Cancer Antigen 125 and tumor grading for Noninvasive Evaluation of Preoperative Assessment of Lymph Node Metastasis in Cases of Endometrial Cancer

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Abstract

Lymph node metastasis in cases with early stage endometrial malignancies has a critical prognostic impact. Full pelvic lymphadenectomy has serious adverse effects. At the same time preoperative imaging alone is not an accurate method. Predictive model for lymph node metastasis using non invasive tools has fewer side effects, its accuracy and feasibility need to be assessed Cancer Antigen 125.

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Introduction:

Cancer antigen 125 is an antigenic tumor marker that is commonly expressed by the epithelial ovarian neoplasms and other tissues such as cells lining the endometrium, fallopian tubes, pleura, peritoneum, and pericardium. The use of CA 125 as a tumor marker for the diagnosis of epithelial ovarian cancers was first suggested in 1983. It was detected by using a monoclonal antibody OC 125, which was developed by immunizing mice through exposure to epithelial ovarian carcinoma cell lines. It was later in 2001 that the genomic sequence of the antigen was elicited and was referred to as the MUC16 **(1, 2)**.

CA 125, an antigenic membrane protein, is a high molecular weight glycoprotein. It is expressed by the cells originating from the coelomic epithelium, such as the Mullerian duct, cell lining of the pleura, peritoneum, and pericardium. Researchers initially identified CA 125 using monoclonal antibody OC 125, followed by the development of several other antibodies in the upcoming years **(2, 3)**.

Currently, three groups of antibodies can be useful for identifying the CA 125 antigen, and all three groups recognize non-overlapping epitopes. The first group involves OC 125 like antibodies, the second involving M 11 like antibodies, and the third involving Ov197 like antibodies **(4)**.

The elevation of cancer antigen 125 (CA125) were first described in patients with recurrent and advanced endometrial cancer by Niloff in 1984. Since then, many studies have confirmed that serum CA125 concentrations in patients with endometrial cancer are associated with deep myometrial invasion, extrauterine spread, positive peritoneal cytology, lymph node metastasis, recurrence, advanced stages, and reduced survival **(5, 6)**.

However, many of these studies had limitations, such as a small number of patients, and the appropriate reference cutoff values of

serum CA125 was inconsistent between these studies, which limited its clinical utility **(7)**.

An analysis was conducted on 995 patients with endometrial cancer to evaluate if preoperative serum CA125 was helpful for gynecologic oncologists to determine the surgical management in endometrial cancer, particularly whether preoperative CA125 serum levels could indicate if a lymphadenectomy was required for clinical stage I patients. It found that preoperative serum CA125 was a good predictor of lymph node metastasis for patients with endometrial cancer, especially patients with clinical stage I **(8)**.

In premenopausal patients with clinical stage I, preoperative serum CA125 was also helpful for those patients who seek to preserve their ovaries. If preoperative serum CA125 was too high in patients with clinical stage I, complete cytoreduction could be considered. Therefore, preoperative serum CA125 is an important predictor for patients with endometrial cancer and it should be taken into consideration when surgical management is determined, especially if a lymphadenectomy should be undertaken in patients with clinical stage I **(9, 10)**.

Tumor Grade

Tumor grade is an important predictive factor for metastatic disease in EC. Unfortunately, the correlation between preoperative tumor grading based on either endometrial biopsy or uterine curettage specimen and final tumor grading after hysterectomy is not satisfactory. The discordance rate can range from 15% to 30% **(11)**.

The carcinoma is classified using a 3-grade system in which:

- Grade 1 carcinomas showed gland formation greater than 95% of the tumor,
- Grade 2 showed a solid pattern in 5% to 50%,
- Grade 3 showed a solid pattern in more than 50% of the tumor.

Tumor grading is one of the most important factors regarding nodal metastasis. Grade 1 and 2 are considered low risk for metastasis while grade 3 is considered high risk for metastasis **(12)**.

According to the 2009 FIGO staging system, grade 2 endometrial carcinomas are defined as tumors with, from 6 to 50% of solid non-glandular, non-squamous growth architectural elements **(13)**. Grade 2 tumors are considered at low to medium risk for node metastasis when combined with other factors, such as the depth of myometrial invasion and lymphovascular invasion **(14)**.

For example, grade 2 endometrioid carcinomas with less than 50% myometrial invasion have a 4.8% probability of lymph node metastasis **(15)**. However, in the case of grade 2 endometrioid tumors that infiltrates more than 50% of the myometrium, the probability of pelvic lymph node metastasis increases to 15% **(16)**.

Risk Stratification

Low-risk ECs include women with grade 1 or grade 2 endometrioidhistologies that are confined to the endometrium, which is a subset of stage IA EC. The overall probability of recurrence in this population is very low following definitive surgical treatment and prognosis is excellent. For this reason, adjuvant therapy is often not recommended for those with low-risk EC. There is a small risk of local recurrence at the vaginal vault (less than 5%), so all patients should be followed in surveillance with pelvic exams to evaluate the vaginal cuff **(17)**.

Intermediate-risk ECs are defined by cancer confined to the uterus but invading into the

myometrium (stage IA or IB) or cancer that demonstrates occult cervical stromal invasion (stage II). This intermediate-risk population can be further subdivided into high and low intermediate-risk groups **(18)**.

The Gynecologic Oncology Group has defined a high intermediate-risk subgroup based on age and the following pathologic factors: presence of deep myometrial invasion (>50% the depth of the myometrium), grade 2 or 3 endometrioid histology, or the presence of lymphovascular space invasion. A woman is considered high intermediate-risk if she is age 70 or older with one risk factor, age 50 to 69 with two risk factors, or age 18 or older with all three risk factors **(17)**.

If these high intermediate-risk criteria are not met, then all other cancers within in the intermediate-risk group are consider low intermediate-risk. For low intermediate-risk EC, observation is recommended because of the overall good prognosis of these patients following surgery. The risks of adjuvant RT outweigh the survival benefits in this population **(19).**

In high intermediate-risk disease, RT should be considered because it can reduce the risk of local recurrence. It is important to note that RT does not appear to improve overall survival and it does not address the risk of distant recurrence. In most situations, vaginal brachytherapy (VBT) alone is recommended for high intermediate-risk disease. VBT has been shown to produce local recurrence rate equivalent to pelvic RT with less side effects **(20)**.

High-risk EC includes all type II histologies (eg, serous, clear cell, carcinosarcoma) regardless of stage, grade 3 deeply invasive endometrioid carcinoma, and pathologic stages III and IV (any histology). Because of their aggressive nature and possibility for early metastasis, multimodality treatment is typically recommended, even in the setting of early stage EC. However, there is no uniform approach to treatment for women with high-risk EC because this group can include any stage **(21)**.

Things to take into consideration when deciding adjuvant treatment recommendations include if the disease is confined to the uterus (ie, early stage; stages I and II), if the disease is locally advanced (stage III), or if there is disease outside of the uterus (stage IV). For women with high-risk, stage IA disease without any myometrial invasion (subset of stage IA), observation versus adjuvant VBT may be considered **(22)**.

Women with invasive IA, IB, or II should be offered adjuvant chemotherapy with or without RT (external beam radiation therapy [EBRT] and/or VBT). Women with stage III or IV disease that has been surgically resected are offered adjuvant chemotherapy, with chemoradiation in select cases. Women with unresectable stage III or IV are treated with chemotherapy, and the role of RT should be individualized based on tumor burden and location of tumor **(23)**.

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