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Clinicopathological features and prognosis of endometrial serous carcinoma

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Summary

Purpose of investigation: To discuss the clinicopathological features, differential diagnosis, and prognosis of endometrial serous carcinoma (ESC). *Materials and Methods*: The clinical information of 33 patients aged 44-73 years, admitted to Yantai Huhuangding Hospital for surgical treatment of ESC between January 2003 and December 2013, were retrospectively reviewed. Immunohistochemistry analysis of estrogen (ER), progesterone (PR), and mutant type p53 (MTP53) markers were performed and their correlation with the clinical features and prognosis of ESC were studied. *Results*: Among all cases, 81.82% were ER− / PR− and 72.73% were MTP53+. Expression of ER, PR, and MTP53 markers were not affected by age, tumor size, infiltration depth, tumor staging or metastasis. P53 mutation might be closely related to the tumorigenesis of ESC and lymphatic metastasis was a predictive factor for poor prognosis. *Conclusion*: This study provided us a better understanding of this rare type of carcinoma and could benefit future works of gynecologists, oncologists, and pathologists.

Key words: Endometrial cancer; Serous carcinoma; Mutant type p53; MTP53; Prognosis.

Introduction

Endometrial carcinoma (also called corpus carcinoma) is a gynecological malignancy that arises from the endometrium and mainly affects perimenopausal and aged women [1, 2]. There are three major subtypes of endometrial cancer: type I is the hormone-dependent endometrioid adenocarcinoma; type II is non-hormonal dependent, including the endometrial serous carcinoma (ESC) and clear cell carcinoma of the endometrium; type III is an autosomal dominant genetic disease, the Lynch syndrome [3, 4]. Among these subtypes, serous carcinoma only comprises 10% of all cases of endometrial carcinomas, however it is responsible for over 50% of the overall mortality [5, 6]. A systematic understanding of the clinicopathological features, diagnosis, differential diagnosis, and prognosis of ESC would greatly benefit the work of gynecologists, oncologists, and pathologists.

Materials and Methods

The clinical information of 33 patients admitted to the present hospital for surgical treatment of ESC between January 2003 and December 2013 were retrospectively reviewed. Patients aged 44-73 years (median age 64). All patients received extensive uterus and bilateral accessory resection combined pelvic lymph node dissection. None of them received chemo- or radio-therapy before the operation. Surgical specimens were confirmed with ESC. Patients' age, clinical presentation, histopathologic examination, and tumor staging were analyzed. Tumor staging were determined according to the International Federation of Gynecology and Obstetrics (FIGO) staging systems for vulva, cervix, endometrium, and sarcomas [7]. Patients were followed 2-64 months (median 25 months) which was from the day of operation until the end of study or the death of patient.

Hematoxylin-eosin stain was routinely performed on tissue sections as previously described [8]. Mutant type p53 (MTP53), estrogen (ER) and progestogen (PR) immunohistologic stain were performed using the EnVision two-step method [9]. Sample was classified as MTP53 positive if ≥ 75% of the nucleus of tumor cells were stained. The classification for ER and PR staining results were: ratio of stained nucleus 0-5% (−), ≥ 6% (+).

Statistical analysis was performed using SPSS 17.0. Data was subjected to χ^2 test and $p < 0.05$ suggested statistically significant difference.

Results

Between January 2003 and December 2013 there was a total of 672 cases of confirmed endometrial cancer and among them 5.02% (33/672) were ESC. Majority of patients were postmenopausal women (31/33, 93.94%). The overall dimension of tumors was 1-12 cm, average 3.87 cm. Imageological results comprised intrauterine space occupying lesions (16/33, 48.48%), endometrial irregular thickening (10/33, 30.30%), and uterine cavity effusion (7/33, 21.21%). The clinical presentation was mainly postmenopausal vaginal bleeding or vaginal discharge (29/33, 87.88%). Three patients

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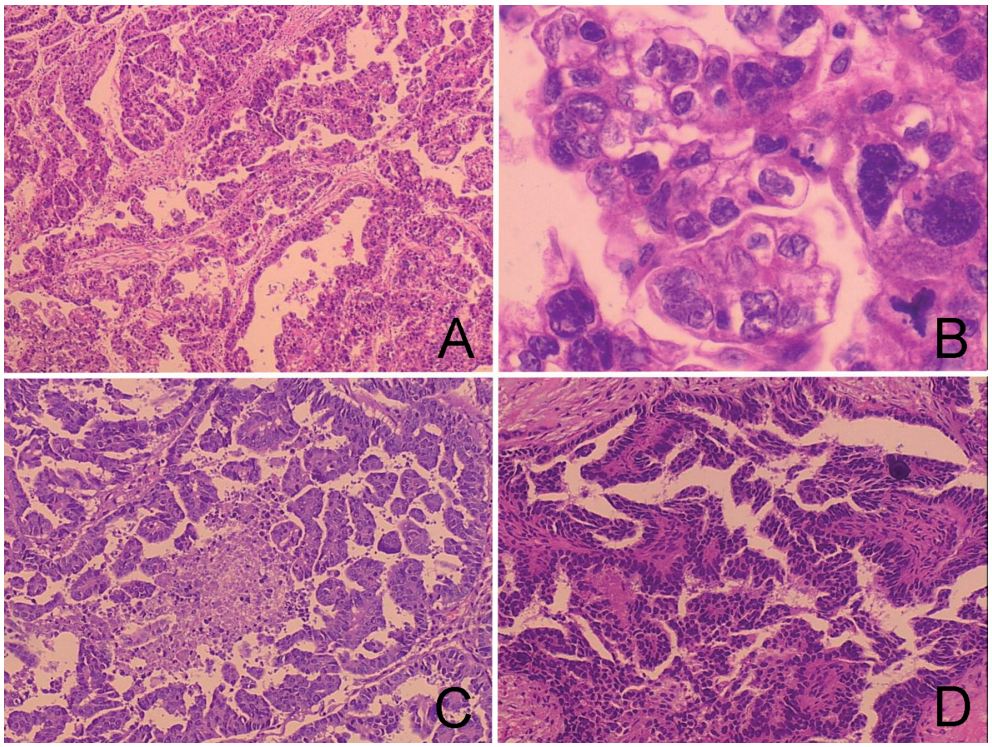

Figure 1. — Histopathologic imaging of ESC sections. A) HE stain of ESC section, ×100 magnification. B) HE stain of ESC section, ×400 magnification. C) focal necrosis, ×100 magnification. D) HE stain of ESC section showing psammoma bodies, ×100 magnification.

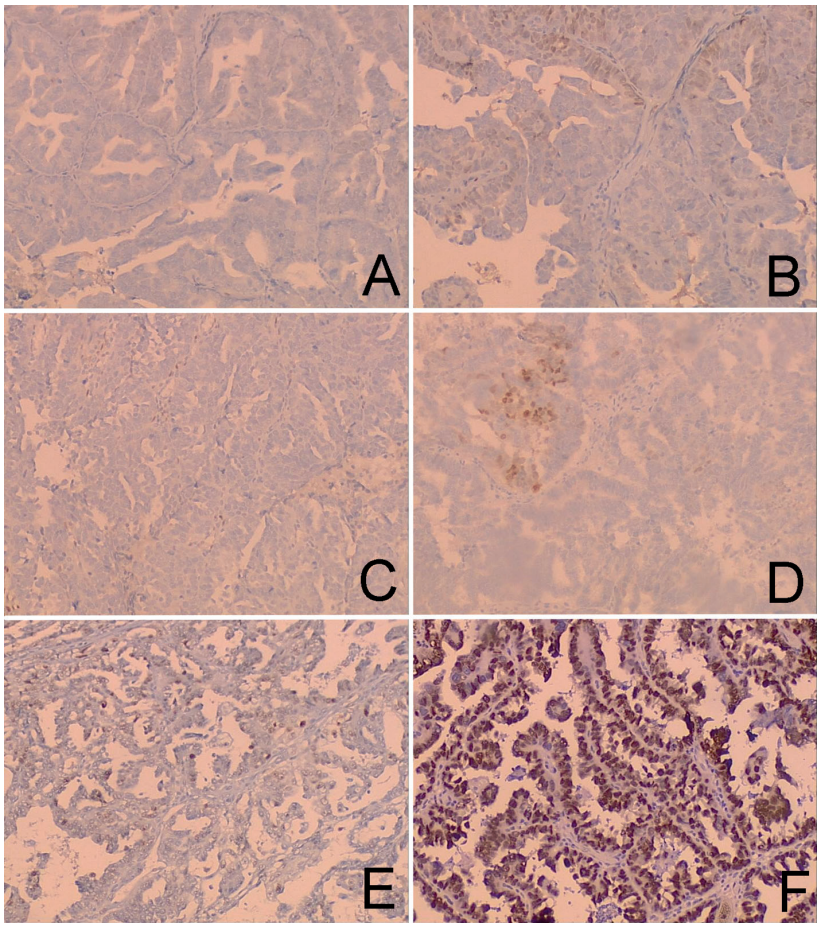

Figure 2. — Immunohistochemistry imaging of ESC sections, ×100 magnification.
A) ER−. B) ER+. C) PR−. D) PR+. E) MTP53−. F) MTP53+.

Table 1. — *ER and PR histoimmunochemistry result.*

No. of cases	Percentage	ER	PR
27	81.82%	−	−
2	6.06%	+	+
3	9.09%	−	+
1	3.03%	+	−

experienced abdominal pain or discomfort (9.09%) and one patient had genital mass prolapse accompanied dysuria (3.03%). Lymphatic metastasis occurred in 14 cases (42.42%). In 19 cases the depth of myometrial invasion (MI) was < 50% (57.58%), among whom 36.84% had lymphatic metastasis (7/19). Twenty cases were in clinical Stage I-II (60.61%) and six of them had lymphatic metastasis (6/20, 30%); 13 cases were in Stages III-IV (39.39%). During the follow-up time, 17 patients died of the disease (51.52%) and the remaining survived.

The common histopathological features of endometrial serous carcinoma were that tumor cells showed complex branching papillary structures arranged as solid nest or glandular tubules with fiber vascular axis in the center of the papillary structures (Figure 1A). Tumor cells were large, with ill-defined margins, eosinophilic or pink-stained cytoplasm, irregular, and various sized lobulated nucleus, crude granular chromatin, prominent eosinophilic nucleoli, and frequent mitotic features (Figure 1B). In eight patients multiple focal necrosis was observed within the tumor tissues (21.21%) (Figure 1C) and psammoma bodies were visible in seven patients (24.24%) (Figure 1D).

The immunohistochemical staining results of ER and PR are shown in Table 1 and in Figure 2. Twenty-four cases were MTR53+ (72.73%) and nine were MTR53− (27.27%). The correlation between ER, PR or MTP53 and the main clinicopathological parameters and prognosis of ESC are summarized in Table 2. Statistical analysis showed that the expression of ER, PR, and MTP53 markers were not significantly different among different age group, tumor sizes, infiltration depths, tumor staging, and metastasis. The prognosis of ESC patients was not affected by the above parameters aside from their lymphatic metastasis status ($p = 0.043$).

Table 2. — *Correlation of the patients' clinicopathological parameters, histoimmunochemistry markers, and prognosis.*

Clinicopathological parameters	No. of Cases	ER +	ER −	PR +	PR −	MTP53 +	MTP53 −	Survival Alive	Survival DOD
Age (years)									
≥ 64	17	2	15	3	14	14	3	8	9
< 64	16	1	15	2	14	10	6	8	8
Tumor size (cm)									
≥ 3.87	16	2	14	4	12	12	4	8	8
< 3.87	17	1	16	1	16	12	5	8	9
Clinical Stage									
I-II	20	2	18	3	17	13	7	8	12
III-IV	13	1	12	2	11	11	2	8	5
Infiltration depth									
MI < 50%	19	1	18	3	16	15	4	11	8
MI ≥ 50%	14	2	12	2	12	9	5	5	9
Lymphatic metastasis									
Yes	14	2	12	3	11	11	3	4*	10*
No	19	1	18	2	17	13	6	12*	7*
Survival									
Alive	16	2	14	2	14	10	6		
DOD	17	1	16	3	14	14	3		

MI: myometrial invasion; DOD: death of disease; * $p < 0.05$.

Discussion

In the present study, the occurrence of ESC among all endometrial carcinomas was 5.02%, with 93.94% patients being post-menopausal women, which was similar to previous report [10]. Tumor metastasis occurred in 36.84% of tumors with MI < 50% and in 30% of Stages I-II tumors. The fact that about one-third of ESC would become metastatic despite early staging or low infiltration grade was possibly the reason for the poor prognosis of ESC [11, 12].

The differential diagnoses of ESC are: (1) endometrial intraepithelial carcinoma (EIC), which is a premalignant lesion of the uterine lining that predisposes to endometrioid endometrial adenocarcinoma and mostly occurs in postmenopausal women. It mainly presents as endometrial polyp and obvious atypia pleomorphism in the glandular epithelium or protective epithelium of the endometrial glands. EIC has strong MTP53 expression, but with no invasive growth of the pleomorphic neoplasm and with no complex branching papillary structure, which could be distinguished from ESC [13, 14]. (2) Endometrioid adenocarcinoma (EA) cells arrange as glandular tubules, papillae or cribriform pattern and differentiated tumor cells could arrange as solid nest. Highly-differentiated tumor cells are accompanied with slight atypia pleomorphism, while medium or poorly differentiated cells show as obvious atypia pleomorphism and mitotic figures. Metaplasia of squamous epithelium, mucous gland and ciliated epithelium can be found in EA tissues [15]. Tumor cells readily express ER and RP markers and MTP53 only expresses in poorly differentiated EA tumors [16], which can be used to distinguish from ESC. (3) Ovarian serous carcinoma involving the endometrium (OSEC): ovary is the predilection site for serous carcinomas, in which the neoplasm can metastasize to the abdomen or along the oviduct to endometrium. Tumors that localize to the ovary indicate OSEC. If the tumor mainly locates in the endometrium with no apparent lesions in the ovary but with only tumor embolus in the lymphatic vessels or minor infiltration in the ovarian cortex, the diagnosis is often ESC with ovary metastasis [17]. (4) Cervical adenocarcinoma involving the endometrium (CEA) cells often show infiltrative

growth of glandular tubules with internal papillary structure. Tumor cells have obvious atypia pleomorphism and mitotic features. Intracytoplasmic mucus is visible in well-differentiated tumors [18]. CEA could be differential diagnosed by keratin, vimentin, p16 or carcino-embryonic antigen histoimmunochemistry staining [19]. (5) Clear-cell carcinoma of the uterine body (UCCC) is a type-II endometrial carcinoma and often presents three types of cells and organization structures: laminated clear cells, papillary eosinocytes, and glandular tubular hobnail cells. Histoimmunochemistry analysis of UCCC often shows expression of CK7, Leu-M1, and CyclinE markers, which can be differentiated from ESC [20, 21]. (6) Endometrial transitional cell carcinoma (ETCC) is very rare [22]. Cells arrange as solid nest or papillary structure and resemble bladder transitional cell carcinoma in appearance. ETCC cells normally do not express ER and PR markers but retain the $CK7^{+}$/CK20− immunophenotype [23].

The present results showed that in only a few cases ESC expressed ER and PR markers, while 72.73% patients were MTP53 positive. Zhu *et al.* compared the immunophenotype between EA and ESC and found that ESC had a significantly higher rate of positive MTP53 marker and lower positive ER and PR markers than EA [24]. Kovalev *et al.* and King *et al.* reported a 53% and 73% occurrence rate of mutant type p53 in 33 and 22 uterine papillary serous carcinoma (UPSC) patients respectively [25, 26]. Zheng *et al.* proposed that p53 alteration may be an early event in the development of UPSC and may be related to its clinical aggressiveness, while it is a late event in uterine endometrioid carcinomas (UEC) [27]. The present results showed that the expression of ER, PR, and MTP53 markers was not affected by the patients' age, tumor size, staging, infiltration or metastasis of ESC, indicating that ESC was non-hormone-dependent. P53 mutation might play an important role in the tumorigenesis of ESC while not obviously involved in the progression, invasion, and metastasis of the tumor.

Currently, controversies still exist regarding the prognostic factors of ESC. Some researchers believe that clinical staging, depth of myometrial invasion, and the lympho-vascular involvement (LVI) are predictive factors for prognosis [28]. Another study reported LVI to be the only independent predictive factor for prognosis [29]. The present data showed that the overall survival of patients with or without lymphatic metastasis were 28.57% (4/14) and 63.16% (12/19), respectively, which was significantly different, while other factors were not the predictive factors for prognosis. The disagreement of results among multiple studies might be caused by the differences in sample size and follow-up time.

Conclusions

In summary, in this study the author discussed the clinicopathological features, differential diagnosis, and prognosis of ESC. ESC is a rare type of endometrial cancer that mostly affects postmenopausal women with postmenopausal vaginal bleeding or vaginal discharge as the main symptom. Imageological tests often showed intrauterine space occupying lesions. P53 mutation might be closely related to the tumorigenesis of ESC. Lymphatic metastasis could occur in early stage and is a predictive factor for poor prognosis.

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References

[1] SGO Clinical Practice Endometrial Cancer Working Group, Burke W.M., Orr J., Leitao M., Salom E., Gehrig P., *et al.*: "Endometrial cancer: a review and current management strategies: part I". *Gynecol. Oncol.* 2014, *134*, 385.
[2] Porter S.: "Endometrial cancer". *Semin. Oncol. Nurs.* 2002; 18:200.
[3] Berchuck A., Boyd J. "Molecular basis of endometrial cancer". *Cancer*, 1995, *76*, 2034.
[4] Wang Y., Xue F., Broaddus R.R., Tao X., Xie S.S., Zhu Y.: "Clinicopathological features in endometrial carcinoma associated with Lynch syndrome in China". *Int. J. Gynecol. Cancer*, 2009, *19*, 651.
[5] Setiawan V.W., Yang H.P., Pike M.C., McCann S.E., Yu H., Xiang Y.B., *et al.*: "Type I and II endometrial cancers: have they different risk factors?". *J. Clin. Oncol.*, 2013, *31*, 2607.
[6] Park J.Y., Nam J.H., Kim Y.T., Kim Y.M., Kim J.H., Kim D.Y., *et al.*: "Poor prognosis of uterine serous carcinoma compared with grade 3 endometrioid carcinoma in early stage patients". *Virchows. Arch.*, 2013, *462*, 289.
[7] Oncology F.C.o.G: "Current FIGO staging for cancer of the vagina, fallopian tube, ovary, and gestational trophoblastic neoplasia". *Int. J. Gynaecol. Obstet.*, 2009, *105*, 3.
[8] Kiernan J.A.: *Histological and Histochemical Methods: Theory and Practice. 4th ed.* Bloxham, UK: Scion, 2008.
[9] Sun D.Z., Xu L., Wei P.K., Liu L., He J.: "Syndrome differentiation in traditional Chinese medicine and E-cadherin/ICAM-1 gene protein expression in gastric carcinoma". *World J. Gastroenterol.*, 2007, *13*, 4321.
[10] Daniilidou K., Frangou-Plemenou M., Grammatikakis J., Grigoriou O., Vitoratos N., Kondi-Pafiti A.: "Prognostic significance and diagnostic value of PTEN and p53 expression in endometrial carcinoma. A retrospective clinicopathological and immunohistochemical study". *J. BUON.*, 2013, *18*, 195.
[11] Semaan A., Mert I., Munkarah A.R., Bandyopadhyay S., Mahdi H.S., Winer I.S., *et al.*: "Clinical and pathologic characteristics of serous carcinoma confined to the endometrium: a multi-institutional study". *Int. J. Gynecol. Pathol.*, 2013, *32*, 181.
[12] Garg G., Gao F., Wright J.D., Hagemann A.R., Zighelboim I., Mutch D.G., Powell M.A.: "The risk of lymph node metastasis with positive peritoneal cytology in endometrial cancer". *Int. J. Gynecol. Cancer*, 2013, *23*, 90.
[13] Owings R.A., Quick C.M.: "Endometrial intraepithelial neoplasia". *Arch. Pathol. Lab. Med.*, 2014, *138*, 484.
[14] Semere L.G., Ko E., Johnson N.R., Vitonis A.F., Phang L.J., Cramer D.W., Mutter G.L.: "Endometrial intraepithelial neoplasia: clinical correlates and outcomes". *Obstet. Gynecol.*,2011, *118*, 21.

[15] Darvishian F., Hummer A.J., Thaler H.T., Bhargava R., Linkov I., Asher M., Soslow R.A.: "Serous endometrial cancers that mimic endometrioid adenocarcinomas: a clinicopathologic and immunohistochemical study of a group of problematic cases". *Am. J. Surg. Pathol.*, 2004, *28*, 1568.
[16] Mhawech-Fauceglia P., Yan L., Liu S., Pejovic T.: "ER+ /PR+ /TFF3+ /IMP3- immunoprofile distinguishes endometrioid from serous and clear cell carcinomas of the endometrium: a study of 401 cases". *Histopathology*, 2013, *62*, 976.
[17] Silva E.G., Deavers M.T., Parlow A.F., Gershenson D.M., Malpica A.: "Calcifications in ovary and endometrium and their neoplasms". *Mod. Pathol.*, 2003, *16*, 219.
[18] Singh P., Scurry J., Proietto A.: "Lethal endometrial recurrence after cone biopsy for microinvasive cervical adenocarcinoma". *J. Obstet. Gynaecol. Res.*, 2008, *34*, 413.
[19] Hu W.W., Tao J.H., Li G.M., Xu X., Yang X.M.: "Value of ER, VIM, CEA and p16 detection in the diagnosis and differential diagnosis of primary endocervical and endometrial adenocarcinomas". *J. Southern. Med. Univ.*, 2010, *30*, 526.
[20] Vang R., Whitaker B.P., Farhood A.I., Silva E.G., Ro J.Y., Deavers M.T.: "Immunohistochemical analysis of clear cell carcinoma of the gynecologic tract". *Int. J. Gynecol. Pathol.*, 2001, *20*, 252.
[21] Arai T., Watanabe J., Kawaguchi M., Kamata Y., Nishimura Y., Jobo T., Kuramoto H.: "Clear cell adenocarcinoma of the endometrium is a biologically distinct entity from endometrioid adenocarcinoma". *Int. J. Gynecol. Cancer*, 2006, *16*, 391.
[22] Marino-Enriquez A., Gonzalez-Rocha T., Burgos E., Stolnicu S., Mendiola M., Nogales F.F., Hardisson D.: "Transitional cell carcinoma of the endometrium and endometrial carcinoma with transitional cell differentiation: a clinicopathologic study of 5 cases and review of the literature". *Hum. Pathol.*, 2008, *39*, 1606.
[23] Zhang A.M., Zhang L.X., Zhang H.J. "Transitional cell carcinoma of the endometrium: a clinicopathological study of 3 cases". *Chin. J. Clin. Exp. Pathol.*, 2007, *23*, 524.
[24] Zhu J., Sun H.: "Respective analysis of 54 cases uterine serous carcinoma". *Fudan Univ. J. Med. Sci*., 2008, *35*, 914.
[25] Kovalev S., Marchenko N.D., Gugliotta B.G., Chalas E., Chumas J., Moll U.M.: "Loss of p53 function in uterine papillary serous carcinoma". *Hum. Pathol.* 1998, *29*, 613.
[26] King S.A., Adas A.A., LiVolsi V.A., Takahashi H., Behbakht K., McGovern P., *et al.*: "Expression and mutation analysis of the p53 gene in uterine papillary serous carcinoma". *Cancer*, 1995, *75*, 2700.
[27] Zheng W., Cao P., Zheng M., Kramer E.E., Godwin T.A. "p53 overexpression and bcl-2 persistence in endometrial carcinoma: comparison of papillary serous and endometrioid subtypes". *Gynecol. Oncol.*, 1996, *61*, 167.
[28] Li M.Z., Wang Z.Q., Zhao L.J., Li X.P., Wang J.L., Zhang C.F., Wei L.H.: "Predictors of recurrence and prognosis in patients with stage I and II endometrial carcinoma". *Chin. J. Obstet. Gynecol.*, 2014, *49*, 455.
[29] Mhawech-Fauceglia P., Herrmann R.F., Kesterson J., Izevbaye I., Lele S., Odunsi K.: "Prognostic factors in stages II/III/IV and stages III/IV endometrioid and serous adenocarcinoma of the endometrium". *Eur. J. Surg. Oncol.*, 2010, *36*, 1195.

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