Role of 18F-FDG PET/CT in Ovarian Malignant Tumors

Thesis

Submitted for partial fulfillment of M.D. degree
In nuclear medicine

Ahmed Mohamed Esam El- Din Tawakol M.Sc.

Principle supervisor

Dr. Sherif Mohamed El-Refaei

Professor of Nuclear Medicine Faculty of Medicine - Cairo University

Supervisors

Dr. Emad Mahmoud Mohamed Hamada

Professor of oncology Faculty of Medicine - Cairo University

Dr. Amr Osama Mohamed A. Azab

Professor of radiology
Faculty of Medicine - Cairo University

Faculty of medicine- Cairo University **2013**

ABSTRACT

Ovarian cancer is the leading cause of ceath from gynecologic malignancies.

Despite good response to therapy, a large number of these patients experience

relapse. PET/CT is an imaging technology with evolving potential. Its advantage

lies in its ability to detect metabolic changes in cancer cells even before the

manifestation of the anatomic changes such as (CT). This study aims to evaluate

role of PET/CT in early detection of recurrence in the settings of suspected

biochemical recurrence with negative or equivocal conventional imaging and in

assessment of response to therapy.

Keywords: PET/CT - CA-125 - Ovarian recurrence

Acknowledgements

I was fortunate to carry this work under the guidance of **Prof. Dr. Sherif El-Refaei**, professor of nuclear medicine, faculty of medicine, Cairo University, who offered me a lot of his time and experience. He contributed greatly to bring this work to its form through his suggestions, valuable observations and meticulous revision of every possible detail. To him I owe what is beyond expression.

I would like also to express my deep gratitude to **Prof. Dr.**Amr Osama, professor of radiology, Faculty of Medicine,

Cairo University, for his continuous generous care and

outstanding support and valuable radiological teaching

points.

My special thanks to Prof. **Dr. Emad Hamada,** professor of oncology, Faculty of Medicine, Cairo University, for his kind supervision. As a clinician he offered me valuable directions.

Also, I would like to thank all my colleagues in nuclear department, for their support and encouragement specially my friend and senior colleague **Dr. Yasser Gaber** for his support, directions, co-operation and statistical work that brings a meaningful results of that work.

To my family, especially my father, my profound love and appreciation for all what they have done for me to be what I am.

Table of contents

| Acknowledgment | i |
|---|------|
| Table of contents | ii |
| List of figures | iv |
| List of tables | viii |
| List of abbreviations | X |
| Introduction | 1 |
| Aim of work | 2 |
| Epidemiology | 3 |
| Incidence | 3 |
| Risk Factors | 3 |
| Prognostic Factors | 5 |
| Clinical considerations regarding histopathological types | 6 |
| Ovarian epithelial Carcinoma | 6 |
| Carcinosarcoma | 8 |
| Platinum-free interval | 10 |
| Malignant Ovarian Germ Cell Tumor | 12 |
| Malignant Sex Cord Stromal Tumors | 15 |
| Characterization of Adnexal Mass | 19 |
| Radiological Imaging | 19 |
| PET and PET/CT Imaging | 24 |

| Ovarian cancer staging | 28 |
|--|-----|
| TNM and FIGO classifications | 29 |
| Pre-operative imaging in staging ovarian Cancer | 30 |
| Image-Guided Core Biopsy | 36 |
| Radiological imaging of patterns of tumor spread | 37 |
| Role of PET/CT in Ovarian cancer Staging | 44 |
| Ovarian Cancer Recurrence | 48 |
| Tumor Markers | 49 |
| Cross-sectional Imaging | 50 |
| 18F-FDG PET Imaging | 51 |
| 18F- FDG PET/CT Imaging | 53 |
| PET/CT patterns in ovarian metastases | 58 |
| PET/CT and response to therapy | 64 |
| Patients and Methods | 70 |
| Results | 78 |
| Case presentations | 102 |
| Discussion | 110 |
| Conclusion and recommendations | 128 |
| Summary | 129 |
| References | 132 |
| Arabic Summary | 166 |

LIST OF FIGURES

| Figures | Page |
|--|------|
| Fig.1: NCCN guidelines for follow up of OEC | 11 |
| Fig.2: NCCN guidelines for recurrence therapies of OEC. | 11 |
| Fig.3 NCCN guidelines for management of MOGCTs. | 14 |
| Fig.4: NCCN guidelines for management of SCSTs. | 17 |
| Fig.5: TVUS image of suspicious adnexal mass | 20 |
| Fig.6: Adnexal mass on MRI with malignant characteristics | 22 |
| Fig.7: Pathway of imaging and intervention for suspected OC. | 23 |
| Fig. 8: Physiological FDG uptake by corpus luteum | 24 |
| Fig.9: A patient with a doubtful mass in the right ovary | 26 |
| Fig.10: A patient with right ovarian mass. Histology demonstrated the presence of a cystoadenoma | 26 |
| Fig.11: A woman had an endometrioid adenocarcinoma arising from ovarian endometrioma | 27 |
| Fig.12: Diagram illustrating OC stages | 28 |
| Fig.13: CT images for liver disease. | 34 |
| Fig.14: Peritoneal metastases with involvement of the falciform ligament and porta-hepatis | 34 |
| Fig.15: Extensive peritoneal disease in the upper abdomen with surface metastases of the diaphragm, liver and spleen | 35 |
| Fig.16: CT-guided core biopsy of the omentum in a patient with suspected ovarian cancer | 36 |
| Fig.17: MRI for local tumor spread with rectal invasion of a right ovarian cancer | 37 |

| Fig.18: CT images for Different patterns of abdominal peritoneal metastases in various patients with stage III ovarian cancer. | 39 |
|--|----|
| Fig.19: CT images for abdominal peritoneal metastases in A female with ascites and markedly elevated Ca-125 levels | 40 |
| Fig.20: Gadolinium-enhanced MR image of a woman with treated stage III ovarian cancer image through upper abdomen shows enhancing perisplenic and perihepatic peritoneal tumor | 40 |
| Fig.21: Limitation of CT in detecting small peritoneal implants | 41 |
| Fig.22: Axial Ce-CT image showing diffuse peritoneal enhancement | 42 |
| Fig.23: CT images for the spectrum of liver metastases in ovarian cancer | 43 |
| Fig.24: A 60-year-old patient with left ovarian malignant lesion shown to be serous papillary adenocarcinoma at histology | 45 |
| Fig.25: CT and PET/CT images for a 50-year-old woman of stage IIIC with pelvic LN metastases | 46 |
| Fig.26: CT and PET/CT images for a 57-year-old woman of stage IIIB with peritoneal dissemination. | 46 |
| Fig.27: CT and PET/CT images for a patient representing with increase in serum CA 125 showing peritoneal nodules. | 54 |
| Fig.28: A woman with recurrent lesions consisting of tiny peritoneal dissemination and tiny LN metastasis | 56 |
| Fig.29: PET/CT and MRI images for a woman with suspicion of recurrent ovarian cancer due to increasing level of CA-125. | 57 |
| Fig.30: Representative PET/CT images of 4 distinct patterns of peritoneal carcinomatosis. | 59 |
| Fig.31: Woman with recurrent undifferentiated adenocarcinoma of the right ovary. PET/CT revealed single nodular hypermetabolic lesion in the pelvic cavity, suggestive of seeding nodule. Ce-CT reported a negative finding | 59 |

| Fig.32: False-negative PET results in a woman with miliary peritoneal carcinomatosis, elevated CA-125 levels, and a history of (TAH), (BSO), omentectomy, lymph node dissection, and chemotherapy for stage IIIC ovarian mucinous cystadenocarcinoma. | 60 |
|---|----|
| Fig.33: Metastasis to the umbilicus in a 56-year-old woman with stage IIIC serous papillary adenocarcinoma | 60 |
| Fig.34: CT and PET/CT images in 72-year-old woman treated 16 years earlier for ovarian papillary serous adenocarcinoma showing calcified lymph nodes in supraclavicular, left parasternal and third in right external iliac areas. | 62 |
| Fig.35: CT and PET/CT images in a woman with markedly elevated CA-125 levels and a history of surgery and chemotherapy for stage IIIC serous papillary adenocarcinoma for normal-sized, FDG-avid para-aortic metastatic lymph nodes | 63 |
| Fig.36: A woman with ovarian cancer. Transaxial PET, CT and fused PET/CT images show peritoneal, liver and vertebral metastases. | 63 |
| Fig.37: A woman presented with rising CA-125 levels and normal findings on CT, referred for restaging and assessment of response to chemotherapy | 66 |
| Fig.38: Comparison of EORTC & PERCIST 1.0. | 67 |
| Fig.39: Comparison of WHO, RECIST & RECIST 1. | 69 |
| Fig.40: ROC-Analyses of the difference in accuracy between PET, Ce-CT & combined PET/CT on study-basis | 85 |
| Fig.41: ROC-Analyses of the difference in accuracy between PET, Ce-CT & combined PET/CT on study-basis in patients with elevated tumor markers | 88 |
| Fig 42: PET/CT results in patients with elevated tumor marker in relation to Ce-CT results | 88 |
| Fig.43: ROC-Analyses of the difference in accuracy between PET, Ce-CT & PET/CT on study-basis in patients with normal T.M. | 90 |

| Fig.44: PET/CT results in patients with normal tumor marker in relation to the Ce-CT result | 90 |
|--|-----|
| Fig.45: Distribution of disease among 236 positive sites*. | 92 |
| Fig.46: ROC curve analysis for accuracy of CE-CT and PET/CT in detection of peritoneal metastases. | 93 |
| Fig.47: Patterns of peritoneal metastases in positive PET/CT studies. | 94 |
| Fig.48: ROC curve analysis for differences in the overall accuracy in classifying response to therapy between CE-CT and PET/CT. | 100 |

LIST OF TABLES

| TABLE | Page |
|--|------|
| Table 1: OEC Histologic Subtypes and Their Characteristics | 9 |
| Table 2: Histological classification of MOVGTs | 13 |
| Table 3: WHO histologic classification of SCSTs | 16 |
| Table 4: Evaluation of adnexal masses and (RMI). | 20 |
| Table 5: Adnexal mass MRI-features suggestive of benignity and malignancy | 21 |
| Table 6: TNM and FIGO Classifications for Ovarian Cancer | 29 |
| Table 7: Criteria for non-resectability | 33 |
| Table 8: General characteristics of the patients enrolled in the work. | 79 |
| Table 9: characteristics of patients in group 1: Post primary treatment tumor surveillance according to PET/CT study-based analysis | 80 |
| Table 10: Characteristics of patients in group 2: assessment of response to second treatment | 81 |
| Table 11: Study-based analysis of the diagnostic performances of PET/CT, PET and Ce-CT in 136 Studies. | 82 |
| Table 12: Differences in sensitivity, specificity and accuracy between PET and PET/CT on study-basis. | 83 |
| Table 13: Differences in sensitivity, specificity and accuracy between Ce-CT and PET/CT on Study-basis | 84 |
| Table 14: Classification of 136 post-treatment tumor surveillance PET/CT studies according to the results of Ce-CT and tumor markers. | 85 |
| Table 15: Diagnostic performances of PET/CT and Ce-CT in studies with elevated and normal tumor markers groups. | 86 |

| | _ |
|--|-----|
| Table 16: Differences in sensitivity, specificity and accuracy between Ce-CT and PET/CT on study-basis for patients with <i>elevated tumor markers</i> . | 87 |
| Table 17: Differences in sensitivity, specificity and accuracy between Ce-CT and PET/CT on study-basis for patients with <i>normal tumor markers</i> . | 89 |
| Table 18: Distribution of disease according to final follow up | 91 |
| Table 19: Lesion site-based analyses diagnostic performances of PET/CT, PET and Ce-CT for the peritoneum. | 93 |
| Table 20: Lesion site-based analysis diagnostic performances of PET/CT, PET and Ce-CT for <i>local tumor site</i> . | 95 |
| Table 21: Lesion site-based analysis diagnostic performances of PET/CT, PET and Ce-CT for the pelvic and abdominal lymph nodes. | 96 |
| Table 22: Lesion site-based analysis diagnostic performances of PET/CT, PET and Ce-CT for other sites (liver, lung, bone, brain, pleura, spleen, adrenal & muscles). | 97 |
| Table 23: McNemar Testing for statistical difference in sensitivity & specificity and accuracy between PET/CT versus PET in different sub-sites. | 98 |
| Table 24: McNemar Testing for statistical difference in sensitivity & specificity and accuracy between PET/CT versus Ce-CT in different sub-sites. | 98 |
| Table 25: Patient-based analysis of the diagnostic performances of PET/CT and Ce-CT in assessment of response to therapy. | 99 |
| Table 26: Cross-tabulation of CE-CT and PET/CT in relation to final follow up results | 101 |

List of abbreviations

PET: Positron emission tomography.

FDG: Fluoro-2-deoxy-d-glucose.

CT: Computed tomography.

OC: Ovarian cancer.

HRT: Hormone replacement therapy.

OEC: Ovarian epithelial carcinoma.

HBOC: Hereditary breast-ovarian cancer syndrome

HNPCC: Hereditary non-polyposis colorectal cancer

FIGO: Féderation Internationale de Gynécologie et d'Obstétrique

LGSCs: Low grade serous carcinomas.

HGSCs: High grade serous carcinomas.

BOTs: Borderline ovarian tumors.

CCCs: Clear cell carcinomas.

PFI: Platinum-free interval

NNCN: National Cancer comprehensive network

BEP: Bleomycin, etoposide and cisplatin

MMMT: Malignant Mixed Müllerian Tumors

MOGCTs: Malignant Ovarian Germ Cell Tumors.

SCSTs: Sex Cord Stromal Tumors

HCG: Human chorionic gonadotropin.

AFP: Alfa Fetoprotien.

TVUS: Trans-vaginal ultrasound.

US: ultrasound.

MRI: Magnetic resonance imaging.

RMI: Risk of malignancy index.

NPV: Negative predictive value.

PPV: Positive predictive value.

FN: False negative.

FP: False positive.

DWI: Diffusion weighted imaging.

ADC: Apparent diffusion coefficient.

IGCB: Image-guided core biopsy.

MDCT: Multi-detector computed tomography.

Ce-CT: Contrast enhanced computed tomography.

Id-CT: Low Dose computed tomography.

P-W: Peritoneal wash

SLL: Second-look laparotomy

T.M: Tumor marker

CEA: Carcino-embryonic antigen

CA-125: Cancer antigen 125

CA 19-9: Cancer antigen 19-9

CA 153: cancer antigen 153.

MIP: maximum intensity projection.

TAH: Total abdominal hysterectomy.

BSO: Bilateral salpingo-oopherectomy.

SUV: Standard uptake value.

WHO: World Health Organization

PERCIST: PET Response Criteria in Solid Tumors

RECIST: The Response Evaluation Criteria in Solid Tumors

EORTC: The European Organization for Research and Treatment of

Cancer.

FN: False negative

FP: False positive

TN: True negative

TP: True positive

Introduction

Worldwide, ovarian cancer accounts for 4% of all female cancers with over 190,000 new cases diagnosed each year. Ovarian cancer has been termed a 'silent' killer with the majority of patients, up to 70% presenting with advanced disease due to the vague, nonspecific nature of the presenting symptoms [1]. The most important determinant of survival for ovarian cancer patients is the disease stage at diagnosis [2]. However there are no valid methods for screening and early diagnosis of ovarian cancer, and the available follow-up protocols are not efficient for an early detection of tumor relapse [3].

In the late 1990s, positron emission tomography (PET) with 2-[18F] fluoro-2-deoxy-d-glucose (FDG), which exploits the increased utilization of glucose by malignant cells and their high uptake of glucose, opened a new field in clinical oncologic imaging. Originally, PET lacks anatomic information, and precise localization of any suspicious lesions. Integrated PET/CT has made it possible to acquire both metabolic and anatomic imaging data using a single device in a single diagnostic session and provides precise anatomic localization of suspicious areas of increased FDG uptake [4]. In the clinical setting, FDG-PET/CT has achieved a significant improvement in diagnostic accuracy and exerted a considerable impact on patient management including diagnosis, staging, optimization of treatment, restaging, therapy monitoring, and prognostic prediction of various malignant tumors [5, 6]. We herein review the current and future role of FDG-PET/CT in the management of ovarian cancer, discussing its usefulness and limitations in the imaging of these patients.