Conventional and New Diagnostic Modalities for Ovarian Cancer

OVER KANSERİNDE KLASİK VE YENİ TANI YÖNTEMLERİ

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SUMMARY

Objective: To review the conventional and new diagnostic modalities for ovarian cancer

Institution: The University of Texas, M.D. Anderson Cancer Center, Departments of Gynecologic Oncology and Diagnostic Radiology

Materials and Methods: The literature of review

Findings: Most patients with ovarian cancer have advanced disase at diagnosis. Endovaginal ultrasound can detect cancerous masses in these patients with high specificity and sensitivity at earlier stages of disase. Alternatively, cross-sectional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) have a high negative predictive value for such tumors, but their sensitivity remains low. Thus, new diagnostic imaging models such as immunoscintigraphy and positron emission tomography (PET) have been developed. Recent multicenter clinical trials have demonstrated that In-CYT-103 immunoscintigraphy and PET are highly effective, noninvasive, and cost-e fective.

Results PET has greater positive and negative predictive values than both CT and immunoscintigraphy in the diagnosis of pelvic malignancies. Furthermore, when PET and CT results are combined, their negative predictive value together approaches 100%.

Key words: Ovarian cancer, Ultrasound, PET, Immunoscintigraphy, CT, MRI

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ÖZET

Amaç: Över kanser tanısında yeni ve klasik tanı yöntemlerinin güvenirliliğini gözden geçirmek.

Çalışmanın yapıldığı yen The University of Texas, M.D. Anderson Cancer Center, Jinekolojik Onkoloji ve Diagnostik Radyoloji Bölümleri

Materyal **ve** Metod: Literatürün gözden geçirilmesi

Bulgular: Över kanserli hastaların çoğu tanı konulduğunda ileri evrededir. Erken evredeki malign tümörler, endovajinal ultrason kullanılarak, yüksek speslfite ve sensitivite ile saptanabilir. Alternatif tanı aracı olarak bu tümörlerin tanısında kullanılan komputerize tomografi (CT) ve manyetik rezonans gibi görüntüleme (MRI) tekniklerinin, negatif prediktif değeri (NPV) yüksektir, ancak sensitiviteleri düşüktür. Bu nedenle Immünosintigrafi ve pozitron émission tomografi gibi yeni tanı araçları geliştirilmiştir. Çok merkezli yapılan klinik çalışmalarda Immünosintigrafi ve pozitron émission tomografisinin (PET) oldukça effektif, invaziv olmayan ve düşük maliyetli tanı aracı olduktan gösterilmiştir.

Sonuç: Pelvik malignansilerln tanısında PET'inin pozitif ve negatif prediktif değerleri, CT ve immunosintlgrafiye göre daha yüksektir. Bunların dışında, PET ve CT'nin birlikte kullanıldığı vakalarda negatif prediktif değer %100'e yaklaşır.

Anahtar kelimeler: Ovarian kanser, ultrason, immünosintigrafi, CT, MRI

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Among gynecologic tumors, ovarian cancer remains the leading cause of death. This is true in part because current morphologic imaging techniques are poor at diagnosing, staging, or identifying recurrent disease. For example, in about two thirds of all patients with ovarian cancer, the tumor has already spread beyond the pelvis at the time of diagnosis (1). **The standard diagnostic procedures for making the primary diagnosis and for determining progression or regression of ovarian cancer include laporatomy with extensive exploration of the abdominopefvlc cavity, ultrasonography (US), computed tomography (CT), and magnetic resonance imaging** (MRI). **However US is effectively used for making the primary disease and usually there is no need the further imaging technique such as** MRI, **CT, PET or immunoscintigraphy. Therefore the further imaging thecniques are commonly used for**

making the secondary, recurrent and refractory diseases. These procedures are expensive, are to a large extent ineffective, and may increase morbidity. Thus, more specific and precise nonivasive methods are needed to identify ovarian cancers, especially peritoneal implants and lymph node metastases. Such methods, which include immunoscintigraphy and positron emission tomography (PET), migh also prove useful in monitoring the response of tumors to postsurgery adjuvant therapy.

Ultrasonography

As demonstrated in comparative retrospective and prospective studies, transvaginal US has a decided technical advantage over transabdominal US. Scans produced by the transvaginal method are of better diagnostic quality in 79-87% of cases (2).

Several transvaginal US-based scoring systems have been reported for detecting and distinguishing between benign and malignant ovarian masses. One of the first was proposed by Sasson et al. and utilizes echoarchitectural criteria such as wall thickness, contour, septa, and degree of sonolucency (3). In the hands of Sasson et al., this system had 100% sensitivity and 83% specificity (3). Another system, which was first described by Baber et al. in the literature of assisted reproductive technology, uses Doppler US to assess vascular flow to adnexal structures (4). Using transvaginal US color flow and Doppler US, Weiner et al. (5) and Kurjak et al. (6) showed that resistance index values could be used to detect tumor by taking advantage of the fact that intratumoral vessels in malignant ovarian masses have low resistance index values (<1) and benign ovarian tumors have high index values. Kurjak et al. (6) in particular devised a color-flow imaging scoring system that takes into account not only a tumor's vascular quality (resistance) but also vascular location (peripheral, central, pericystic, or septal) and type (no vessels seen, vessels regularly separated, or vessels randomly dispersed). In the hands of Kurjak et al., the color-flow imaging scoring system had 97.3% sensitivity, 100% specificity, and 99.4% accuracy in delineating benign versus malignant adnexal masses. Endovaginal ultrasound can detect cancerous masses in these patients with high specificity and sensitivity at earlier stages of disease but nit at later stages or recurrence.

Computed tomography (CT) is the preferred imaging modality for assessing therapeutic response in ovarian cancer. CT imaging can clearly visualize subclinical ascitic fluid collections and implants >1 cm in diameter, although it may miss nodules <1-2 cm diameter (7,8). The sensitivity of CT in detecting primary lesions has improved over the years and has been reported to be 40 to 92.3% (9-11). However, it has not

replaced second-look operations since its negative predictive value is only 45-50% (12,13). Nevertheless, when enhanced with contrast, CT may be able to help define staging information, provide additional staging information, and help define peritoneal tumor implants as small as 5 mm in diameter as well as ascites, plaque-like lesions, and omental cakes. For instance, CT can detect malignant ascites and tumor implants whose diameters exceed 2 cm with an accuracy exceeding 90% (14).

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has become an essential imaging technique for evaluating central nervous system disorders, but it has also found increasing utility in other organ sites. MRI can detect solid masses as well as cystic tumors with a wall thickness exceeding 3 mm or with nodular walls, features that suggest ovarian malignancy (15). However, MRI has only been used in the staging and monitoring of patients with ovarian cancer for a relatively short time, and its role is still evolving. For example, Hata et al. reported that MRI of 68 ovarian neoplasms with a 1.5 T system that produced TI- and T2-weighted images, yielded a specificity of 97.1% but a sensitivity of only 66.7% (16). Like CT, MRI is poor at detecting lymph node involvement; neither technique can distinguish benign from malignant nodal disease. This poor screening potential notwithstanding, MRI certainly can play a role in delineating, as benign or malignant, some lesions detected through screening.

Immunoscintigraphy

Immunoscintigraphy is the scintigraphic imaging of lesions with radiolabeled monoclonal antibodies directed to tumor-associated antigens; it has been shown to be valuable in diagnosing and staging cancer (17,18). Recently published multicenter clinical trials have demonstrated the usefulness of¹¹¹In-CYT-103 immuoscintigraphy in determining the location and extent of disease in patients evaluated for recurrent ovarian carcinoma (19). The sensitivity of this method for ovarian adenocarcinomas in those studies was 68% (19),¹¹¹In-CYT-103 immunoscintigraphy was also successful in identifying occult disease in patients with subsequently confirmed ovarian adenocarcinoma, including those with an otherwise negative presurgical work-up and a normal serum CA-125 level (19). The specificity was less than optimal, however, with positive predictive values of 72% in patients with primary disease and 83% in patients evaluated for recurrent disease (19). Together, these data suggest that, in the absence of other presurgical diagnostic information, antibody imaging is not useful for making the differential diagnosis of benign versus malignant disease in patients

with an undiagnosed pelvic mass (19).

Positron Emission Tomography

Positron emission tomography (PET) is a form of CT whose images reflect the biochemistry of tissues (20). Since cancer is essentially a series of molecular perturbations that result in abnormal cellular metabolism and growth, PET imaging therefot > has the potential to reveal the biochemical differences between normal and malignant cells and to image malignancies at any primary or metastatic sites (21). This is done by first translating data from PET images into standardized uptake values (SUVs) for normal and neoplastic tissues and then comparing the tissue SWs in order to distinguish between the tissues. For example, an SW of >3.0 strongly indicates malignancy. PET has the advantage over CT in having greater positive and negative predictive values for the diagnosis of pelvic malignancies. Yet, when PET and CT results are combined, their negative predictive value together approaches 100% (22).

One problem in gynecological oncology that seems particularly appropriate for the application of PET technology is recurrent ovarian cancer, which is notoriously difficult to diagnose. Serum tumor marker levels and conventional radiographic imaging techniques are not specific or sensitive enough to delineate disease status accurately. And even on open visual examination at second-look surgery, disease status cannot be accurately determined when no gross tumor is seen (23). As Karlan et al (23) have shown, CT scans of primary ovarian cancer have a sensitivity and specificity of 82% and 53%, respectively, compared with 93% and 82%, respectively, for [FJFDG PET. However, when both imaging methods are used, the negative predictive value approaches 100% (this supports the findings of Hubner et al. mentioned above (22)). These results, along with encouraging results obtained using FDG PET in patients with primary or recurrent ovarian cancer (24,25), suggest two things: (a) whole-body PET is a sensitive, noninvasive, in vivo method for staging and taking second looks at tumors, and (b) it can be done with little patient discomfort, with reasonably fast patient throughout, and at a reasonable cost.

Conclusion

Compared with PET and immuoscintigraphy, conventional diagnostic modalities such as CT, MRI, and US are expensive and ineffective. CT has not replaced second-look operations as a way to detect primary lesions since the negative predictive value of CT is only 50%. Yet, the need for second-look operations could be diminished if methods sensitive and specific enough to detect occult disease were available.

'''In-CYT-103 immunoscintigraphy has been considered for this since (a) it may help detect disease or disease recurrence earlier in patients with ovarian cancer and (b) its sensitivity in ovarian adenocarcinoma compares favorably with that of immunoscintigraphy done using other monoclonal antibodies in similar tumors (25). However, '''In-CYT-103 immunoscintigraphy's specificity is less than optimal. This suggests that, in the absence of other presurgical diagnostic information, antibody imaging is not useful for making the differential diagnosis of benign versus malignant disease in patients with an undiagnosed pelvic mass.

PET seems to be the more promising modality because of its diagnostic and staging potential. It has greater positive and negative predictive values than CT and immunoscintigraphy in diagnosing pelvic malignancies. The preliminary data indicate that PET can effectively supplement clinical evaluation and CT scans in the staging of ovarian cancer. Furthermore, PET is sensitive in detecting recurrent or metastatic tumor. Even though the number of cases studied so far is small, PET findings have correlated well with biopsy results and clinical outcome. For these reasons, PET promises to be a powerful yet cost-effective, noninvasive imaging procedure for patients with suspected recurrent or metastatic ovarian cancer. In the near future, PET might even replace or at least postpone some second-look operations in patients who have suspicious CT scan findings or rising tumor marker levels.

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