, Boheringer Ingelheim, Basel, Switzerland) or, if that was contraindicated, 1 mg of glucagon (GlucaGen®), Novo Nordisk, Basgvaerd, Denmark)).

The MR acquisition protocol included the whole abdomen. All our sequences were performed using the generalised autocalibrating partially parallel acquisition (GRAPPA) technique with and acceleration factor of 2. The axial plane was covered with two acquisitions of each sequence, centred on the upper and lower abdomen, respectively.

We started with axial and coronal breath-hold T2-weigthed half-Fourier single-shot turbo spin-echo acquisitions (HASTE; repetition time (TR), 1200ms; echo time (TE), 89 ms; echo-train length (ETL), 256; number of excitations (NEX),1; matrix size, 320x240; section thickness/gap, 3/0.3 mmm), followed by axial and coronal three-D-VIBE (three-dimensional volumetric interpolation breath-hold examination) MR-sequences (TR, 4.6ms; TE, 1.7ms; ETL, 1; flip angle 9°; NEX 1;matrix size, 448×336; section thickness/gap, 4/0.8mm before and at 70 seconds after an i.v. gadolinium (Gd-)DOTA injection acquired in portal venous phase (Dotarem®, 0.2mmol/kg of body weight) followed by a 40ml of flush of 0.9% Na saline.

Before i.v. Gadolinium injection, we performed axial free-breathing fat-suppressed diffusion-weighted single-shot echo-planar MR-sequences (DW-SS-EPI, TR, 6500 ms; TE, 66ms; ETL, 1; receiver bandwidth, 1698 Hz/pixel; NEX, 3; matrix size, 168×126; section thickness/gap, 6/1.8mm) while applying diffusion gradients in three orthogonal directions (section, phase, and frequency encoding directions), with increasing *b*-values (0, 300, 600 sec/mm^2). The voxel size of the DWI-SS-EPI sequence was 2.3×2.3×6.0 mm and acquisition time approximately 7 minutes.

^{18}F-FDG PET/CT

All patients were fasting for ≥6 h and had a glucose plasma level ≤6.1 mmol/l before the ^{18}F-FDG intravenous injection. PET/CT (Discovery LS, GE Healthcare Milwaukee, WI) included a whole body acquisition (from skull base to mid-thighs) performed 70±6 min after i.v. injection of 5.5MBq/kg of ^{18}F-FDG. PET acquisition was preceded by a craniocaudal unenhanced acquisition of MDCT (16-row-detector) used for attenuation correction and localization (140kV, 80mA; pitch 1.5, 0.5 sec/rotation, 5-mm slice thickness). PET data were subsequently reconstructed using an ordered-subset

expectation maximization method with 8 subsets and 2 iterations. A late PET/CT acquisition was also performed 104±6 min after FDG injection and just after a bolus i.v. injection of an antiperistaltic agent (20 mg scopolaminbutylbromide or 1mg of glucagon).

Image Analysis

Reference standard were surgical exploration and histopathology. To allow for the best comparison between the three imaging modalities and our reference standard and for the best description of disease extension, we used the internationally recognized peritoneal cancer index (PCI) proposed by Sugarbaker with a subtle modification[16]. For our image analysis we reduced the possible implant sites from twelve to nine (Fig. 1), still covering the whole peritoneal cavity including the pelvis, but without differentiating the implants attached on the peritoneal surface from the ones attached to the bowel serosa. Thus, we simplified the comparison between our imaging modalities, but still assessed the exact topography of tumor extension (Fig. 1).

Additionally, we included three sites of possible lymph node involvement, i.e. retroperitoneal, iliac and inguinal, and basal pleural carcinomatosis. On each modality possible ascites was also evaluated including the maximal standard uptake value (SUV_{max}) of the pleural and abdominal fluid, when detected on PET/CT images.

According to Sugarbaker[16], not the number of peritoneal nodules was scored on the MDCT- and MR-images, but the size of the largest implant detected in each quadrant by means of a four-point grading system (Likert scale): LS0 = no implant, LS1 = implant ≤0.5cm, LS2 = implant ≤5cm, LS3 = implant >5cm or confluent implants. In the case of any lymph node involvement their small diameter was measured.

When analysing the PET/CT-images we also took account of the nine anatomical regions including the three lymph node sites, but without scoring the size of implants nor of lymph nodes, but by measuring the SUV_{max} per quadrant and per lymph node site.

Blinded to all clinical information and independently, one radiologist (14 years of experience in abdominal imaging) read the anonymous MRI- and MDCT-images, while one nuclear physician (10 years of experience in PET/CT) read the anonymous PET/CT images. To reduce recall bias the radiologist read the CT-images two months later than the MR-images. Each item was graded on a five-point confidence scale (definitely absent, probably absent, undetermined, probably present, and definitely present).

In a joint reading session both readers then compared MDCT-, MR- and PET/CT-images still evaluating each quadrant separately on a lesion-by-lesion basis

The same above-described scoring system was used by the operating gynaecologist, who filled in the evaluation form during surgery indicating location and size of implants.

For statistical analyses we used the software Stata 11.1. Sensitivity and Specifity were evaluated for each technique. Each item was considered positive, when evaluated with one of the three upper confidence levels. The chi-square test according to Pearson and Receiver Operating Curves (ROC) with our five-point confidence scale for calculating the area under the curve (AUC) of each technique were performed. Using Spearman's rank correlation we compared lesions' sizes measured on MDCT and MRI. Finally, the interobserver agreement between MDCT and MRI was evaluated according to the kappa statistics[17]: kappa 0-0.20 = slight, 0.21-0.40 = fair, 0.41-0.60 =moderate, 0.61-0.80 = substantial and 0.81-1 = perfect agreement.

All statistical differences were considered significant for a p-value <0.05.

RESULTS

The interval between imaging and surgery was 8.1 ± 2.4 days (range = 1-29). In all 15 women, ovarian cancer was histopathologically proven and peritoneal carcinomatosis was associated in 10 (67%) out of them, either stage III (n=4) or stage IV (n=6). Histopathology revealed five serous cystadenocarcinomas, three endometroid adenocarcinomas, three poorly differentiated adenocarcinomas, one clear cell adenocarcinoma, two serous borderline tumours and one mucinous borderline tumour. In six (40%) women the ovarian cancer involved both ovaries.

Altogether, we evaluated 135 abdominopelvic sites for PC and compared them with our reference standard.

For 74 (55%) anatomical sites PC was proven, among them 13 (17%) with the largest implants measuring ≤ 0.5cm, 40 sites (54%) measuring ≤ 5cm, and 21 sites (29%) measuring >5cm.

Nine patients had ascites, among them eight with PC (Fig. 2) and one woman without PC (Fig. 3). Pleural carcinomatosis was proven in three patients (20%) and in two women (8%) the sigmoid colon was infiltrated.

Table 1 demonstrates our diagnostic results for each technique that is for the detection of PC as separated finding as well as for PC including pleural carcinomatosis and infiltrated lymph nodes. Fig. 4 and Fig. 5 show the correspondent ROC-analyses without any significant difference in the area under the curve (AUC) between the three techniques ($p = 0.12$ and $p = 0.11$, respectively). Although there were no statistically significant differences, MRI had the highest sensitivity and negative predictive value,

PET/CT had the highest specificity and positive predictive value, as well as accuracy and ROC AUC.

There was substantial agreement (kappa = 0.68) between the interpretation of MDCT and MRI examinations with readings agreeing in 79% of the lesions.

MDCT was more sensitive than MRI and PET/CT for detecting ascites with an AUC of 0.92 [95% CI 0.75-1.0], 0.83 [0.50–1.0], and 0.83 [0.53–1.0], respectively, at ROC analysis, however not significant (p=0.59)

According to Spearman's rank correlation the lesions' size measured on MRI and MDCT compared with the histopathological results did not show any significant differences between the two techniques (MDCT 0.917 [0.89–0.94]), MRI 0.98 [0.84–0.90]), respectively.

Sensitivity and specificity for detecting infiltrated lymph nodes was 77% [46–95%] and 98% [87–100%] for MDCT, 100% [75–100%] and 98% [87–100%] for MRI, and 93% [64–100%] and 95% [83–100%] for PET/CT, corresponding to an AUC of 0.88 [0.75–1.0], 1.0 [0.99–1.0] and 0.96 [0.88–1.0], respectively, at ROC analysis, which statistically means a trend in favour of MRI (p=0.071).

For the detection of basal pleural carcinomatosis, there was a trend (p=0.067) for differences in AUC in favour of PET/CT (MDCT 0.92 [0.75–1.0], MRI 0.67 [0.34–0.99], PET/CT 1.0 [0.99–1.0]).

Of note, PET/CT showed increased uptake (SUV 4.2±1.1 g/mL, range 3.4–5.4) in thoracic lymph nodes in 3 patients (20%), which were very suspicious of metastases, but no histologic confirmation could be obtained. These supradiaphragmatic disease extensions were not detected on CT and were not investigated by MRI.

DISCUSSION

There is no universally accepted gold standard for imaging of PC[18]. Our study did not reveal significant differences between MDCT, MRI and PET/CT, but all sensitivity values were >90%, as well as specificities, except for MRI. Preoperative imaging is crucial to determine patients' exact tumor extension. If PC, non-invasively assessed by initial staging, is too extensive for complete debulking, the women had better be treated by neoadjuvant chemotherapy first. After downstaging, patients' operability and clinical prognosis will be improved, as it was already proven for the management of other abdominal malignancies, such as oesophageal[19] or rectal cancer[20].

To the best of our knowledge, there has been one prospective comparison of the three modalities, MDCT, MRI and PET, performed simultaneously in ovarian cancer. Including seven patients it focuses on the ovarian tumour instead of highlighting PC, however[13].

Table 2 summarizes the results of previous studies investigating one or two of our evaluated techniques for PC in ovarian cancer or in other abdominal malignancies[2, 3, 10-12,18,21,-23]. Their diagnostic values are mostly inferior or similar to ours (Table 2). Patient-based analyses yield higher diagnostic performance than site-based analyses, no matter the imaging modality. This certainly results from the frequently small size of single peritoneal implants and the subtle contrast difference with the surrounding anatomical structures[24].

MDCT, known for excellent spatial resolution, rapidity, robustness and reproducibility of image acquisition, is today considered the "work-horse" of oncologic imaging. Unlike MRI, MDCT is particularly robust, when a large amount of ascites is present, as seen in 9 (60%) of our patients. Nevertheless, since 13 of our quadrants (17%) showed

implants measuring ≤0.5cm only, an excellent contrast resolution was required, which is the unique advantage of MRI.

The sensitivity of MRI for PC has been reported to increase by adding diffusion-weighted (DWI) MR-sequences compared to using conventional MR-sequences alone[9,25], provided that DWI is interpreted with the other acquired MR-sequences[6,24,26,27]. In our study, MRI turned out the most sensitive technique for PC, however without statistically significant difference to MDCT and PET/CT. Our MRI results agree with these reported by Fujii *et al.* evaluating MRI with DWI for PC in various gynecological malignancies[26].

Unlike MRI and MDCT, the decisive advantage of PET/CT is the whole-body coverage. Known as modality of choice for detecting recurrent ovarian cancer[28-30], PET/CT is not yet routinely performed for initial ovarian cancer staging. PET with integrated MDCT is superior to PET alone for detecting PC, because of better spatial attribution of focal radiotracer uptake[18,25,28-29]. However, the limited spatial resolution remains an important issue[10]. It may explain why in our study PET/CT showed a slightly lower sensitivity for PC than MDCT and MRI, however without reaching statistically significance. These results agree with these reported by Soussan *et al.,* who directly compared PET/CT with MRI for PC arising from gastrointestinal malignancies[23]. Thus, PET/CT can miss miliary peritoneal implants, especially when image misregistration due to respiratory and bowel movements occurs, or in patients with little mesenteric fat, in whom the intestinal loops are clustered together.

In some patients, MRI, and possibly MDCT also, lead to overstaging, which can be inferred from our lower specificity we obtained for MRI (84%) and MDCT (92%) compared to PET/CT (96%). This misinterpretation arise in presence of large quantities

of ascites, in which the peritoneal vascularisation prominently appears, thus rendering very difficult the exclusion of small peritoneal implants located between these serpiginous and often dilated vessels (Fig 4**).** Therefore, we believe that in these cases PET/CT is advantageous, especially if diagnostic aspiration of the peritoneal fluid cannot be performed. With PET/CT, massive ascites helps detecting small peritoneal implants[15], possibly because of the greater distance between the different bowel loops among each other, allowing for easier distinction between the physiologic intestinal activities from peritoneal implants attached to the bowel serosa.

Due to its whole-body coverage, PET/CT detected metastatic disease, not seen on MDCT or MRI in 20% of the patients. This may be particularly important, as the detection of supradiaphragmatic disease means Stage IV; these women would not benefit from optimal cytoreductive surgery and have shorter survivals[31].

Shortcomings of PET/CT remain limited availability and higher costs, while the additional radiation exposure may not be an issue in these severely ill women. However, the initial higher costs for PET/CT may then be compensated with further, straightforward patients' management, especially in case of clinically unexpected supradiaphragmatic disease extension that would be unexpectedly discovered by PET/CT. Indeed, the cost effectiveness could be at best studied in large patient population, for instance in the frame existing national oncology PET registries.[29-31]

Our study has limitations: First, the daily organisation in our department imposed us to use a 3.0-T instead of a 1.5-T MR-magnet, despite important quantities of ascites in some women. Since this large amount of intraperitoneal fluid is a highly conductive medium, 3.0 T magnets present more, or even new, artefacts compared to 1.5 T

scanners. This hampers the diagnostic quality of MR-images[34]. However, MRI, and in particular DWI, have been proven feasible at 3.0 T in advanced ovarian cancer[35].

Unlike other authors[25], we deliberately refrained from a sequential analysis of our MR-images (first without DWI sequences, then including them). We think that DWI has now become an integrated part of abdominal oncological imaging protocols and should be analysed in conjunction with the other MR-sequences. We also refrained from measuring the apparent diffusion coefficient (ADC), mainly because of the small size of many peritoneal implants.

We also performed only non-contrast-enhanced PET/CT to compare MDCT vs. PET/CT. It is possible that contrast-enhanced PET/CT might have better performance characteristics than MDCT and PET/CT, but this was not assessed here.

Finally, although our study population has been quite small, we believe our results represent valid findings for a single centre. We would like to confirm them by a larger multicentre trial.

In conclusion, our study yielded no significant differences between MDCT, MRI and PET/CT for detecting PC in ovarian cancer patients. MRI was the most sensitive technique, and PET/CT the most specific one. Thus, MDCT, known as fastest, most economical and widely available modality, may be the examination of choice, if there is only one to be performed. If MDCT is negative or inconclusive, PET/CT or MRI may offer additional insights. PET/CT, as a whole-body modality, may provide more accurate preoperative evaluation of supradiaphragmatic metastatic extension.

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Figure legends

Figure 1: We analysed our images according to nine quadrants covering the whole peritoneal cavity including the pelvis. Each quadrant was considered as a possible implant site and was evaluated separately.

The horizontal borderline between the three upper and three middle row sites were defined as the level of the twelfth costal arch and the horizontal borderline between the three middle and the three lower row sites were defined as the upper border of the iliac crests. Vertically, the different quadrants were separated by the medioclavicular lines.

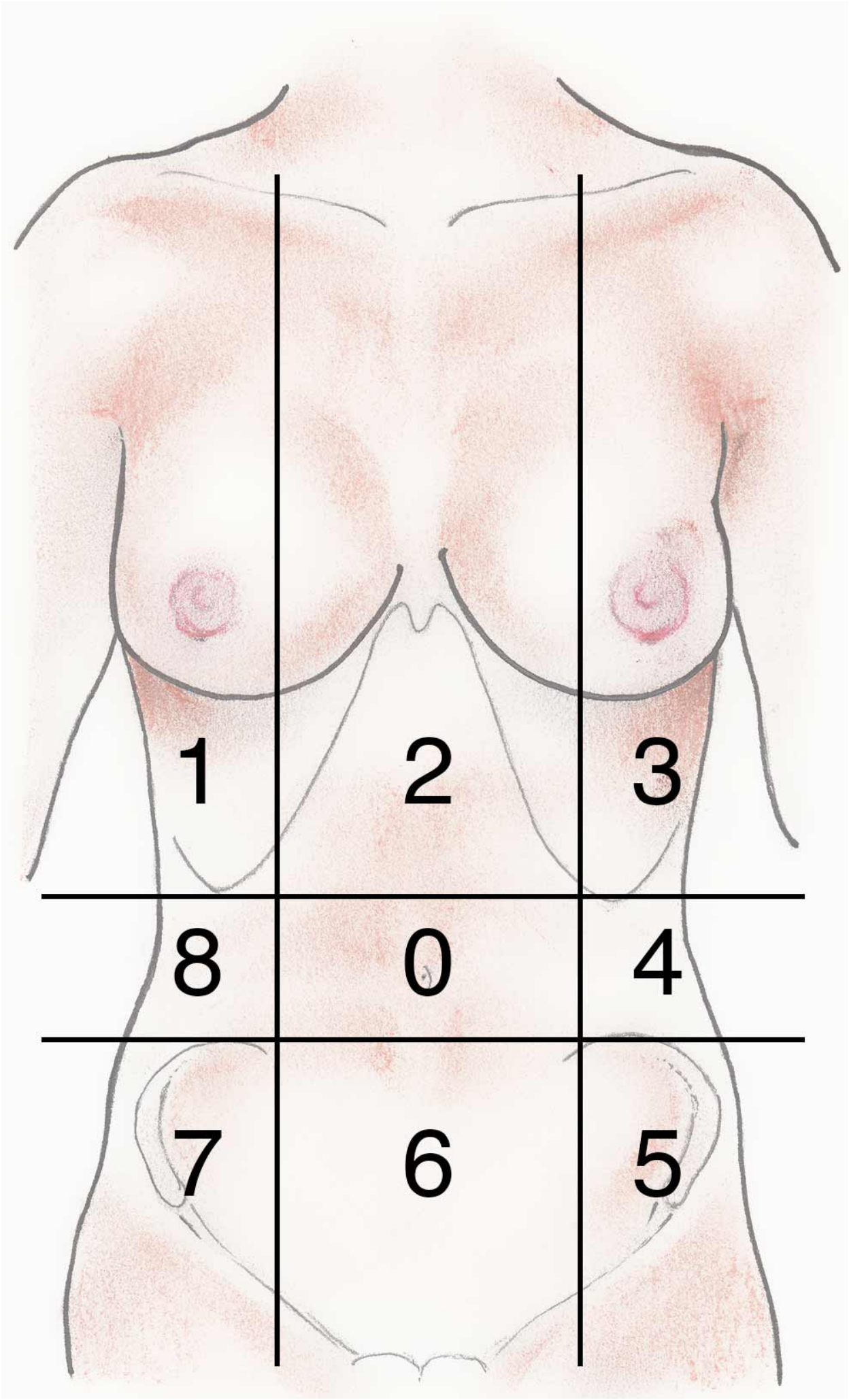
The quadrants were numbered as follows: 0 = central, 1 = right upper, 2 = epigastrium, 3= left upper, 4 = left flank, 5 = lower left, 6 = pelvis, 7 = right lower, 8 = right flank.

Figure 2: Bilateral ovarian tumour in a 48-year-old woman. The concomitant peritoneal carcinomatosis *(arrows)* was well detected by all the three imaging modalities, MDCT **(a),** MRI **(b)** and ^{18}F-FDG PET/CT **(c),** and finally confirmed by surgery and histopathology. Note the additional retroperitoneal lymphadenopathy (*arrowhead*), equally detected by each technique.

Figure 3: Ovarian cancer (**a-b,** *asterisk*) in an 80-year-old woman with an important quantity of ascites. The latter is well seen on MRI- **(a-c)** and ^{18}F-FDG PET/CT-images **(d).** The apparent peritoneal thickening (*arrows*) seen on coronal T1-w Gd-image **(a)** as well as on coronal **(b)** and axial **(c)** T2-w images lead to the misdiagnosis of PC on MRI, while ^{18}F-FDG PET/CT **(d)** was clearly negative. Surgery and histopathology confirmed ovarian tumor with ascites, but not PC, although suggested by MRI.

Fig 4: Receiver operating curve (ROC) demonstrating the area under the curve (AUC) of each of the three imaging techniques, MDCT, MRI and ^{18}F-FDG PET/CT, for the detection of peritoneal carcinomatosis as separated finding, compared to surgery and histopathology. No significant difference between the three modalities is seen (p=0.12).

Fig 5: Receiver operating curve (ROC) demonstrating the area under the curve (AUC) of each of the three imaging techniques, MDCT, MRI and ^{18}F-FDG PET/CT, for the detection of peritoneal carcinomatosis including positive lymph nodes and basal pleural carcinomatosis compared to surgery and histopathology. No significant difference between the three modalities is seen (p=0.11).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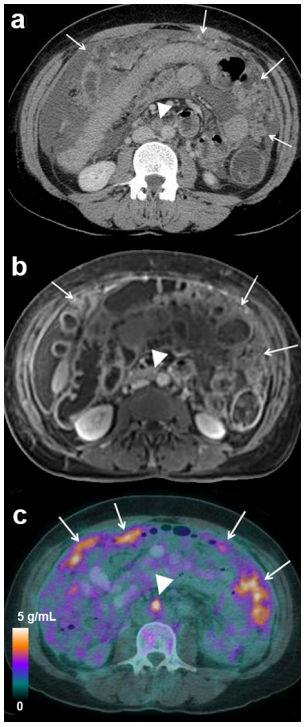
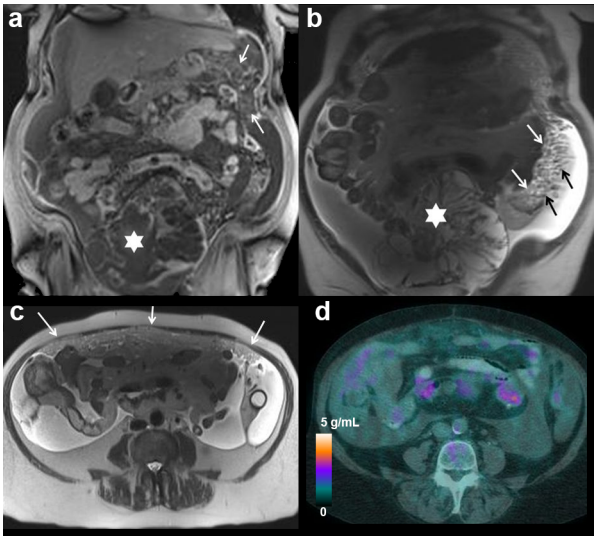
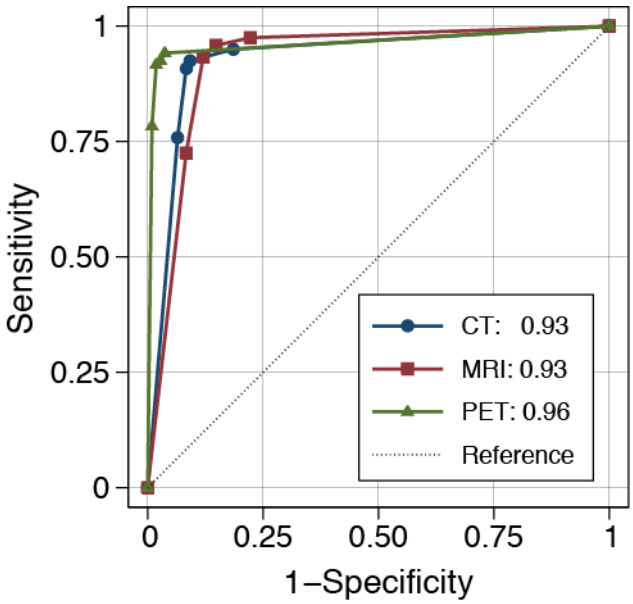
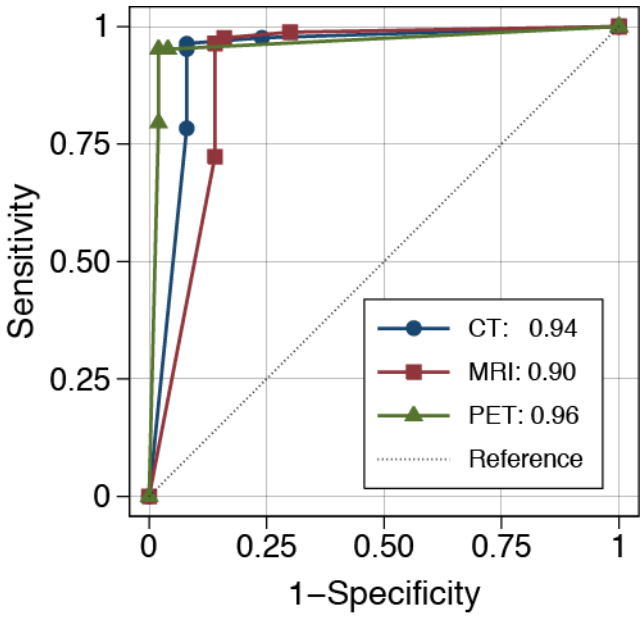

a
b
c
5 g/mL
0


a
b
c
d
5 g/mL
0


Sensitivity
1
0.75
0.50
0.25
0
0
0.25
0.50
0.75
1
1–Specificity
CT: 0.93
MRI: 0.93
PET: 0.96
Reference


1
0.75
0.50
0.25
0
Sensitivity
0
0.25
0.50
0.75
1
1−Specificity
CT: 0.94
MRI: 0.90
PET: 0.96
Reference