



Efficacy of endocervical curettage and CA-125 measurement in endometrial serous carcinoma: A case series and literature review

Endometrial seröz karsinomda endoservikal küretajın ve CA-125 ölçümünün etkinliği: Olgu serisi ve literatür derlemesi

Ahmet Cem İyibozkurt, Murat Doğan, Ercan Baştu, Hamdullah Sözen, Doğan Vatanserver, Samet Topuz, Sinan Berkman

Istanbul University Istanbul Faculty of Medicine, Department of Obstetrics and Gynecology, Istanbul, Turkey

Abstract

Objective: This is a case series and literature review of patients with endometrial serous carcinoma (ESC) in which endocervical curettage (ECC) and CA-125 measurement were utilized as a diagnostic procedure in preoperative staging.

Materials and Methods: The patients were treated in the gynecologic oncology clinic of Istanbul University Faculty of Medicine between January 2005, and January 2015. A total of 37 patients were included in the final analysis.

Results: ECC accurately predicted ESC in 22 patients (59.5%). The mean pre-operative serum CA-125 level was 73.24±3.30 IU/mL; pre-operative serum CA-125 levels were elevated above 35 IU/mL in 25 patients (69%).

Conclusion: ECC is an acceptable diagnostic tool to predict the presence or absence of cervical involvement in endometrial cancer. On the other hand, its accuracy in specific subgroups requires further analysis in carefully designed prospective studies. Furthermore, pre-operative serum CA-125 levels may be important for management and counseling in the subgroup of women with ESC.

Keywords: CA-125, endometrial cancer, endocervical curettage, endometrial serous carcinoma

Öz

Amaç: Bu olgu serisi ve derlemede amaç endometrial seröz karsinom (ESK) hastalarında endoservikal küretajın (ESK) ve kanda CA-125 ölçümünün cerrahi yaklaşım öncesi uygulamalarında etkinliğini araştırmaktır.

Gereç ve Yöntem: İstanbul Üniversitesi Tıp Fakültesi'nin Jinekolojik Onkoloji Kliniği'ne başvurmuş hastalar Ocak 2005 ve Ocak 2015 arası retrospektif olarak taranmış ve son çalışmaya 37 hasta dahil edilmiştir.

Bulgular: Endometrial küretaj 22 hastada ESK tanısını koymuştur. Cerrahi yaklaşım öncesi kanda CA-125 seviyesi 73,24±3,30 IU/ml bulunmuştur. Yirmi beş hastanın, CA-125 seviyesi 35 IU/mL'nin üzerinde çıkmıştır.

Sonuç: Endometrial küretaj, endometrial kanserde servikal yayılmanın varlığının tanısında etkin bir araçtır. Öte yandan endometrial kanserlerin alt gruplarında etkinliğini ölçmede prospektif çalışmalarla halen ihtiyaç vardır. Ek olarak, cerrahi yaklaşım öncesi kanda CA-125 ölçümü endometrial seröz karsinom hastalarının yönetiminde katkı sağlayabilir.

Anahtar Kelimeler: CA-125, endometrial kanser, endoservikal küretaj, endometrial seröz karsinom

Introduction

Endometrial carcinoma is the most common gynecologic malignancy⁽¹⁾. It includes carcinomas composed of glands that look like endometrium (endometrioid subtype)⁽²⁾ as well as differentiated epithelial neoplasms, which usually appear in the extended Müllerian system^(3,4). Endometrial endometrioid carcinoma is the most frequent subtype of endometrial carcinoma; endometrial serous carcinoma (ESC) is a well-

recognized but rare subtype that is usually associated with aggressive behavior and poor clinical survival^(3,5-7).

Endocervical curettage (ECC) has been commonly used to evaluate cervical involvement, but its accuracy remains debatable⁽⁸⁻¹⁴⁾. As a result, pathologic diagnosis may not be accurate due to the presence of metaplastic changes that may hide or look like a malignancy. This is a serious concern, especially for postmenopausal patients, in which

Address for Correspondence/Yazışma Adresi: Ercan Baştu, MD, Istanbul University Istanbul Faculty of Medicine, Department of Obstetrics and Gynecology, Istanbul, Turkey
Phone: +90 532 413 41 95 E-mail: ercan.bastu@istanbul.edu.tr

Received /Geliş Tarihi : 08.05.2015

Accepted/Kabul Tarihi : 11.09.2015

endometrial cancers are generally an important diagnostic consideration.

Elevated levels of tumor-associated antigen CA-125 were first described in patients with recurrent and advanced endometrial cancer by Niloff et al.⁽¹⁵⁾ in 1984. Several studies have since shown that elevated pre-operative serum CA-125 correlates with extra-uterine tumor spread⁽¹⁶⁻¹⁹⁾. However, all these studies included different types of histology. To our knowledge, none of the previous studies in the literature have evaluated the potential clinical implications of pre-operative serum CA-125 solely in patients diagnosed as having ESC.

This is a case series and literature review of patients with ESC in which ECC and CA-125 measurements were utilized as diagnostic procedures in preoperative staging. We hypothesized that these tools would have an impact on prognosis in patients with ESC.

Material and Methods

For this retrospective study, consecutive patients with endometrial cancer (n=754) treated in the gynecologic oncology clinic of İstanbul University School of Medicine between January 2005, and January 2015 were reviewed. Forty-three patients with histologically-verified ESC who underwent primary surgery at our institution were identified. We excluded 6 patients from the analysis because of incomplete data. A total of 37 patients were included in the final analysis. All clinical records were reviewed for demographics, treatment details, and outcomes. The study protocol was approved by the Ethics Committee of İstanbul University and informed consent was waived due to the retrospective nature of the study.

In every case, the surgery was performed by a gynecologic oncologist. Staging surgery was in accordance with the International Federation of Gynecology and Obstetrics (FIGO) adopted system⁽²⁰⁾ and included peritoneal washing for cytology, total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy.

CA-125 levels were pre-operatively measured in all 37 patients. In each case, the diagnosis was confirmed by a specialist gynecologic pathologist following post-surgery pathology review. Preoperative histopathologic assessment of cervical involvement was also performed through ECC in all 37 patients. Surgical pathologic information was gathered from the pathology reports, which included histologic tumor type, grade, FIGO stage, and tumor features, such as lymphovascular invasion (LVI).

Continuous variables were described as mean \pm SD and categorical data were expressed in number and percentage.

Results

The mean age of the patients was 63.20 \pm 10.72 years (range, 38 to 85 years). ECC accurately predicted ESC in 22 patients (59.5%). The mean pre-operative serum CA-125 level was

73.24 \pm 3.30 IU/mL; pre-operative serum CA-125 levels were elevated above 35 IU/mL in 25 patients (69%).

Post-operative pathology revealed endometrioid carcinoma in 9 patients (24.3%) (grade 1 in 1 patient, grade 2/3 in 8 patients), clear cell carcinoma in 3 patients (8.1%), mixed epithelial and stromal tumor in 2 patients (5.4%), malignant mixed Müllerian tumor, also known as carcinosarcoma, in 1 patient (2.7%).

Of the 25 patients (67.6%) who underwent lymph node dissection, pelvic lymph node metastases were detected in 2 patients, and LVI was present in 50% of patients.

Discussion

When the diagnostic value of ECC in predicting ESC was analyzed in our study, ECC accurately predicted ESC in nearly 60% of cases. Misclassification occurred in approximately 40% of all cases. Positive predictive values of ECC varied in previous studies (15.1-62.5%) in patients with endometrial cancer^(10,12,21-23). These differences can partly be explained by heterogeneity in patient selection and differences in the curettage assessment. It is also important to note that no previous studies have solely focused on the subgroup of patients with ESC.

The tumor antigen, CA-125, was first introduced by Bast et al.⁽²⁴⁾ in 1981. Since then, it has been evaluated for ovarian cancer screening,⁽²⁵⁻²⁷⁾ diagnosis,⁽²⁸⁻³⁰⁾ and post-treatment monitoring⁽³¹⁻³⁴⁾. Thus far, the literature does not support the routine clinical use of CA-125. However, it helps in diagnosis and has become an accepted method of monitoring response to treatment, as well as disease recurrence and progression. In endometrial cancer, the use of pre-operative CA-125 has been evaluated in several studies. In most of these studies, elevation of CA-125 correlated to the presence of extra-uterine disease^(18,35-39). However, none of these studies performed a subgroup analysis of ESC, probably because of the limited number of patients. To our knowledge, this present study is the first to evaluate the role of pre-operative serum CA-125 exclusively in patients with confirmed ESC. Our study revealed an elevation of CA-125 in nearly 70% of patients with ESC, which is in line with previous findings.

Lesions in this morphologic range have to be accurately diagnosed because the prognostic profile of ESC is distinct. Therefore, an additional method of assessing for the presence of extra-uterine disease such as serum CA-125 seems a reasonable pre-operative approach and would be of benefit in pathologic diagnosis and clinical management. Assessment of HER2 immunohistochemistry was also recently recommended in ESC because of the significant heterogeneity of HER2 protein expression⁽⁴⁰⁾. However, further studies are needed to confirm its efficacy for routine clinical use.

The major limitation of this study is the small number of patients involved; however, this is accounted for because ESC is a rare subtype and is much less common than its endometrial counterparts.

Conclusion

ECC is an acceptable diagnostic tool to predict the presence or absence of cervical involvement in endometrial cancer. On the other hand, its accuracy in specific subgroups requires further analysis in carefully designed prospective studies. This study contributes to the growing literature on the use of pre-operative serum CA-125 in patients with endometrial cancer. Moreover, it suggests that pre-operative serum CA-125 levels may be important for management and counseling in the subgroup of women with ESC.

Ethics Committee Approval and Consent: The study protocol was approved by the Ethics Committee of İstanbul University and informed consent was waived due to the retrospective nature of the study, **Concept:** Ahmet Cem İyibozkurt, **Design:** Sinan Berkman, **Data Collection:** Hamdullah Sözen, **Analysis:** Samet Topuz, **Literature Search:** Doğan Cansever, **Writing:** Ercan Bastu, **Peer-review:** External and Internal peer-reviewed, **Conflict of Interest:** No conflict of interest was declared by the authors, **Financial Disclosure:** The authors declared that this study has received no financial support.

References

- Gurpide E. Endometrial cancer: biochemical and clinical correlates. *J Natl Cancer Inst* 1991;83:405-16.
- Christopherson WM, Alberhasky RC, Connelly PJ. Carcinoma of the endometrium: I. A clinicopathologic study of clear-cell carcinoma and secretory carcinoma. *Cancer* 1982;49:1511-23.
- Lauchlan SC. Tubal (serous) carcinoma of the endometrium. *Arch Pathol Lab Med* 1981;105:615-8.
- Lauchlan SC. The secondary müllerian system revisited. *Int J Gynecol Pathol* 1994;13:73-9.
- Fanning J, Evans MC, Peters AJ, Samuel M, Harmon ER, Bates JS. Endometrial adenocarcinoma histologic subtypes: clinical and pathologic profile. *Gynecol Oncol* 1989;32:288-91.
- Hendrickson M, Ross J, Eifel P, Martinez A, Kempson R. Uterine papillary serous carcinoma: a highly malignant form of endometrial adenocarcinoma. *Am J Surg Pathol* 1982;6:93-108.
- Walker AN, Mills SE. Serous papillary carcinoma of the endometrium. A clinicopathologic study of 11 cases. *Diagn Gynecol Obstet* 1982;4:261-7.
- Frumovitz M, Slomovitz BM, Singh DK, Broaddus RR, Abrams J, Sun CC, et al. Frozen section analyses as predictors of lymphatic spread in patients with early-stage uterine cancer. *J Am Coll Surg* 2004;199:388-93.
- Kietlinska Z, Stelmachow J, Antczak A, Timorek A, Sawicki W, Tyminska B. [Preoperative evaluation of cervical involvement in endometrial cancer]. *Ginekol Pol* 1998;69:247-51.
- Leminen A, Forss M, Lehtovirta P. Endometrial adenocarcinoma with clinical evidence of cervical involvement: accuracy of diagnostic procedures, clinical course, and prognostic factors. *Acta Obstet Gynecol Scand* 1995;74:61-6.
- Mannel RS, Berman ML, Walker JL, Manetta A, DiSaia PJ. Management of endometrial cancer with suspected cervical involvement. *Obstet Gynecol* 1990;75:1016-22.
- Morimura Y, Soeda S, Hashimoto T, Takano Y, Ohwada M, Yamada H, et al. The value of pre-operative diagnostic procedures for cervical involvement in uterine corpus carcinoma. *Fukushima J Med Sci* 2000;46:1-11.
- Pete I, Godeny M, Toth E, Rado J, Pete B, Pulay T. Prediction of cervical infiltration in Stage II endometrial cancer by different preoperative evaluation techniques (D&C, US, CT, MRI). *Eur J Gynaecol Oncol* 2003;24:517-22.
- Rubin SC, Hoskins WJ, Saigo PE, Nori D, Mychalczak B, Chapman D, et al. Management of endometrial adenocarcinoma with cervical involvement. *Gynecol Oncol* 1992;45:294-8.
- Niloff JM, Klug TL, Schaeztl E, Zurawski VR Jr, Knapp RC, Bast RC, Jr. Elevation of serum CA125 in carcinomas of the fallopian tube, endometrium, and endocervix. *Am J Obstet Gynecol* 1984;148:1057-8.
- Duk JM, Aalders JG, Fleuren GJ, de Bruijn HW. CA 125: a useful marker in endometrial carcinoma. *Am J Obstet Gynecol* 1986;155:1097-102.
- Jhang H, Chuang L, Visintainer P, Ramaswamy G. CA 125 levels in the preoperative assessment of advanced-stage uterine cancer. *Am J Obstet Gynecol* 2003;188:1195-7.
- Powell JL, Hill KA, Shiro BC, Diehl SJ, Gajewski WH. Preoperative serum CA-125 levels in treating endometrial cancer. *J Reprod Med* 2005;50:585-90.
- Soper JT, Hunter VJ, Daly L, Tanner M, Creasman WT, Bast RC Jr. Preoperative serum tumor-associated antigen levels in women with pelvic masses. *Obstet Gynecol* 1990;75:249-54.
- Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* 2009;105:103-4.
- Kietlinska Z, Stelmachow J, Antczak-Judycka A, Timorek A, Sawicki W, Tyminska B. Fractional curettage, hysteroscopy and imaging techniques: transvaginal sonography (TVS), magnetic resonance imaging (MRI) and computed tomography (CT) in the diagnosis of cervical canal involvement in cases of endometrial carcinoma. *Eur J Gynaecol Oncol* 1998;19:561-4.
- Lampe B, Kurzl R, Dimpfl T, Fawzi H. Accuracy of preoperative histology and macroscopic assessment of cervical involvement in endometrial carcinoma. *Eur J Obstet Gynecol Reprod Biol* 1997;74:205-9.
- Toki T, Oka K, Nakayama K, Oguchi O, Fujii S. A comparative study of pre-operative procedures to assess cervical invasion by endometrial carcinoma. *Br J Obstet Gynaecol* 1998;105:512-6.
- Bast RC Jr, Feeney M, Lazarus H, Nadler LM, Colvin RB, Knapp RC. Reactivity of a monoclonal antibody with human ovarian carcinoma. *J Clin Invest* 1981;68:1331-7.
- Alberico S, Facca MC, Millo R, Radillo L, Mandruzzato GP. Tumoral markers (CA 125--CEA) in the screening of ovarian cancer. *Eur J Gynaecol Oncol* 1988;9:485-9.
- Jacobs I, Davies AP, Bridges J, Stabile I, Fay T, Lower A, et al. Prevalence screening for ovarian cancer in postmenopausal women by CA 125 measurement and ultrasonography. *BMJ* 1993;306:1030-4.
- Skates SJ, Singer DE. Quantifying the potential benefit of CA 125 screening for ovarian cancer. *J Clin Epidemiol* 1991;44:365-80.
- Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol* 1990;97:922-9.
- Mogensen O, Mogensen B, Jakobsen A, Sell A. Preoperative measurement of cancer antigen 125 (CA 125) in the differential diagnosis of ovarian tumors. *Acta oncol* 1989;28:471-3.
- Zurawski VR Jr, Orjaseter H, Andersen A, Jellum E. Elevated serum CA 125 levels prior to diagnosis of ovarian neoplasia: relevance for early detection of ovarian cancer. *Int J Cancer* 1988;42:677-80.

31. Niloff JM, Knapp RC, Lavin PT, Malkasian GD, Berek JS, Mortel R, et al. The CA 125 assay as a predictor of clinical recurrence in epithelial ovarian cancer. *Am J Obstet Gynecol* 1986;155:56-60.
32. Santillan A, Garg R, Zahurak ML, Gardner GJ, Giuntoli RL 2nd, Armstrong DK, et al. Risk of epithelial ovarian cancer recurrence in patients with rising serum CA-125 levels within the normal range. *J Clin Oncol* 2005;23:9338-43.
33. Schilthuis MS, Aalders JG, Bouma J, Kooi H, Fleuren GJ, Willemse PH, et al. Serum CA 125 levels in epithelial ovarian cancer: relation with findings at second-look operations and their role in the detection of tumour recurrence. *Br J Obstet Gynaecol* 1987;94:202-7.
34. van der Burg ME, Lammes FB, Verweij J. The role of CA 125 in the early diagnosis of progressive disease in ovarian cancer. *Ann Oncol* 1990;1:301-2.
35. Chung HH, Kim JW, Park NH, Song YS, Kang SB, Lee HP. Use of preoperative serum CA-125 levels for prediction of lymph node metastasis and prognosis in endometrial cancer. *Acta Obstet Gynecol Scand* 2006;85:1501-5.
36. Dotters DJ. Preoperative CA 125 in endometrial cancer: is it useful? *Am J Obstet Gynecol* 2000;182:1328-34.
37. Hsieh CH, ChangChien CC, Lin H, Huang EY, Huang CC, Lan KC, et al. Can a preoperative CA 125 level be a criterion for full pelvic lymphadenectomy in surgical staging of endometrial cancer? *Gynecol Oncol* 2002;86:28-33.
38. Santala M, Talvensaaari-Mattila A, Kauppila A. Peritoneal cytology and preoperative serum CA 125 level are important prognostic indicators of overall survival in advanced endometrial cancer. *Anticancer Res* 2003;23:3097-103.
39. Sood AK, Buller RE, Burger RA, Dawson JD, Sorosky JI, Berman M. Value of preoperative CA 125 level in the management of uterine cancer and prediction of clinical outcome. *Obstet Gynecol* 1997;90:441-7.
40. Buza N, English DP, Santin AD, Hui P. Toward standard HER2 testing of endometrial serous carcinoma: 4-year experience at a large academic center and recommendations for clinical practice. *Mod pathol* 2013;26:1605-12.