Review article:

Evaluation of Recurrent Ovarian Cancer: An Evolution

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Abstract:

Ovarian cancer is one of the top five cancers among female. It is treated with surgery and chemotherapy. Besides the well-known tumor marker CA-125, the treatment response is monitored by radiological imaging. Computed tomography (CT) and magnetic resonance imaging are used to be the primary modalities. With the emergence of positron emission tomography (PET), the detection of residual or recurrence disease can be made more accurate. The fusion of PET/CT has higher sensitivity and specificity.

Keywords: Ovarian cancer, CA 125, positron emission tomography, PET/CT

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Introduction

Ovarian cancer comprised 5.8% of all female malignancies and is placed as the 4th most common cancer. 685 new cases were reported in 2006 in Malaysia, with an incidence of 7.0 per 100,000 populations. Ovarian cancer shows age distribution, with a peak after the age of 40 years. The age-standardized incident rate was highest in the Malay population comprised of 60.5%, followed by Chinese 30.1% and Indian 9.4%.1 Ovarian cancer is silent in nature and is the leading cause of mortality among female who develops gynaecologic cancer. Most patients usually present with advanced disease, stage III or IV with abdominal distension or pain. Patients generally do not have any symptoms in early stage of ovarian cancer. Therefore, it is challenging to make an early diagnosis of this cancer. The fiveyear survival rate for patient with ovarian cancer at stage III or IV is very low, ranging from less than 5% to 20%.2,3

Total clinical remission can be expected in the majority of women with ovarian cancer. Residual

or recurrent diseases are more commonly seen as high as 70% of patients who were diagnosed with advanced-stage disease. Evaluation for this group of patients has evolved, from tumor markers to anatomic imaging with CT and MRI, however small volume tumors may be missed. Thus F-18 FDG PET/CT has been introduced to as one of the studied modalities to detect minute emerge of the cancerous cell, which already demonstrates functionality uptake earlier than morphological changes. The fusion of information between CT and PET would further speed up the rate of detection by increasing the sensitivity and specificity, picking up the earliest lesion.

Another method formerly used to evaluate recurrence disease in ovarian cancer after completed treatment was monitoring the CA-125 level. This method has been used for many as increasing levels of CA-125 precede signs and symptoms by 3-5 months.⁷ The United States monitors CA-125 levels every three months during the early years after primary therapy to

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detect early disease recurrence in ovarian cancer.⁸ Unfortunately, normal levels of CA-125 and no proof of gross disease on imaging modalities after cytoreductive surgery and chemotherapy do not indicate that the patient is in complete clinical response. This is because most of patients in 'complete respond' will have macroscopic or microscopic disease if 'second look' operations are performed. Moreover, even when second look surgery demonstrates no disease, more than half of patients will have relapse of the disease after a few months or years.⁸

Risk Factor

One of the risk factors for ovarian cancer is advanced age. The peak age of incidence is 80 years old, and ovarian cancer causes more deaths compared with other female reproductive cancers. Other risk factors include early onset of menstrual, nulliparity, family history of ovarian cancer, breast cancer, and late menopause. It was reported that after diagnosis of ovarian cancer, seventy-six percent of patients could live up to 1 year only. The 5-year survival rate is 46% for all stages. The silent nature of the disease is one of the major factors for the poor outcome, as ovarian cancer patients often presented at advanced stage.

Clinical Manifestation

Epithelial ovarian cancer may manifest with unspecific symptoms such as bloating, abdominal distension or pain, bladder outlet obstruction, difficulty in passing motion, dyspepsia, dyspnoea, lethargic, reduce appetite, and weight.

Management of Recurrence

One treatment for patients with newly diagnosed epithelial ovarian cancer is cytoreductive surgery. This method has been proven to improve survival for the patient. However, in patients with recurrent ovarian cancer, surgery does not play a crucial role. Most patients with recurrence will undergo chemotherapy treatment. Platinum combination chemotherapy is the standard treatment for platinum-sensitive recurrent ovarian cancer.

CA-125 and Recurrence

Traditionally screening for elevated specific tumor marker, which is CA-125, has been practiced and relied on. It is also used to monitor response to treatment. High level of CA-125 upon completion of treatment with surgery or chemotherapy indicates residual disease. Unfortunately, the sensitivity is low evidenced by during a second-

look operation, more than half of the patients still have small-volume disease despite a normal level of CA-125.8

High serum CA-125 does not give any clue regarding the exact location of recurrent disease. CA-125 is an antigenic determinant on a high-molecular-weight glycoprotein. It is recognized by a monoclonal antibody and has been raised using an ovarian cancer cell line as an immunogen. The CA-125 determinant is expressed by epithelial ovarian tumors, normal tissues of Mullerian origin and other pathologies. CA-125 may be elevated not just in ovarian cancer but also found in pregnancy, endometriosis, and menstruations.¹¹

MRI and Ultrasound in Detecting Recurrence

Transvaginal ultrasound (US) is useful for evaluating the site of origin of a pelvic mass and to characterize the lesion. A combination of morphology on transvaginal US and Doppler waveform analysis may provide an accurate risk assessment for adnexal lesions. MRI is excellent for characterizing adnexal masses that are indeterminate by US.¹² MRI without and with contrast may be useful following equivocal CT but is usually not the best initial procedure for ovarian cancer staging. US are useful for evaluating adnexal disease but have limited utility for staging ovarian cancer.

MRI is an excellent problem-solving technique by virtue of its ability to define common conditions such as fibroids, dermoid cysts, endometriomas, and other benign lesions. Gadolinium enhancement and diffusion-weighted imaging offer improved diagnostic confidence and tissue characterization. The role of MRI has been limited because the use of intraluminal gastrointestinal contrast agents with MRI is not routine as it is with CT, MRI generally costs more than CT, there are fewer experienced radiologists to interpret MRI, and patient motion is a greater problem for MRI than for CT.

MRI is recommended for patients with a contraindication to the use of iodinated contrast agents (e.g., allergy, mild-to-moderate renal insufficiency), patients who are pregnant, patients of childbearing age with borderline tumors (to minimize the ionizing radiation exposure) and those for whom CT findings are inconclusive. Higher-field MRI scans may improve the accuracy of MRI for staging ovarian cancer.¹³

¹⁸F-FDG PET/CT and Recurrent Ovarian Cancer

¹⁸F-FDG PET/CT is not indicated for the initial diagnosis of ovarian cancer. It is indicated for staging and to look for distant metastases. It is also beneficial for monitoring the disease after treatment, especially to optimize neoadjuvant chemotherapy protocols. This imaging modality is also useful to detect recurrent disease, especially in cases of increased tumor markers and negative CT/MRI

¹⁸F-FDG PET/CT is powerful because it can detect diffuse or macroscopic peritoneal deposits within the entire abdomen. A positive ¹⁸F-FDG PET/CT after treatment is strongly suggestive of recurrent or residual disease. This may help the primary team to avoid invasive interventions that may cause patient morbidity. It should be noted that a negative ¹⁸F-FDG PET/CT following the primary treatment does not entirely exclude the presence of microscopic residual disease. However, some recent data may indicate that in patients with a high-risk ovarian cancer treated by chemotherapy and with a negative ¹⁸F-FDG PET/ CT after treatment, the prognostic value is similar for those who had negative finding in second-look laparotomy.14

The sensitivity and specificity of ¹⁸F-FDG PET/CT in detecting recurrent disease in ovarian cancer is superior compared to CT or MRI, 83%-91% and 66%-93%, respectively. Sensitivity and specificity of CT and MRI are 45%-91% and 46%-84%, respectively. ¹⁵ It was reported that ¹⁸F-FDG PET/CT has significantly higher sensitivity and specificity in depicting disease in recurrent ovarian cancer compared to CT/MRI or CA-125 levels.

They reported that the sensitivity of ¹⁸F-FDG PET/CT was 84.6%, and specificity of ¹⁸F-FDG PET/CT was 100% for evaluation of recurrent tumor in ovarian cancer. ¹⁶ The sensitivity of ¹⁸F-FDG PET/CT is less when the lesions are smaller than 5-10 mm. However, ¹⁸F-FDG PET/CT remains a useful imaging tool in investigating recurrent disease in cases in which CA-125 is increasing trend or negative conventional imaging studies. ¹⁷

¹⁸F-FDG PET/CT influences the management decision because it helps to detect early recurrence. ¹⁸F-FDG PET/CT findings may up-stage or downstage the disease and alter the clinical staging and its management. It was reported that ¹⁸F-FDG PET/CT showed higher sensitivity and specificity of 94% and 100%, respectively, in comparison with CECT alone to diagnose recurrent ovarian cancer. ¹⁸ The results of ¹⁸F-FDG PET/CT also showed changes in term of treatment planning in 44% of the ovarian cancer patients.

Another similar study by Simcock *et al.* showed that ¹⁸F-FDG PET/CT significantly changed treatment option in 57% of the patients.¹⁹ Preliminary data by Schwarz *et al*, Grigsby et al. also showed that ¹⁸F-FDG PET/CT changes the management of recurrent ovarian cancer in approximately a third of cases and reduces overall treatment costs.²⁰

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References:

- Ministry of Health Malaysia. Malaysian National Cancer Registry Report. In: Registry NC, editor. Putrajaya, Malaysia: National Cancer Institute; 2015, p. 228
- Sharpless N, Seiden M. Advanced ovarian cancer: recent progress and current challenges. Contemporary Ob-Gyn. 1998;43(4):123-137.
- Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. Journal of Clinical Oncology. 2001;19(14):3312-22.
- DeVita V, Hellman S, Rosenberg S. Cancer: Principles and Practice of Oncology. 1997. Philadelphia and New York: Lippincott-Raven Publishers. 1997,1541-616.
- Sari O, Kaya B, Kara PO, Gedik GK, Celik C, Ozbek O, et al. The role of FDG-PET/CT in ovarian cancer patients with high tumor markers or suspicious lesion on contrast-enhanced CT in evaluation of recurrence and/or in determination of intraabdominal metastases. Revista Espanola de Medicina Nuclear e Imagen Molecular. 2012;31(1):3-8.
- Pannu HK, Bristow RE, Cohade C, Fishman EK, Wahl RL. PET-CT in recurrent ovarian cancer: initial observations. Radiographics. 2004;24(1):209-23.
- Rustin G, Nelstrop A, Tuxen M, Lambert H. Defining progression of ovarian carcinoma during follow-up according to CA 125: a North Thames Ovary Group Study. Annals of Oncology. 1996;7(4):361-4
- Bast Jr RC. CA 125 and the detection of recurrent ovarian cancer: a reasonably accurate biomarker for a difficult disease. Cancer. 2010;116(12):2850-3.
- Tempany CM, Zou KH, Silverman SG, Brown DL, Kurtz AB, McNeil BJ. Staging of advanced ovarian cancer: comparison of imaging modalities—report from the Radiological Diagnostic Oncology Group. Radiology. 2000;215(3):761-7.
- Eisenkop SM, Friedman RL, Spirtos NM. The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. Cancer. 2000;88(1):144-53.

- 11. Jacobs I, Bast Jr RC. The CA 125 tumour-associated antigen: a review of the literature. Human Reproduction. 1989;4(1):1-12.
- Liu J, Xu Y, Wang J. Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis of ovarian carcinoma. European Journal of Radiology. 2007;62(3):328-34.
- Booth S, Turnbull L, Poole D, Richmond I. The accurate staging of ovarian cancer using 3T magnetic resonance imaging—a realistic option. BJOG: An International Journal of Obstetrics & Gynaecology. 2008;115(7):894-901.
- 14. Kim S, Chung J-K, Kang S-B, Kim M-H, Jeong JM, Lee DS, et al. [18 F] FDG PET as a substitute for second-look laparotomy in patients with advanced ovarian carcinoma. European Journal of Nuclear Medicine and Molecular Imaging. 2004;31(2):196-201.
- Delbeke D, Martin WH. Positron emission tomography imaging in oncology. Radiologic Clinics of North America. 2001;39(5):883-917.
- Tsukada H, Kondo A, Hirasawa T, Murakami M, Yasuda S, Mikami M. Usefulness of combined PET/ CT for patient with epithelial ovarian cancer showing recurrence based on tumor marker CA125. The Tokai J Exp Clin Med. 2007;32(1):23-7.
- 17. Pandit-Taskar N. Oncologic imaging in gynecologic malignancies. Journal of Nuclear Medicine. 2005;46(11):1842-50.
- Thrall MM, DeLoia JA, Gallion H, Avril N. Clinical use of combined positron emission tomography and computed tomography (FDG-PET/CT) in recurrent ovarian cancer. Gynecologic Oncology. 2007;105(1):17-22.
- Simcock B, Neesham D, Quinn M, Drummond E, Milner A, Hicks RJ. The impact of PET/CT in the management of recurrent ovarian cancer. Gynecologic Oncology. 2006;103(1):271-6.
- Schwarz JK, Grigsby PW, Dehdashti F, Delbeke D. The role of 18F-FDG PET in assessing therapy response in cancer of the cervix and ovaries. Journal of Nuclear Medicine. 2009;50(suppl. 1):645-735