Open Access

Original Article

Role of 18-Fluorine Fluoro-deoxy Glucose Positron Emission Tomography (FDG-PET/CT scan) in Suspected Relapsed Ovarian Cancer; an Institutional Experience.

Abdul Wahab, Muhammad Rashid Hanif, Saima Riaz*, Shafquat Ali Khan, Musa Azhar, Neelam Siddiqui.

Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital, Lahore Pakistan, *Department of Nuclear Medicine, Shaukat Khanum Memorial Cancer Hospital, Lahore Pakistan.

ABSTRACT

Objectives: To determine the role of 18-Fluorine Fluoro-deoxy glucose Positron Emission Tomography (18F FDG-PET/CT scan) in suspected relapsed ovarian cancer patients.

Study Design: Cross-sectional study.

Place and Duration of Study: Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore Pakistan, from Jan 2010 to Dec 2017.

Methodology: A total of 964 patients of epithelial ovarian carcinoma who had histologically proven ovarian cancer diagnosed from January 2010 until December 2017 were reviewed. 70 patients on surveillance who had FDG-PET/CT scan for suspected relapse were included in our study. Data collected from the digital Hospital Information System after Institutional review board approval.

Results: Average age for our study group was 48.6 years ± 11.4 SD. Serous pathology was predominant in 47/70(67.1%) patients followed by Endometroid (14.3%). FDG-PET/CT scan changed the stage in 30% patients. Sensitivity, specificity, positive predictive value, and negative predictive value of FDG-PET/CT were 96%, 72%, 89% and 88% respectively while it is 92%, 76%, 90%, and 80% respectively for conventional CT scan. Average Cancer antigen-125 (CA-125) at suspected relapse is 290. 21 patients (75%) showed FDG avid disease on PET scan in whom CA-125 was normal.

Conclusion: PET scan has better negative predictive value than conventional CT scan to detect relapse in ovarian cancer, its overall sensitivity is comparable to contrast-enhanced CT scan. CA-125 is not a reliable marker for the detection of relapse in ovarian cancer patients.

Keywords: CA-125, Ovarian cancer, 18-Fluorine Fluoro-deoxy glucose Positron Emission Tomography (FDG-PET/CT scan).

How to Cite This Article: *Wahab A, Hanif MR, Riaz S, Khan SA, Azhar M, Siddiqui N. Role of 18-Fluorine Fluoro-deoxy glucose Positron Emission Tomography (FDG-PET/CT scan) in suspected relapsed Ovarian Cancer; an Institutional experience. Pak Armed Forces Med J 2024; 74(Suppl-2): S92-S97. DOI: https://doi.org/10.51253/pafmj.v74iSUPPL-2.4896*

INTRODUCTION

Ovarian cancer is one of the most common gynecological malignancies.[1] It is the most common cause of death amongst all gynecological cancers. It is divided into three broad categories; epithelial origin cancers, germ cell tumors and stromal cancers, among which epithelial ovarian cancers are commonest ones.[2] It is usually asymptomatic in early stages that's why most of the patients are diagnosed at advanced stage leading to high mortality of ovarian cancer. The standard management for ovarian cancer is radical surgery with the aim of total macroscopic clearance followed by platinum-based chemotherapy. De-bulking surgery leads to improved disease-free survival (DFS) and overall survival (OS) even in advanced stage disease. After standard treatment, these patients require regular follow up with careful monitoring, as there is a high risk of disease relapse in many patients. The 5-years OS is estimated to be 17% for advanced disease.[3]

Patients who relapse with ovarian cancer have a poor prognosis, that is why early detection of relapse is very crucial in this aspect. The aim of treatment at relapse is directed to improve the quality of life, improve symptoms and possibly increase survival.[4] According to the current practice, these patients have regular follow up usually at three monthly intervals. Targeted history, physical examination including pelvic exam should be performed at each visit along with CA-125 levels. Pelvic imaging including trans-abdominal or trans-vaginal ultrasound performed as clinically indicated. Whenever there is a high suspicion of relapse, further radiological imaging is performed to confirm relapse.[5]

18-Fluorine Fluorodeoxy glucose (FDG) Positron Emission Tomography (PET/CT scan) has recently established its role in many malignancies like lym-

Correspondence: Dr Abdul Wahab, Department of Medical Oncology, Shaukat Khanum Memorial Cancer Hospital, Lahore Pakistan.

Received: 30 Jul 2020; revision received: 02 Oct 2020; accepted: 04 Nov 2020

phomas and gastric cancer.[6] It is gradually becoming a common modality to detect relapse even in early stages with normal or rising tumor markers in various cancers. 18F FDG-PET/CT scan provides valuable information, which is based on glucose uptake in cancer cells and highlights metabolic abnormalities earlier than the morphologic alterations.[7] 18F FDG-PET/CT can be used to monitor response to therapy, before planning surgical de-bulking, assessment for response to chemotherapy and to detect relapse in various studies.

There are several recent studies in last decade which showed that 18F FDG-PET/CT gives more accurate information regarding cancer stage and extent of disease in ovarian cancer patients.[8] 18F FDG-PET/CT scan is used to detect recurrence at multiple sites, which is crucial for further treatment planning. It also has a better predictive and prognostic value as compared to conventional CT scan. It is most useful for the patients with suspected relapse based on symptoms, CA-125 levels, or radiological findings on conventional imaging.[9]

Our study aims to evaluate the role of 18F FDG-PET/CT scan in suspected relapsed ovarian cancer patients.

METHODOLOGY

We conducted a cross sectional study at Shaukat Khanum Memorial Cancer Hospital and research Centre, Lahore Pakistan. We retrospectively reviewed all the 964 patients of epithelial ovarian carcinoma who had histologically proven ovarian cancer diagnosed at our institute from January 2010 until December 2017. Institutional review board (IRB) approved our study and waived off the requirement of informed consent for this retrospective analysis (Reference number EX-03-07-19-05).

Inclusion Criteria: Patients of epithelial ovarian carcinoma who had histologically proven ovarian cancer, and had a conventional CT scan and PET/CT was performed within 4 weeks of were included.

Exclusion Criteria: Nil

We identified the patients who had a FDG-PET/CT scan due to suspicion of relapse in this period. Relapse was suspected on the basis of clinical symptoms like abdominal pain or ascites, rising biochemical markers like CA-125 or on routine radiological imaging like conventional CT scan (CeCT) or ultrasound abdomen. Whenever there is clear cut evidence of relapse, these patients were started on second line chemotherapy but many patients underwent a FDG-PET/CT scan on the basis of Multidisciplinary team (MDT) meeting discussion or physician's choice where additional information is required for planning for second line treatment. CT scan. A few patients had more than one PET/CT scan performed but only the first PET/CT scan at suspected first relapse was included in our study. We identified 70(7.2%) patients fulfilling our criteria to include in the study.

Data was collected from the digital Hospital Information System (HIS) at our institute. The pre-requisite of 6 hours fasting was followed by all before the FDG administration. The allowed limit for the blood sugar levels was below 180mg/dl. The scan was acquired 60 minutes after the intravenous administration of FDG on a dedicated PET/CT scanner (Phillips Gemini TOF) with 8-9 bed positions (3 min for each position). The parameters for CT scan were; a voltage of 70-140 kVp and a tube current of 80 mA. PET-CT images were reviewed visually for the areas of hyper metabolic activity and quantitatively with standardized uptake value (SUV) estimation of the metabolic activity. Maximum SUV values (SUVmax) were recorded.

The data was analyzed by using statistical package for social sciences (SPSS v 20). Mean±SD was used for the quantitative data while percentages and frequencies were calculated for the categorical variables. Overall survival (OS) was defined as the duration from PET/CT scan till death or last follow up. The Kaplan-Meier method was generated to estimate survival as a function of time. The survival differences were analyzed using the log-rank test. *p*-value ≤0.05 was considered statistically significant.

RESULTS

Overall survival: Out of our total 70 patients, 41(58%) patients were dead at the last follow up among which 32 were PET positive. Twenty nine (42%) were alive at last follow up among which 21 were PET positive. Median overall survival for PET scan positive patients was 25 months while it is 29 months for PET scan negative patients. However, this 4 months difference is not statistically significant (Log rank *p*-value 0.383).

Baseline characteristics: The average age of our study group was 48.6 years ± 11.4 SD. Average CA-125 was 1915 at baseline while it was 290 at suspected relapse. Nine patients (13%) were suspected for relapse based on clinical symptoms, 37(53%) based on

increasing CA-125 levels, and 24(34%) based on radiological findings on follow up conventional CT scan.

Table-I: Median Overall Survival of PET Positive and Negative Patients (n=70)

Accuracy of PET scan	Median			
	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
PET positive	25.000	4.269	16.632	33.368
PET negative	29.000	3.394	22.347	35.653
Overall	28.000	2.145	23.796	32.204

Table-II: Patients' and Disease Characteristics (n=70)

Feature	Value
Age	
Mean (range)	48.6(17-72) years
Family history of cancer(N)	18(26%)
Histopathology	
Serous	47(67%)
Mucinous	4(5.7%)
Endometroid	10(14.3%)
Clear cell	5(7.1%)
Leiomyosarcoma	3(4.3%)
Adenosarcoma	1(1.4%)
Cancer Stage at diagnosis	
I	19(27%)
II	10(14%)
III	34(49%)
IV	7(10%)
CA-125 (mean)	
At baseline	1915
At relapse	290
Standard uptake value [SUV Max] (mean)	7.6
Median Follow up after Positron emission tomography(PET) scan (months)	22.5±16.5

Table-III. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value of Different Modalities at Relapse (n=70)

Values (%)	CA-125	CT scan	FDG-PET/CT scan
Sensitivity	63%	92%	96%
Specificity	48%	76%	72%
Positive predictive value	74%	90%	89%
Negative predictive value	38%	80%	88%

Among histopathological sub-types, serous pathology was predominant with 47/70(67.1%) patients.

18F FDG PET/CT findings: The hypermetabolic sites were identified on 18F FDG-PET/CT in; pelvis 20(28.6%), abdomen 24(34.3%), chest 3(4.3%) and distant nodal sites 6(8.6%). The average SUVmax at the most avid sites on relapse was 7.6±3.2 SD. Of all patients, 36(51%) had a PET/CT scan for suspected relapse within 1 year from end of treatment while 23(33%) had a scan within 1-3 years and 11(15.7%) patients had it after 3 years.

Of 70 patients, 53(75.7%) had an FDG avid disease on PET/CT scan (47 were true positives). No FDG avid disease was detected in 17(24.3%) cases; of which two were false negatives. Sensitivity of FDG-PET/CT scan was 96%, specificity of 72%, positive predictive value of 89%, and negative predictive value of 88%.

CT scan findings: Of all patients, 50(71%) patients had disease identified on conventional CT scan among which 45/50(90%) were true positives. In 20/70(29%) cases, the CT scan was unremarkable, of which 16(80%) were true negatives. Conventional CT scan has sensitivity of 92%, specificity of 76%, positive predictive value of 90%, and negative predictive value of 80%.

18F FDG PET/CT scan versus CT scan: FDG-PET/CT scan provided additional information in 44/70 patients (63%) as compared to CT alone. FDG-PET/CT scan upstaged the disease in 14/70 (20%) patients and down staged in 7/70(10%) patients.

CA-125 levels and FDG PET/CT scan: Of 70 patients, 42(60%) were positive for relapse based on rising CA-125 levels of which 31/42(74%) were true positives while 28/70(40%) were negative based on CA-125 levels among which 10(38%) were true negatives. Sensitivity of CA-125 was 63%, specificity of 48%, positive predictive value of 74%, and negative predictive value of 38%. However, among 42 patients with raised CA-125 levels, 32(76%) were positive on FDG-PET/CT scan. Among 28 patients with normal CA-125 levels, 21(75%) showed FDG avid disease leading to the conclusion of non-specific nature of CA-125 in relapsed setting.

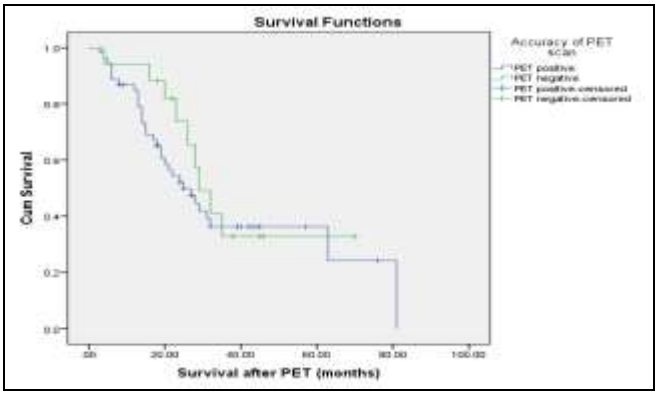

Figure: Comparison of Survival in PET Positive and PET Negative Patients.

DISCUSSION

In ovarian cancer, the role of 18F FDG PET/CT scan is emerging and in clinical practice as well, however, the current recommendations do not suggest its routine use.[10,11] The 18F FDG-PET/CT scan is used in ovarian cancer patients to assess disease spread before surgery, response evaluation after chemotherapy or surgery, post-treatment surveillance, and detecting relapse. Many recent studies established the role of 18F FDG-PET/CT scan in the detection of relapse in ovarian cancer patients even with normal tumor markers.[9] A few studies report changes in management plan based on FDG-PET/CT scan results.[12]

CA-125 levels have been thought to rise several months before actual relapse and many guidelines in past recommended its routine use[13]; however, this hypothesis has been challenged in recent studies in the last decade. Medical research council (MRC) 05 was the first landmark trial in this regard which was published in 2010.[14] It showed no survival advantages with early treatment of ovarian cancer relapse based only on rising CA-125 levels. In our study, CA-125 levels showed increased mean levels at baseline but 10 times less mean levels at relapse and sensitivity and specificity of 63% and 48% respectively favoring its limited role in detecting relapse in patients on follow up. The current guidelines recommend monitoring CA-125 levels on an individual basis rather than routine performing on every patient.[15,16]

From our data, the FDG-PET/CT scan proved to be a sensitive imaging modality to detect relapse in ovarian cancer. Patients usually relapse within the abdomen or pelvis mainly involving peritoneum, as shown in our study. It is sometimes difficult to distinguish disease due to physiologic bowel uptake and bladder activity and PET scan may give false-positive results.[17] However, the delayed PET/CT scan acquisition (dual point time imaging) helps to rule out physiological bowel activity from the disease involvement.[18] Additionally, the smaller lesions can be missed on PET scan due to its limited resolution below 0.7cmas shown in previous studies. El Hariri *et al* [19] published their data on the usefulness of PET/CT scan in relapsed ovarian cancer patients. They observed PET sensitivity of 100% in detecting local pelvic lesions and 76% in detecting peritoneal disease.

Abdel-Hafez Y *et al* [20] performed a prospective study to evaluate FDG-PET/CT scan in suspected ovarian cancer recurrence with normal tumor markers. They evaluated 54 studies in 41 patients among which 26 studies were true positive for relapse. FDG-PET/CT scan identified 25 true positive studies showing sensitivity of 92%, specificity of 93%, and accuracy of 93%, while conventional CT scan showed sensitivity of 73%, specificity of 57%, and accuracy of 65%.

In our study, contrast-enhanced CT scan (CeCT) also proved to be a useful modality and had comparable sensitivity and specificity to the FDG-PET CT scan in evaluating the suspected relapsed ovarian cancer patients. Our results are consistent with a similar study conducted by Takeuchi *et al* 21 who evaluated the role of PET scan to detect recurrence in relapsed ovarian carcinoma. Sensitivity of PET/CT scan in detecting recurrence was 94%, specificity of 100 % and diagnostic accuracy of 97% while CeCT has sensitivity of 89%, specificity of 95% and diagnostic accuracy of 93%. However, the difference in sensitivity between FDG-PET/CT scan and CT scan was not statistically significant. Therefore, a conventional CT scan has an excellent sensitivity in detecting relapse and can be used if facilities of PET scan are not available in resource-limited countries like ours.

Several other studies show the non-inferiority of CeCT over the FDG-PET/CT scan.[22,23] In our study, FDG-PET/CT scan provided additional findings in 44/70(63%) patients as compared to CT alone in establishing the exact extent of the disease. It also changed the cancer stage at relapse in 21/70(30%) patients. However, our study was not designed to see the impact of these additional findings of PET scan with respect to change in subsequent management.

Hynninen *et al*[24] also conducted a prospective study to evaluate the role of upfront FDG-PET/CT scan compared to CT scan in patients with epithelial ovarian cancer before surgery. They also failed to establish the superiority of the FDG-PET/CT scan over CeCT scan. Moreover, they found that the sensitivity of both FDG-PET/CT and CeCT was poor in certain areas of the abdomen like small bowel mesentery and upper abdomen. However, FDG-PET CT was superior to CT scan in the detection of extra-abdominal disease.[19]

EJ Han *et al*[25] conducted a study to assess the role of FDG-PET/CT scan in patients with ovarian malignancy. They showed that the mean overall survival time was significantly higher in PET negative patients as compared to PET-positive patients. However, our study failed to show any survival benefit of PET positivity or negativity in the long term with respect to overall survival. It might be because of a small cohort included in our study (7.2%), and most

of these patients were high risk and subsequently relapsed in the course of disease.

The limitations of our study include a relatively smaller number of patients who underwent FDG-PET CT scan. We also lack a prospective study. FDG-PET CT was performed in relatively few patients as compared to all follow-up patients and there was no random selection and this decision was based upon primary physician's choice or discussion in MDT where CT scan results were equivocal and additional information before surgery was required. We also lack definitive gold standard for confirmation of relapse and true relapse was based on follow up imaging, worsening of clinical symptoms, or persistent rise in tumor markers. Very few patients had histopathological confirmation at relapse.

CONCLUSION

FDG PET/CT scan has better negative predictive value than conventional CT scan to detect relapse in ovarian cancer, however, its overall sensitivity is comparable to the contrast-enhanced CT scan. 18F FDG PET scan provides better information regarding spread of the disease in a single survey, which might help in devising further management options. Our study shows that CA-125 alone is not a reliable marker for the detection of relapse and its use in collaboration with clinical symptoms and radiological findings is advisable. Further larger prospective studies are required to establish the role of 18F FDG-PET/CT scan in relapsed ovarian cancer.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AW & MRH: Study design, data interpretation, critical review, approval of the final version to be published.

SR & SAK: Data acquisition, data analysis, approval of the final version to be published.

MA & NS: Concept, crital review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Jayson GC, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. Lancet 2014; 384(9951): 1376-1388.
2. Meinhold-Heerlein I, Fotopoulou C, Harter P, Kurzeder C, Mustea A, Wimberger P, et al. The new WHO classification of ovarian, fallopian tube, and primary peritoneal cancer and its clinical implications. Arch Gynecol Obstet 2016; 293(4): 695-700.
3. Peres LC, Cushing-Haugen KL, Köbel M, Harris HR, Berchuck A, Rossing MA, et al. Invasive epithelial ovarian cancer survival by histotype and disease stage. J Natl Cancer Inst 2019; 111(1): 60-68.
4. Gadducci A, Cosio S. Surveillance of patients after initial treatment of ovarian cancer. Crit Rev Oncol Hematol 2009; 71(1): 43-52.
5. Podoloff DA, Advani RH, Allred C, Benson AB, Brown E, Burstein HJ, et al. NCCN task force report: positron emission tomography (PET)/computed tomography (CT) scanning in cancer. J Natl Compr Canc Netw 2007; 5(Suppl 1): S1-22.
6. Blodgett TM, Meltzer CC, Townsend DW. PET/CT: form and function. Radiology 2007; 242(2): 360-385.
7. Kitajima K, Murakami K, Yamasaki E, Kaji Y, Fukasawa I, et al. Diagnostic accuracy of integrated FDG-PET/contrast-enhanced CT in staging ovarian cancer: comparison with enhanced CT. Eur J Nucl Med Mol Imaging 2008; 35(10): 1912-1920.
8. Cook SA, Wilson D, Pourghiasian M, Tinker AV. The Value of PET-CT in Ovarian Epithelial Carcinoma: A Population-Based Study in British Columbia, Canada. J Med Imaging Radiat Sci 2020.
9. Ghosh J, Thulkar S, Kumar R, Malhotra A, Kumar A, Kumar L. Role of 18F-fluorodeoxy glucose PET-CT in asymptomatic epithelial ovarian cancer with rising serum CA-125: A pilot study. Natl Med J India 2013; 26: 327-331.
10. Forstner R, Meissnitzer M, Cunha TM. Update on imaging of ovarian cancer. Curr Radiol Rep 2016; 4(6): 31.
11. Kang SK, Reinhold C, Atri M, Benson CB, Bhosale PR, Jhingran A, et al. ACR appropriateness criteria® staging and follow-up of ovarian cancer. J Am Coll Radiol 2018; 15(5): S198-S207.
12. Bilici A, Ustaalioglu BBO, Seker M, Canpolat N, Tekinsoy B, Salepci T, et al. Clinical value of FDG PET/CT in the diagnosis of suspected recurrent ovarian cancer: is there an impact of FDG PET/CT on patient management? Eur J Nucl Med Mol Imaging 2010; 37(7): 1259-1269.
13. Bottoni P, Scatena R. The role of CA 125 as tumor marker: biochemical and clinical aspects. Advances in Cancer Biomarkers: Springer; 2015.
14. Rustin GJ, Van Der Burg ME, Griffin CL, Guthrie D, Lamont A, Jayson GC, et al. Early versus delayed treatment of relapsed ovarian cancer (MRC OV05/EORTC 55955): a randomized trial. Lancet 2010; 376(9747): 1155-1163.
15. Morgan RJ, Armstrong DK, Alvarez RD, Bakkum-Gamez JN, Behbakht K, Chen L-m, et al. Ovarian cancer, version 1.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2016; 14(9): 1134-1163.
16. National Comprehensive Cancer network, ovarian cancer guidelines. Available at https://www.nccn.org, Version 1.2020-March 11,2020 (Accessed 6/8/2020).
17. Iyer VR, Lee SI. MRI, CT, and PET/CT for ovarian cancer detection and adnexal lesion characterization. AJR Am J Roentgenol 2010; 194(2): 311-321.
18. Naganawa S, Yoshikawa T, Yasaka K, Maeda E, Hayashi N, Abe O. Role of delayed-time-point imaging during abdominal and pelvic cancer screening using FDG-PET/CT in the general population. Medicine (2017)96: 46(e8832).
19. ElHariri MAG, Harira M, Riad MM. Usefulness of PET–CT in the evaluation of suspected recurrent ovarian carcinoma. Egypt J Radiol Nucl Med 2019; 50(1): 1-8.
20. Abdelhafez Y, Tawakol A, Osama A, Hamada E, El-Refaei S. Role of 18F-FDG PET/CT in the detection of ovarian cancer recurrence in the setting of normal tumor markers. Egypt J Radiol Nucl Med 2016; 47(4): 1787-1794.
21. Takeuchi S, Lucchini M, Schmeler KM, Coleman RL, Gershenson DM, Munsell MF, et al. Utility of 18F-FDG PET/CT in follow-up of patients with low-grade serous carcinoma of the ovary. Gynecol Oncol 2014; 133(1): 100-104.

22. Sala E, Kataoka M, Pandit-Taskar N, Ishill N, Mironov S, Moskowitz CS, et al. Recurrent ovarian cancer: use of contrast-enhanced CT and PET/CT to accurately localize tumor recurrence and to predict patients' survival. Radiology 2010; 257(1): 125-34.
23. Funicelli L, Travaini L, Landoni F, Trifirò G, Bonello L, Bellomi M. Peritoneal carcinomatosis from ovarian cancer: the role of CT and [18 F] FDG-PET/CT. Abdom imaging 2010; 35(6): 701-707.
24. Hynninen J, Kemppainen J, Lavonius M, Virtanen J, Matomäki J, Oksa S, et al. A prospective comparison of integrated FDG-PET/contrast-enhanced CT and contrast-enhanced CT for pretreatment imaging of advanced epithelial ovarian cancer. Gynecol Oncol 2013; 131(2): 389-394.
25. Han EJ, Park HL, Lee YS, Park EK, Song MJ, Yoo IR, et al. Clinical usefulness of post-treatment FDG PET/CT in patients with ovarian malignancy. Ann Nucl Med 2016; 30(9): 600-607.