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ORIGINAL ARTICLE

One Stop Centre Staging by Contrast-Enhanced 18F-FDG PET/CT in Preoperative Assessment of Ovarian Cancer and Proposed Diagnostic Imaging Algorithm: A single centre experience in Malaysia

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ABSTRACT

Introduction: Suspicious adnexal masses need to be investigated thoroughly as it may represent ovarian cancer, which is the fourth most common gynaecological cancer in Malaysia. Conventional cross sectional imaging may reveal non-specific findings, thus lead to unnecessary biopsies. 18F-Fluorodeoxyglucose positron emission tomography/ computed tomography (18F-FDG PET/CT) has emerged as a useful tool, for characterization of indeterminate adnexal masses. Most studies have been conducted in Western population, and little information is available in Asian population in general and Malaysian population in particular. **Methods:** Prospective study of women with suspicious adnexal masses, referred to the Centre for Nuclear Diagnostic Imaging, Universiti Putra Malaysia to undergo pre-operative whole-body contrast-enhanced 18F-FDG PET/CT scans from January 2014 to January 2016. Subjects underwent Contrast-Enhanced Computed Tomography (CECT) scans followed by positron emission tomography (PET) scans using a hybrid scanner. Two radiologists analyzed the CECT and PET/CT images by consensus; blinded to the HPE results. Then the PET/CT findings were correlated with HPE results as the gold standard. **Results:** 11 whole-body PET/CT scans and 18 adnexal masses (12 HPE-proven malignant lesions and 6 benign lesions) were analyzed. The sensitivity, specificity, PPV, and NPV of CECT alone compared to PET/CT was 91.7%, 50.0%, 78.6%, and 75.0% vs. 91.7%, 100%, 100% and 85.7% respectively. **Conclusions:** Improved diagnostic accuracy for characterizing benign and malignant adnexal masses can be achieved using contrast-enhanced 18F-FDG PET/CT, making it a potential investigation of choice which can help in treatment planning.

Keywords*:* Postiron emision tomography, Ovarian carcinoma, Adnexal malignancy

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INTRODUCTION

Suspicious adnexal masses poses a potential risk of being diagnosed as ovarian cancers. It is important to thoroughly investigate these masses and to detect ovarian cancer as it is the fourth most common gynaecological cancer in Malaysia and is usually detected at an advanced stage. (1) There are Type I or indolent type of ovarian cancers and Type II aggressive type of ovarian cancers. Type I cancers include low grade serous, low grade endometrioid and mucinous tumors, whereas Type II cancers include high grade serous, high grade endometrioid, undifferentiated and carcinosarcomas. There is experimental evidence that Type II cancers may originate from fimbrial ends of Fallopian tubes as premalignant serous tubal intraepithelial cancer (STIC) lesions and are only detected by conventional imaging when it reaches an advanced stage.(2)

Diagnosis of ovarian cancer is usually made by ultrasound, followed by cross sectional imaging such as computed tomography (CT) scan (3) or magnetic

resonance imaging (MRI) for further characterization and staging (4) and confirmed with histopathological examination (HPE). Screening by transvaginal ultrasound, however, may incidentally detect lesions and lead to unnecessary biopsies.(2) Although surgical staging is the accepted standard of practice, cross sectional imaging such as CT and MRI are essential to guide surgery and decide the intervention pathway.(5) It has been noted that computed tomography alone is not reliable to predict optimal or suboptimal cytoreduction in primary debulking surgery.(6) Hence in the era of molecular imaging, 18F-Fluorodeoxyglucose positron emission tomography/ computed tomography (18F-FDG PET/ CT) has emerged as a useful tool, for characterization of suspicious adnexal masses and staging of ovarian carcinomas.(7) 18F-FDG PET/CT is able to quantify glucose metabolism by cancer cells *in vivo*, thus helps to non-invasively detect and stage malignant tumors.(8)

Most studies have been conducted in Western population, and little information is available in Asian population in general, and Malaysian population in particular. Our aim was to assess the current diagnostic accuracy of contrast-enhanced PET/CT hybrid imaging in characterization of suspicious adnexal masses to differentiate between benign and malignant lesions, using histopathological results as a gold standard of reference, in a Malaysian population.

MATERIAL AND METHODS

We conducted a prospective study and recruited all women with suspicious adnexal masses who were referred to the Centre for Diagnostic Nuclear Imaging, Universiti Putra Malaysia to undergo pre-operative whole-body contrast-enhanced 18F-FDG PET/CT scan between the periods of January 2014 to January 2016. Subjects were referred from Serdang Hospital, a national tertiary referral centre for gynaecological malignancies.

After receiving ethical clearance from our institutional ethical board and national ethical committee (NMRR-13-852-15672 and NMRR-14-1910-19208 IIR), we recruited subjects with suspicious adnexal masses based on ultrasound or conventional CT scan imaging. Inclusion criteria included women aged 18 years and above, having normal serum creatinine level and with suspicious adnexal masses and planned for surgery/ biopsy within 4 weeks after the PET/CT scan. Exclusion criteria were patients with uncontrolled blood sugar levels and those who did not undergo biopsy / surgery.

At our institution, a 64-slice hybrid PET/CT scanner with 3D lutetium oxyorthosilicate (LSO) crystals (Biograph, SIEMENS, Munich, Germany) was used to scan the subjects. The examinations included contrast-enhanced computed tomography (CECT) scans using low osmolar iodinated contrast media, and positron emission tomography scan (PET) scans. Patients were instructed to fast for a minimum of 6 hours before scanning, and blood glucose level was required to be < 7 mmol/L before the injection of 18F-fluorodeoxyglucose (18F-FDG). 18F-FDG was administered within the dose range of 6.72 – 8.26mCi, according to patients' body weight. The CECT is used for anatomic localization of FDG, attenuation correction and diagnostic purposes. Co-registered contrast-enhanced PET/CT images were displayed on the Siemens Leonardo workstation. The fused PET/CT images were used for visual interpretation, tumor volume and maximum standard uptake value (SUV_{max}) measurements. Two radiologists analysed the CECT and PET/CT images separately and by consensus; blinded to the histopathological results. Then our reviewers correlated these findings with HPE results as the gold standard.

The adnexal masses were visually assessed for signs of malignancy such as mixed or solid consistency, presence of internal septations and avid enhancement on CECT scans. Apart from the adnexal regions, nine other regions were evaluated to detect nodal spread and distant metastases i.e. pelvic lymph nodes, abdominal lymph nodes, uterine, urinary bladder, peritoneum, omentum, liver, lungs and bone involvement.

General demographic data of the patient characteristics were described using tables for categorical data, and medians and range for continuous variables. We used SPSS V22.0 for our statistical analysis. Comparison of continuous variables was done by chi square test and Pearson correlation. A p value of <0.05 was considered statistically significant. We also calculated the sensitivity, specificity, positive predictive value and negative predictive value for both the diagnostic tests of CECT and PET/CT compared with the gold standard using histopathological results.

RESULTS

We scanned 16 women who fulfilled our study criteria, but only utilized 11 contrast-enhanced PET/CT scans in the final analysis; because 3 women defaulted our follow up, one was deceased before surgery could be performed, and another had a tumor which was later histopathologically confirmed as a huge leiomyoma arising from the uterus and not originating from the adnexal region. Among the 11 women, 7 of them were found to have bilateral ovarian pathology.

Women with malignant adnexal lesions were aged 18 – 59 years old (mean 43.2 years old, SD 13.07). The 18-year old woman had a dysgerminoma. The rest of the malignant adnexal lesions were epithelial ovarian carcinomas (EOC) comprising of various subtypes. Women with EOC were older (mean age 46.4 years old, SD 9.65); whereas women with benign adnexal lesions

were younger aged 19 – 59 years old (mean 38.6 years old, SD 16.07).

There were altogether 18 lesions analysed; 12 were malignant adnexal lesions and 6 were benign adnexal lesions. The commonest malignant lesions detected were high grade serous carcinomas of the ovaries (HGSC) (n=, 4), followed by mucinous carcinomas of the ovaries (n=2), metastatic ovarian tumors originating from carcinoma of the colon (n=2), one mixed endometrioid and clear cell carcinoma of the ovaries; one dysgerminoma; one pure endometrioid carcinoma and one primary ovarian pseudomyxoma peritoneii. The benign adnexal lesions included corpus luteal cysts (n=2), and one case each of fibroma, mature cystic teratoma, adenomyosis and mucinous cystadenoma. The range of SUV_{max} values for malignant lesions were 1.68– 18.77 g/mL (mean 7.07, SD 4.94) and the SUV_{max} for benign lesions were 1.07 – 2.90 g/mL (mean 1.17, SD 0.76).

DISCUSSION

From our study, there was no statistically significant association between SUV_{max} values with malignant HPE (p=0.11). This was because although generally malignant adnexal lesions tended to have higher SUV_{max} values, there was some overlap of values between malignant and benign adnexal lesions. In particular, two cases of mucinous adenocarcinomas did not demonstrate significantly increased FDG hypermetabolism, and their SUV_{max} values were 1.68 g/mL (Figure 1a) and 4.20 g/mL respectively. Our findings concurred with the known caveat for mucinous carcinoma of the ovary which often demonstrates only mild to near baseline FDG uptake intensity; and can be misinterpreted as a benign adnexal lesion, hence giving a falsely negative finding. (9) Nevertheless, lesions with high SUV_{max} values i.e. demonstrated FDG hypermetabolism, were more likely to be malignant, especially lesions of the serous type (Figure 1b).

Positron emission tomography/ computed tomography (PET/CT) correctly diagnosed all of the benign adnexal lesions and did not give any falsely positive findings. However, CECT alone had three cases that gave falsely positive findings; which were a fibroma, a mucinous adenoma and an adenomyosis. Adenomyosis is a known mimicker of malignancy often giving a falsely positive CECT findings;(3) however, this lesion only demonstrated mild FDG uptake, having SUV_{max} of 2.9 g/mL. Fibromas being predominantly solid lesions, are also easily misdiagnosed as malignant. Nevertheless the fibroma detected in our study had low SUV_{max} value of 2.37 g/mL (Figure 2a) and was correctly interpreted as benign. We also detected a case of mucinous

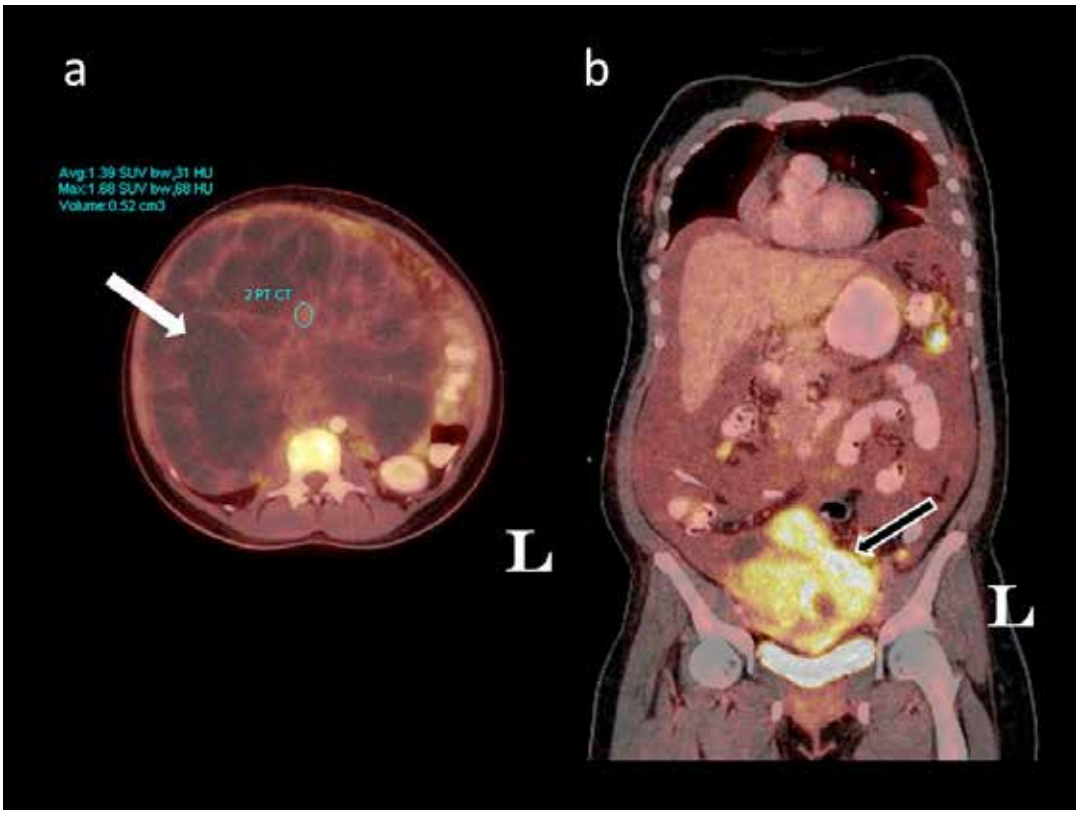

Fig. 1. FDG uptake in malignant adnexal masses. (a): Mucinous adenocarcinomas of the ovary usually do not demonstrate significantly increased FDG hypermetabolism, as evidenced by this tumour with SUVmax value of 1.68 g/mL. (b): Serous adenocarcinomas of the ovary typically show FDG hypermetabolism, as evidenced by this malignant tumour that demonstrated markedly elevated FDG uptake levels (SUVmax 8.50 g/mL) above baseline uptake.

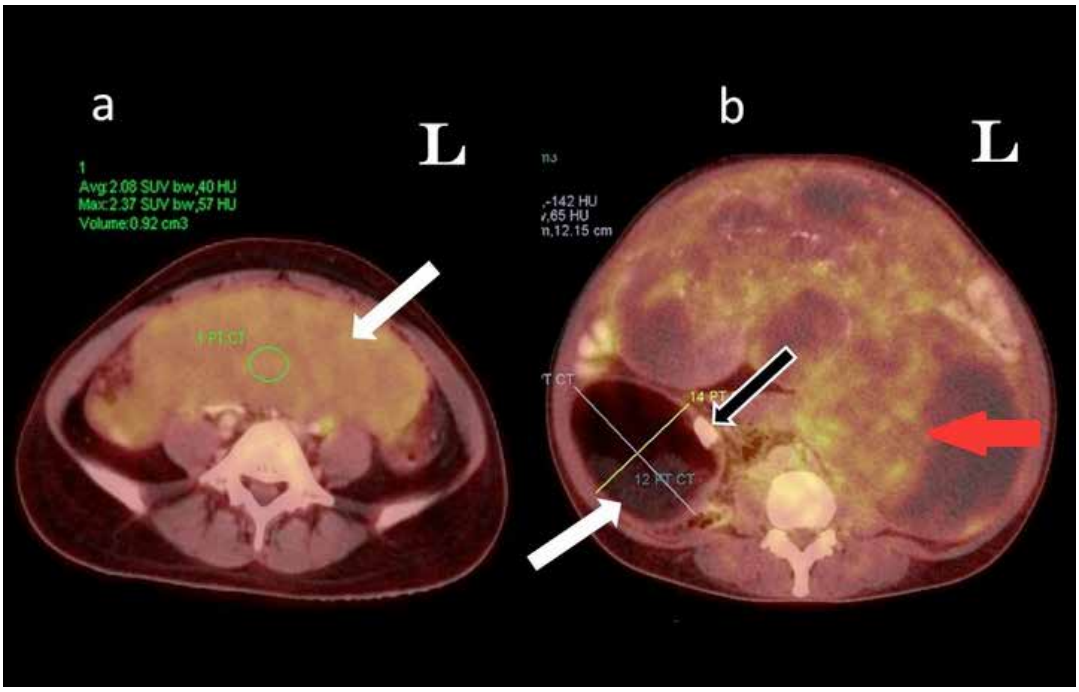

Fig. 2. FDG uptake in benign adnexal masses. (a): Axial view contrast-enhanced PET/CT detection of a solid enhancing lesion (white arrow) was detected on CT which was considered suspicious for malignancy, but due to its non FDG-avidity on PET/CT (SUVmax 2.4g/mL), it was deemed benign based on PET criteria and was later confirmed to be a benign ovarian fibroma. (b): Axial view contrast-enhanced PET/CT detection of a non FDG-avid right adnexal lesion (white arrow), which was predominantly cystic and had fat component and presence of wall calcification (black arrow). HPE confirmed it to be a mature cystic teratoma, in keeping with a true negative finding. The contralateral ovarian mass was confirmed to be mucinous adenocarcinoma.

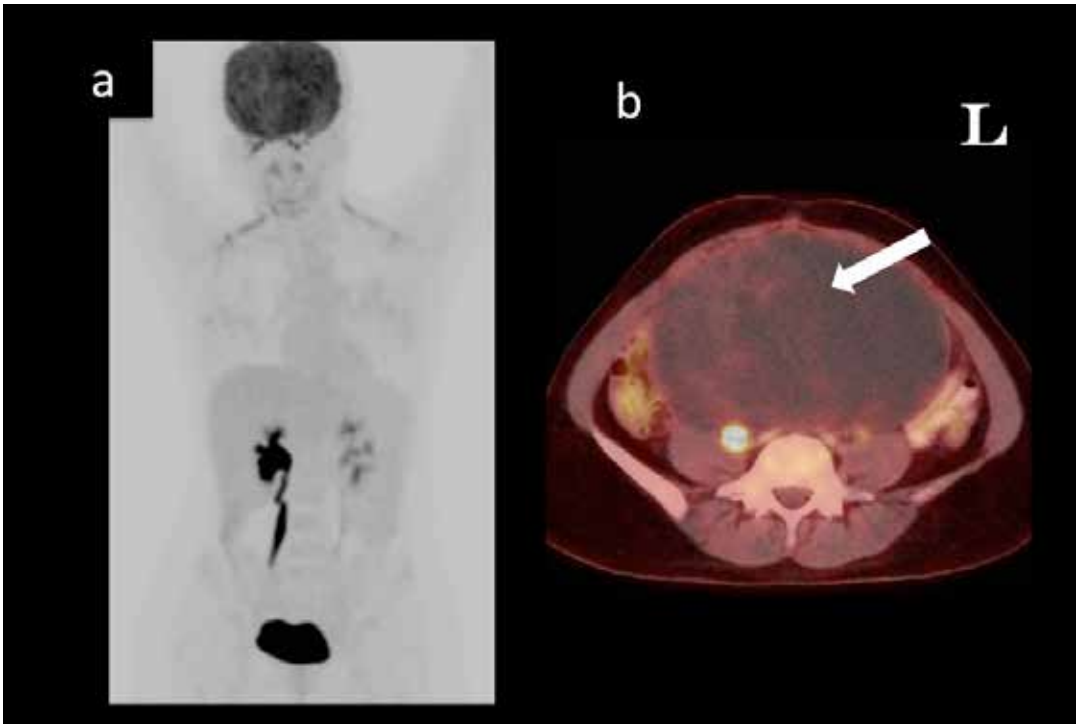

Fig. 3. True negative findings in 18F-FDG PET/CT imaging of suspicious adnexal masses. (a): Maximum intensity projection image of PET demonstrated a non FDG avid large pelvic adnexal tumour causing moderate hydronephrosis. (b): Subsequently, axial view fused PET/CT image of the same patient demonstrated a well-defined non FDG-avid tumour (white arrow), which appeared benign on PET/CT which was later confirmed by HPE to be a benign mucinous cystadenoma.

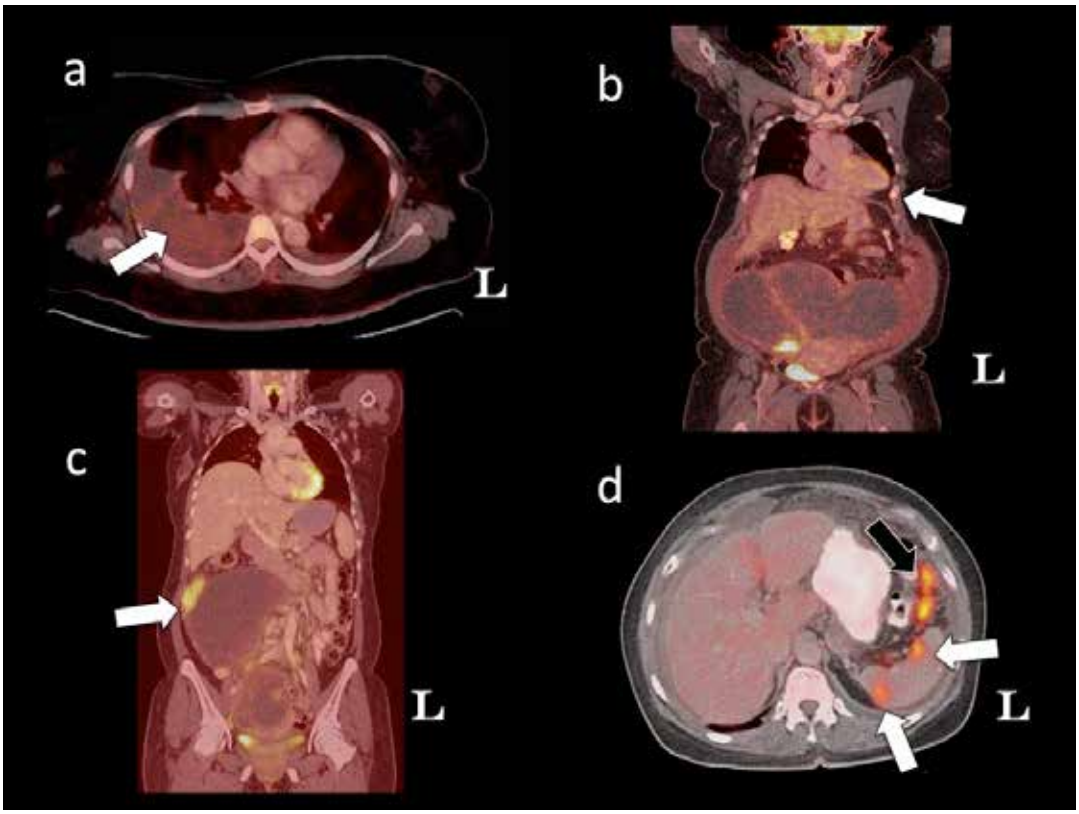

Fig. 4. Fused contrast-enhanced PET/CT images that demonstrate distant or occult metastases. (a): Axial view revealed malignant pleural effusion (white arrow). (b): Left rib metastasis noted on coronal view images (white arrow). (c): Bowel metastasis at the terminal ileum and ascending colon noted in coronal view images (white arrow). (d): Upper abdominal/ subdiaphragmatic lymph node involvement (black arrow), as well as splenic metastases (white arrow), detected on axial view images.

adenocarcinoma of the ovary and a case of mature cystic teratoma (Figure 2b), both of which did not demonstrate increased FDG uptake. Contrast-enhanced PET/CT also correctly diagnosed a benign lesion which presented as a suspicious adnexal mass causing moderate right hydronephrosis (Figure 3).

Previously it has been reported that the sensitivity, specificity, positive predictive value and negative predictive value of PET/CT in detecting ovarian malignancy and metastases were 78%, 75%, 89% and 57% respectively (10) and 87%, 100%, 81% and 100% respectively.(11) Two recent studies also reported sensitivity and specificity of low dose PET/CT in detecting ovarian malignancy and metastases were 90% and 98% respectively(12) and 98.6% and 77.8% respectively.(13) Kitajima et al in 2008(14), stated that for the detection of ovarian cancer; the sensitivity, specificity and accuracy achieved integrated PET with CECT were 69.4%, 97.5% and 94% respectively compared to their results in 2014(15) which were 82.6%, 100% and 86.7% respectively. A prospective study by Hynninen et al (2013) also stated that compared to CT alone, integrated contrast-enhanced PET/CT achieved better detection of carcinomatosis in the subdiaphragmatic peritoneum. (16) These variations in percentage are likely due to do different resolutions of various PET/CT scanners as well as the utility of contrast media that helps improve lesion conspicuity.

Modern PET/CT scanners have resolution of 4 – 5 mm due to developments in scintillation crystal detectors such as LSO that also operate in full 3D mode as well as utilize full system modelling iterative construction, that improve signal to noise ratio.(17) New generation scanners are also able to detect lesions as small as 0.5cm more accurately which can help improve radiation therapy planning.(18) This study achieved sensitivity, specificity, PPV and NPV of 91.7%, 100%, 100% and 85.7% respectively for contrast-enhanced PET/CT. Conversely, CECT alone achieved sensitivity, specificity, PPV and NPV of 91.7%, 50.0%, 78.6%, and 75.0% respectively.

In our study, PET/CT also revealed improved detection of extra-abdominal metastasis, such as malignant pleural effusion (Figure 4a) and bone metastasis such as rib involvement (Figure 4b) as well as bowel involvement (Figure 4c); localization of distant nodal metastases at the abdominal para-aortic lymph nodes, as well as in the peritoneum and omentum. PET/CT accurately detected distant extrapelvic nodal

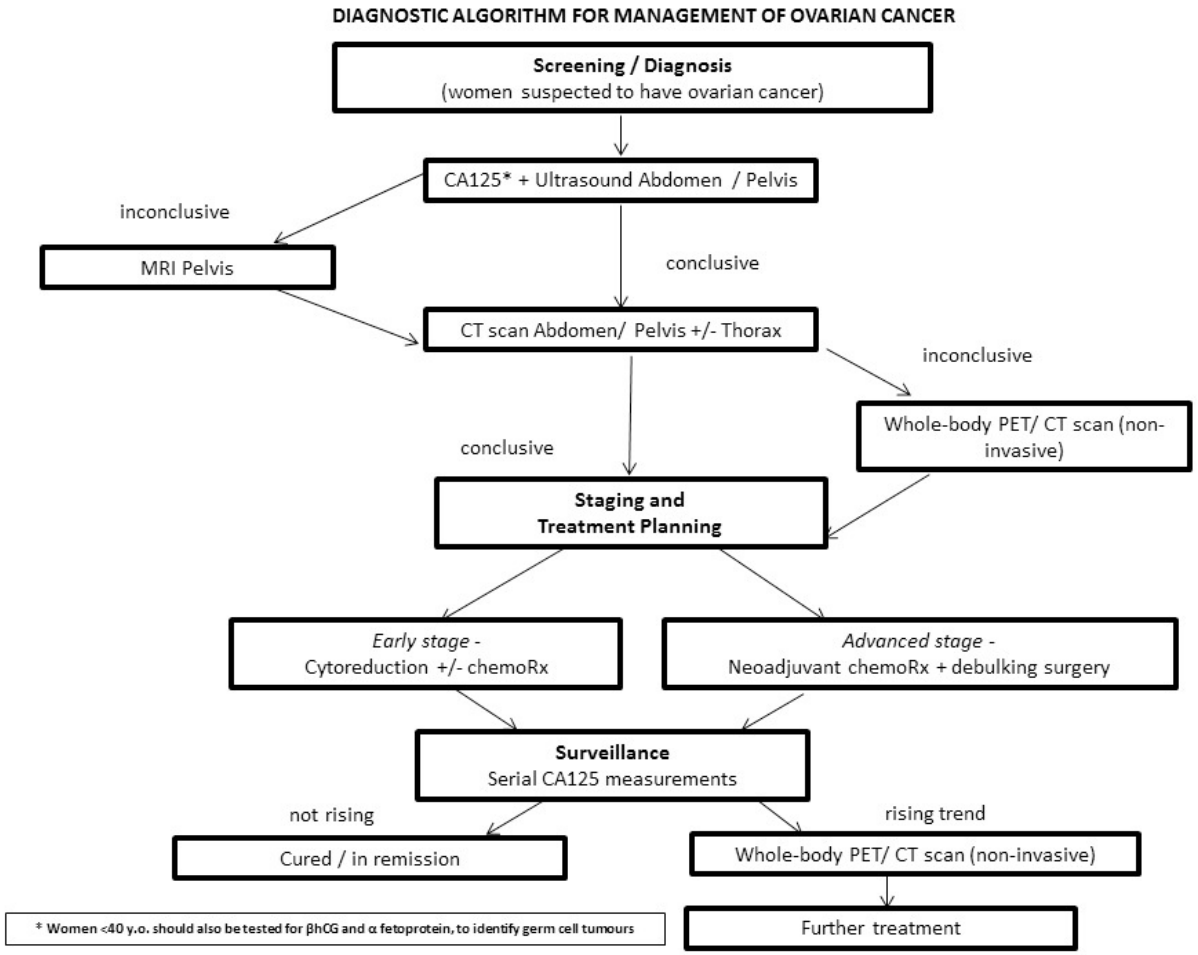

Fig. 5. Proposed diagnostic imaging algorithm for management of ovarian cancer. [Information sourced from Mitchell et al., 2013 and NICE Clinical Guidelines, 2011]

involvement such as subdiaphragmatic lymph nodes (Figure 4d) ; giving sensitivity, specificity, PPV and NPV of 100%, 83.33%, 75.0% and 100% as compared to CT alone which gave results of 66.67%, 83.33%, 66.67% and 83.33% respectively. In addition, PET/CT gave improved detection of peritoneal metastases with sensitivity, specificity, PPV and NPV of 100%, 50.0%, 71.43% and 100% as compared to CT alone which gave 80.0%, 75.0%, 80.0% and 75.0% respectively. Similar findings were noted in previous studies as elucidated by Yoshida et al, 2004.(7) Overall, contrast-enhanced PET/CT was concordant with surgical staging in 7 out of 9 women detected with ovarian malignancy, giving a 78% success rate. PET/CT upstaged one patient by detecting significantly elevated FDG uptake in the ribs and spine.

Contrast-enhanced PET/CT altered the management in 36% of our cases. Furthermore, PET/CT affected stage migration and correctly upstaged 4 patients but wrongly down-staged one patient with borderline mucinous tumor. Traditionally, treatment for advanced disease involves using neoadjuvant chemotherapy i.e. standard platinum- and paclitaxel-based chemotherapy via intravenous and/or intraperitoneal route followed by optimal debulking surgery.(19) Patients at an early stage are likely to undergo primary cytoreduction surgery followed by chemotherapy as approximately 80% of patients show good response to platinum-based chemotherapy.(20)

In two of our patients with suspicious pelvic mass initially thought to be a primary ovarian cancer, PET/CT detected one case to be a primary ovarian carcinoma with bowel metastases (Fig. 4c) and the other was a colon cancer with secondaries to the ovaries. Both cases were initially planned for a primary cytoreductive surgery that included total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO), but later had hemicolectomy added to their treatment. A case of a mucinous cystadenoma presented with a suspicious large pelvic mass as well as predominantly right-sided hydronephrosis (Figure 3) and was planned for bilateral salpingo-oophorectomy, however it appeared benign on contrast-enhanced PET/CT and therefore, fertility conserving cystectomy was performed instead. Two cases had additional treatment regime proposed after reviewing PET/CT; a case of advanced mucinous

carcinoma had NAC regime added on, to reduce the tumor burden detected on PET/CT and the other had radiotherapy proposed after PET/CT detected suspicious bony metastases which were not seen on CT alone (Figure 4b).

American College of Obstetrics and Gynecology (ACOG) guidelines on staging of ovarian cancer recommended that comprehensive surgical staging is necessary to detect occult metastatic disease and that computed tomography or magnetic resonance imaging (MRI) may be used to assess spread of disease and that PET/CT may play a role in detection of recurrence.(5) Thus, we propose a comprehensive diagnostic imaging algorithm for management of ovarian cancer (Figure 5) which is based on NICE Guidelines, 2011(21) as well as from the American College of Radiology (ACR) appropriateness criteria for staging and follow-up of ovarian cancer.(22)"abstract" : "Imaging is used to detect and characterize adnexal masses and to stage ovarian cancer both before and after initial treatment, although the role for imaging in screening for ovarian cancer has not been established. CT and MRI have been used to determine the resectability of tumors, the candidacy of patients for effective cytoreductive surgery, the need for postoperative chemotherapy if debulking is suboptimal, and the need for referral to a gynecologic oncologist. Radiographic studies such as contrast enema and urography have been replaced by CT and other cross-sectional imaging for staging ovarian cancer. Contrast-enhanced CT is the procedure of choice for preoperative staging of ovarian cancer. MRI without and with contrast may be useful after equivocal CT, but is usually not the best initial procedure for ovarian cancer staging. Fluorine-18-2-fluoro-2-deoxy-D-glucose-PET/CT may not be needed preoperatively, but its use is appropriate for detecting and defining post-treatment recurrence. Ultrasound is useful for evaluating adnexal disease, but has limited utility for staging ovarian cancer. The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every 2 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer-reviewed journals and the application of a well-established consensus methodology (modified Delphi The ACR proposes contrast-enhanced CT scan of the abdomen and pelvis as the investigation of choice for staging and follow-up of ovarian cancer, for MRI to be utilized in indeterminate cases, and considers 18F-FDG PET/CT as usually appropriate when investigating for recurrence. Currently, we do not propose for 18F-FDG PET/CT imaging to be utilized as a first line investigation tool because more research is needed to assess the cost benefit ratio of this test. Nevertheless, due to emerging knowledge regarding its clinical benefit, it can be proposed as an alternative imaging in indeterminate cases.

The management of ovarian cancer in our local setting dictates the need for accurate pre-operative imaging. Generally, the treatment of choice for advanced ovarian cancer is neoadjuvant chemotherapy which is indicated when complete surgical debulking is impossible or when patient is unfit for surgery. In Malaysia, some patients with advanced stage resectable ovarian cancer are more likely to undergo primary debulking surgery followed by adjuvant chemotherapy. Although advanced ovarian cancer generally show some response to NAC and optimal debulking surgery, unfortunately, many of them develop recurrence and progressive metastatic disease, which leads to increased mortality.(19) Thus, contrast-enhanced PET/CT has a role to play in correctly staging the disease pre-operatively to aid in optimal resection of malignant tissue. Contrast-enhanced 18F-FDG PET/CT is able to detect recurrence of ovarian cancer accurately in certain equivocal areas on low dose CT; such as in the retrovesical region, pelvic lymph nodes, abdominal lymph nodes, supraclavicular lymph nodes, liver, and bones.(23)

We would like to suggest a one stop centre approach for contrast-enhanced PET/CT as most PET centres do not perform contrast-enhanced scans and only perform low dose CT scans for attenuation correction and anatomical localization. With the introduction of contrast-enhanced PET/CT, complete staging can be performed at one sitting thus reducing extra radiation to the patient. PET can highlight advanced disease better, thus making the clinician more confident about commencing neoadjuvant chemotherapy rather than attempting primary debulking surgery.

The limitation for this study was the small sample size as well as many of the cases were at an advanced stage thus potentially increasing the pre-test likelihood of detecting metastases. Future multi-centre studies in Malaysia may help to improve upon these limitations. Furthermore, a longer period of follow-up of these patients is recommended to assess the prognostic benefits of utilizing 18F-FDG PET/CT imaging in the management of suspicious adnexal masses.

As of yet, there is no standalone investigation that can yield excellent results for the diagnosis and management of ovarian cancers. Nevertheless, non-invasive, improved diagnostic accuracy in the detection of ovarian cancer can be achieved using contrast-enhanced 18F-FDG PET/CT imaging. Although it is not a mainstream investigation, it should be considered as an alternative investigation that can help in treatment planning and prognostication, especially in cases with equivocal findings by conventional imaging.

PET/CT imaging in particular is gaining wider clinical acceptance due to the availability of hybrid scanners and to fulfil the need for functional imaging in the era of personalized medicine. In addition, there is a need

for further research to be done to evaluate the utility of Magnetic resonance / positron emission tomography (MR/PET) in the process of staging ovarian or fallopian tube cancers as it carries less risk of ionizing radiation compared to PET/CT. This can ultimately lead to improved prognosis and survival rates.

CONCLUSIONS

Improved diagnostic accuracy for characterising benign and malignant adnexal masses can be achieved using contrast-enhanced 18F-FDG PET/CT, making it a potential investigation of choice which can help in treatment planning. We recommend the utility of our proposed diagnostic imaging algorithm because it will help in the management of adnexal masses by multidisciplinary teams in general, and radiologists and nuclear medicine physicians specifically.

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