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Microscopic lesions of fallopian tubes in endometrioid carcinoma of the endometrium: How effective are the macroscopic tubal sampling techniques?

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Objective: Extrauterine involvement of endometrial carcinoma has a significant effect on the patients' prognosis and treatment decision. In classical method, macroscopic section is taken from the fallopian tube sparing the fimbrial ends. Fimbrial end of fallopian tube may be involved by tumors and precursor lesions. This study aims to determine the importance of sampling of fimbrial ends of fallopian tube in endometrioid endometrial carcinoma specimens.
Methods: We reevaluated the fallopian tubes of 200 cases of endometrioid endometrial carcinoma cases that have no macroscopic tubal lesion. A hundred cases were sampled with classical method, and the other 100 were sampled with a new method that includes the fimbrial ends. Statistical difference was examined by Fisher's exact test.
Results: No microscopic tubal lesion lesion was detected in cases that were sampled with the classical method. In contrast, there were 4 cases with tubal lesions in patients sampled with the new technique; 3 of them were located in the fimbrial end. Of the 3, there was one microscopic invasive carcinoma and two proliferative endometrial glandular lesions. Endometriosis was detected in two of the 4 cases with tubal lesions.
Conclusion: Including the fimbrial end of fallopian tube to macroscopic sampling could detect more tubal lesions, which might provide additional prognostic and pathogenetic information of endometrioid endometrial carcinoma.

Keywords: Endometrial neoplasms, Endometrioid carcinoma, Endometriosis, Fallopian tube

INTRODUCTION

Endometrial carcinoma is one of the most common tumors of the women's reproductive system. Most of them are well differentiated and usually diagnosed at early stages and have excellent prognosis. In case of metastasis adjunct treatment is necessary [1]. Gross tumors that can be seen macroscopically can be sampled and easily diagnosed but small microscopic tumors may be overlooked. So thorough sampling of the uterus and adnexal structures is very important for appropriate staging.

In recent years multiple study groups started to examine fallopian tubes besides ovaries excised from the patients who carry *BRCA* mutations [2]. In these studies precursor lesions or minimal invasive carcinomas were observed in fallopian tubes. This observation led light to further investigations. By having similar morphologic and immunohistochemical features, serous tubal intraepithelial carcinomas and *p53* mutations suggested that at least some of the pelvic serous carcinomas (ovarian, tubal, and primary peritoneum) arise from fallopian tube epithelium and mostly from the fimbrial end [3,4]. So the

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fallopian tubes become a focus of interest.

Fallopian tube is not only an origin for ovarian serous carcinoma but also an important "passage" for endometriosis and has indirect role in the pathogenesis of endometrioid and clear cell carcinoma. Endometrioid and clear cell ovarian carcinomas may arise from endometriosis foci in ovaries [5]. About one forth of endometrioid endometrial carcinomas has synchronous endometrioid tumors in the ovary and synchronous endometrial and fallopian tube endometrioid type cancers are also present [6]. Fallopian tube is also a passage for metastatic spread of primary ovarian serous carcinoma to the endometrium [7].

In this context, in our department we changed our macroscopic examination and sampling techniques for fallopian tubes in all routine hysterectomy specimens. We started to use a longitudinal sampling method that includes the fimbrial ends. Although the starting point of this change is the hypothesis on the ovarian carcinogenesis, we observed more microscopic lesion in the fimbrial edges (e.g., *in situ* lesions within ovarian cancers, tumor metastasis and hilus cells [8] etc.). To evaluate this observation, we planned a retrospective study for endometrioid endometrial cancers.

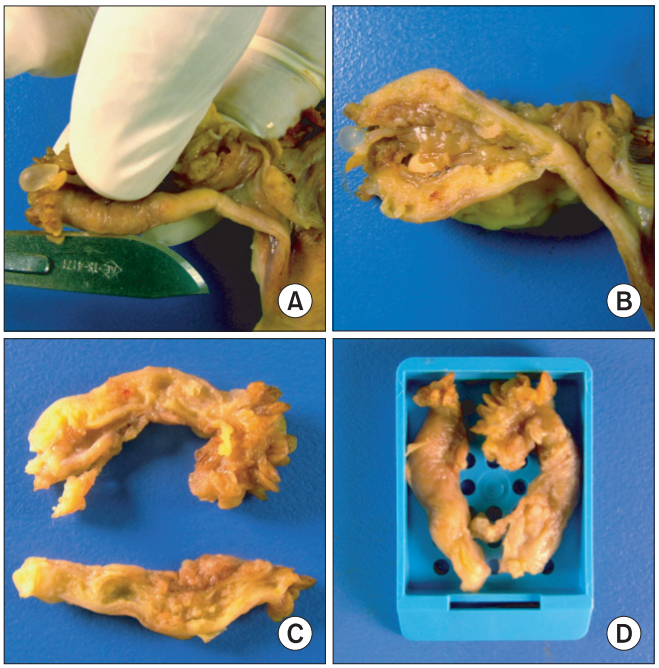

Fig. 1. We cut the fallopian tube into two pieces including the fimbrial end (A, B). If the tube measures less than 2 cm, we sample it totally. If it's more than 2 cm, we take a 2 cm sample including the fimbrial end and sample in one cassette (C, D).

MATERIALS AND METHODS

In our institution, before 2005, fallopian tubes were sampled transversely using classical methods, and usually two ring shape sections were taken from each tube. As this method implies, generally fimbrial ends were not sampled. After 2005, in all cases—if there is no visible macroscopic lesion—we cut a 2 cm piece of fallopian tube including the fimbrial end and then again cut it into two longitudinally and sample whole fimbrial end in one cassette (if the fallopian tube measures less then 2 cm, whole tube was sampled in one cassette) (Fig. 1).

One-hundred endometrioid endometrial carcinoma in which fallopian tubes were sampled with the classical method and 100 cases of endometrioid endometrial carcinoma in which fallopian tubes were sampled by the new method were chosen randomly from patients' reports archive. Only endometrioid type carcinomas were included. Any histologic type other than endometrioid carcinoma and cases with visible macroscopic tubal lesion were excluded in order to focus on the representative efficiency of macroscopic examination of uterine tube for microscopic lesions. All cases with microscopic tubal lesions reexamined by light microscopy. Tumor localization, size and extent of invasion were recorded. The information of all patients' ages, tumor type, tumor grade, depth of tumor invasion, cervical involvement, numbers of samples taken from uterine tubes, number of resected lymph nodes, number of metastatic lymph nodes, type of the surgical procedure were taken from computer based patients records database and also from original pathology reports.

Statistical difference between these two groups was examined by Fisher's exact test.

RESULTS

No microscopic lesion was detected in cases sampled with the classical method. In contrast, there were 4 cases with tubal lesions in cases sampled with the new technique. However statistically the difference was not significant (p=0.121). Mean age of patients was 60.6 in classically sampled group and 58.7 in the group sampled by new method. All the lesions except one were located in the fimbria. Neither invasive nor intraepithelial serous carcinoma of the tube was identified in any of the cases. All the patients with endometrioid endometrial carcinoma having fallopian tube lesions had a history of abnormal vaginal bleeding and all of them were treated with total abdominal hysterectomy, omentectomy, bilateral salphingooopherectomy and bilateral pelvic paraaortic lymphadenectomy. Treatment modalities, tumor grades and the stages of the patients are shown in Table 1.

Table 1. Treatment modalities, tumor grades and stages of the patients

	Classical technique (n=100)	New technique (n=100)
Age (yr, mean)	60.6	58.7
Surgical procedure		
TAH+BSO	5	5
TAH+BSO+appendectomy	1	0
TAH+BSO+BPPALND	14	2
TAH+BSO+BPPALND+omentectomy	72	79
TAH+BSO+BPPALND+appendectomy	3	0
TAH+BSO+BPPALND+omentectomy+appendectomy	5	14
Myometrial Invasion		
None	13	20
<1/2	46	48
≥1/2	41	32
Tumor grade		
1	55	47
2	17	28
3	28	25
Extrauterine extension (except lymph node involvement)	7	14
Endocervical stromal invasion	10	11
Lymph node metastasis	12	19

BSO, bilateral salphingooopherectomy; BPPALND, bilateral pelvic and paraaortic lymph node dissection; TAH, total abdominal histerectomy.

Table 2. Clinical and pathological properties of patients with lesion

Case	Age (yr)	Primary tumor type	Primary tumor grade	Myometrial invasion	Tubal involvement	Endometriosis	Type of involvement	Continuum with tubal epithelium	Localization of tubal involvement	Positive/ harvested lymph node
1	56	Endometrioid	2	≥1/2	Bilateral	Present	Infiltrative carcinoma	Absent	Infundibular - ampullary	0/37
2	57	Endometrioid (with mucinous differentiation)	1	≥1/2	Left	Absent	Infiltrative carcinoma	Present	Fimbrial	1/13 (right external iliac)
3	52	Endometrioid	1	<1/2	Left	Present	Proliferative glandular lesion	Present	Fimbrial	0/42
4	54	Endometrioid	1	≥1/2	Right	Absent	Proliferative glandular lesion	Present	Fimbrial	0/43

Table 2 briefly describes the major pathologic features of four patients' fallopian tubes and major clinical features of the patients'. In three cases there were deep myometrial invasions (case 1, 2, 4) in one case there was superficial myometrial invasion (case 3). Only one case showed cervical stromal involvement (case 4). Only one case had a lymph node metastasis (case 2). Endometriosis was accompanying the neoplastic lesions in case 1 and 3 (Fig. 2). The fallopian tube lesions of the case 1 and case 2 were infiltrative carcinoma showing similar microscopic features with the primary tumor (Fig. 3). The fallopian tube lesions seen in case 3 and case 4 were noninvasive, endometrioid type glandular proliferations (Fig. 4). Endometriosis was accompanying the fallopian tube lesions in two cases. Another interesting finding was the presence of transition between fallopian tube epithelium and the lesions seen in the fallopian tube in all cases except case 1 (Figs. 3, 4).

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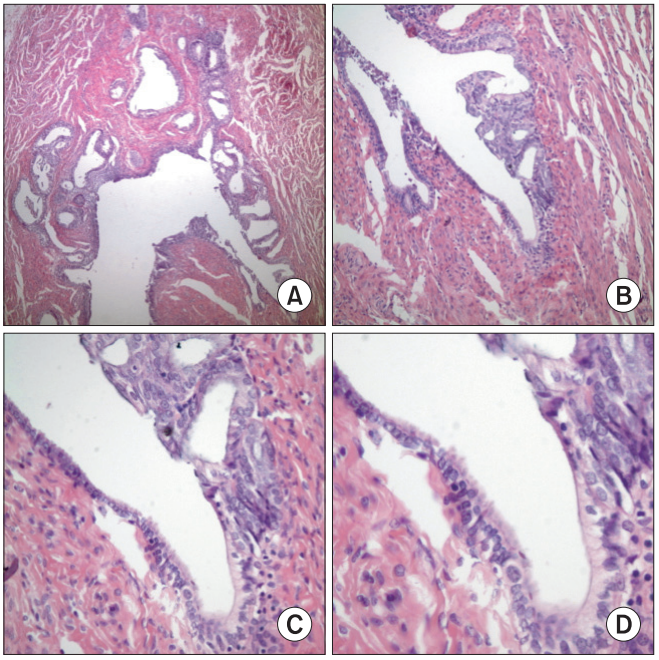

Fig. 2. Presence of endometriosis foci in fallopian tube (A, B). Note the epithelial continuum between tubal epithelium and the endometrioid lesion (C). Closer view of continuum between the lesion and tubal epithelium (D).

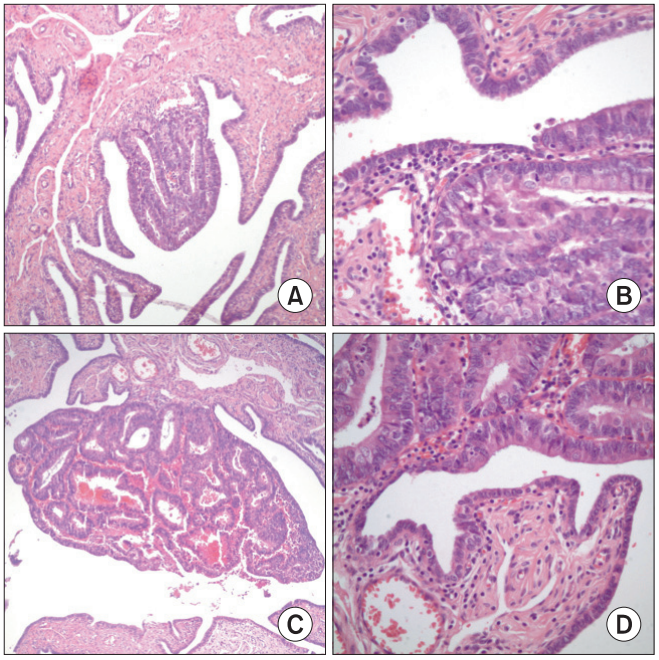

Fig. 4. These proliferative glandular lesions were observed in different areas from the fallopian tubes of the same patient (A–C) and continuum between normal tubal epithelium and the proliferative lesion can easily be seen in both lesions (C, D).

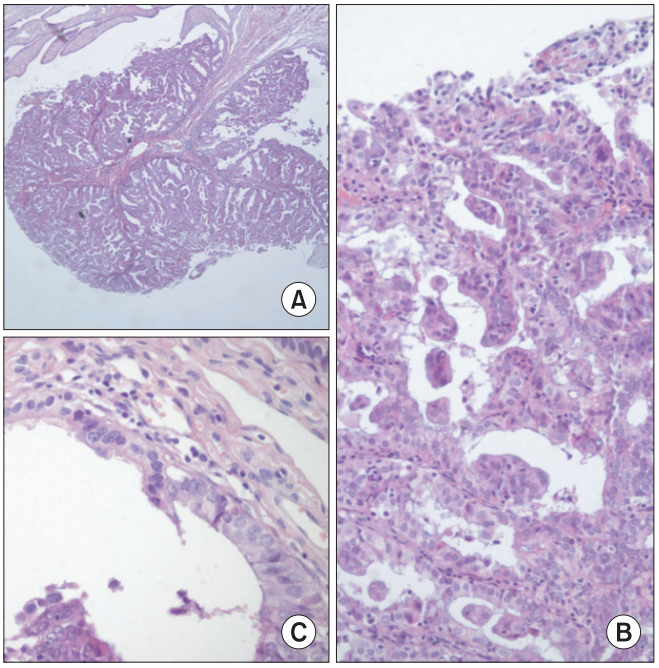

Fig. 3. Focus of infiltrative endometrioid carcinoma; a hanging polypoid lesion in the fimbrial end (A). Closer view of the endometrioid tumor (B). Note the continuity between the carcinoma cells and tubal epithelium (C).

DISCUSSION

Fallopian tube, especially the fimbrial end is noted in these days, because of recent developments pointing that fallopian tubes are not only the source of most of the ovarian high-grade serous papillary carcinoma [3,9-11] but also for low-grade serous tumors [12]. Fallopian tubes are also passages for endometriosis and have indirect role in the pathogenesis of endometrioid and clear cell carcinoma; as the regurgitation theory implies. Tubes are also passages for ovarian serous tumors for endometrial involvement and may be a site for miscellaneous benign lesions [7,8].

Endometrial carcinoma is one of the most common tumors of the woman's reproductive system. Most of them are well differentiated and usually diagnosed at early stage and have excellent prognosis. In case of metastasis, adjunct treatment is necessary [1]. So thorough sampling of the uterus and adnexal structures are very important. Gross tumors that can be seen by naked eye can be sampled and easily diagnosed but small microscopic tumors may be overlooked. We observed more microscopic lesions in the fallopian tubes of endometrial carcinoma patients with longitudinal sampling technique than classical ring shape method as our study suggests. However, this finding is not statistically significant. Interest-

ingly half of the lesions was invasive tumors that may affect the prognosis. As in our case 2, we found a microscopic focus of invasive carcinoma in the fimbrial end of the fallopian tube that can easily be overlooked without sampling this region. Fimbrial lesions are important because they can easily spill over into the abdominal cavity. One of the papers evaluating the synchronous endometrial and tubal endometrioid tumors found that most of the lesions were located on the fimbrial end and none of them were located in the proximal portion of the fallopian tube [6]. Most of the patients with endometrioid carcinomas of the fallopian tube had good prognosis [13]. In contrast the patients with tumors on the fimbrial ends may have more aggressive clinical behavior than located in other parts of the tube [14].

It is a well-known fact that most of the endometrioid tumors found both in the ovary and endometrium are synchronous tumors [15,16]. The most important clue supporting this fact is the good prognosis for these synchronous early stage tumors. It is also known that most of the ovarian endometrioid tumors are associated with endometriosis and field effect is a reasonable explanation for synchronous endometrium and ovarian tumors. A similar phenomenon may also be valid for tubal endometrioid lesions. There are also synchronous tubal and endometrial endometrioid type cancers. Culton et al. [6] published 13 cases of synchronous independent primary endometrial and tubal carcinomas.

Another issue from our results was the presence of proliferation of endometrial type glands in continuity with fallopian tube epithelium; one case with invasive tumor had endometriosis and also proliferative glands with endometrioid morphology and the other cases had no invasive tumor in the fallopian tube but had proliferative endometrioid type glands and all these are in continuity with the fallopian tube epithelium. It is known that only the mucosa of the interstitial portion of tube may have endometrioid type epithelium [17]. We suggested a metaplastic change in the fimbrial end of the tubal epithelium to endometrioid type epithelium. These foci of proliferation may give rise to the endometrioid lesions of the fallopian tube. Whether these endometrioid lesions seen in the fallopian tubes originate from the endometrium or are metaplastic in origin, they seem to be mostly localized on the fimbrial end of the fallopian tubes.

Many institutions all around the world still use the classical sampling technique for fallopian tubes defined in two major books of surgical pathology; *Ackerman-Rosai Surgical Pathology* [18] and previous edition of (5th ed) *Blaustein's Pathology of the Female Genital Tract* [19]. Both books macroscopic guideline recommend classical sampling technique for uterine tubes. These classical texts recommend two "ring shape" sections of various parts of each tube, sparing the fimbrial end of the tubes most of the lesions arise from. In the last edition of *Blaustein's Pathology of the Female Genital Tract*, fimbrial end sampling is recommended for prophylactic salphingo-oophorectomies and for serous pelvic tumors but not for benign and any other malignant conditions [20].

Prophylactic salpingectomies for high-risk patients with familial cancers are widely accepted. Today some surgeons also recommend routine prophylactic removal of the fallopian tubes during hysterectomy or sterilization to prevent tumor development for all patients [21]. We pathologists must have a new method of tubal sampling especially including the fimbrial end for routine hysterectomies. Sectioning and extensively examining the fimbria (SEE-FIM) method is good for familial cases but not practical for all routine salpingectomy specimens, because of the increase in workload due to the serial sections. Although statistically insignificant, with tubal sampling including the fimbrial ends, pathologists may detect lesions more frequently without a major increase in workload. We think that sampling of the fimbrial end of the fallopian tubes may give much more information about the pathogenesis and prognosis of neoplastic gynecologic lesions. We think that for all salpingectomy specimens, it's more logical to sample fimbrial ends of fallopian tubes than other locations.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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