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Comparison of the classical method and SEEFIM protocol in detecting microscopic lesion in fallopian tube with Gynecological pathology – an experience in a medical college.

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Abstract:

Background and objectives: Clinical interest in the fallopian tube continues to increase. Recent studies on the carcinogenesis and origin of ovarian carcinoma have suggested tubal epithelium as a source of high-grade serous carcinoma (HGSC). The objective of this study is to compare the classical, sectioning and extensively examining the Fimbriated end protocol (SEE-FIM) in detecting microscopic lesions in fallopian tube with Gynaecological lesions.

Materials and methods: From a total of 1282 cases, 662 with various parts of both fallopian tubes sampled in three-ring-shaped sections and 620 sampled with the SEE-FIM protocol were included in this study. Pathological findings of cases with endometrial carcinoma, ovarian serous carcinoma, ovarian borderline tumours, and benign lesions were compared.

Results: We detected 1 tubal infiltrative carcinomas among 8 uterine endometrioid adenocarcinomas, 2 serous tubal intraepithelial carcinomas in 4 non-uterine pelvic serous high-grade carcinoma cases, 4 papillary tubal hyperplasias in 8 serous borderline tumour

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cases, and 14 endometriotic foci and four adenomatoid tumours among all cases sampled with the SEE-FIM protocol. Using the classical method, we detected only 1 serous tubal intraepithelial carcinoma in 10 non-uterine pelvic serous high-grade carcinoma cases and 1 papillary tubal hyperplasia cases in 23 serous borderline tumours. We did not identify additional findings in 10 uterine endometrioid carcinoma cases, and neither endometriotic foci nor adenomatoid tumour were shown in other lesions by the classical method.

Conclusion: Benign, premalignant, and malignant lesions can possibly be missed using the classical method. The SEE-FIM protocol should be considered especially in cases of endometrial carcinoma, nonuterine pelvic serous cancers, or serous borderline ovarian tumors. For other lesions, at least a detailed examination of the fimbrial end should be undertaken.

Key wards: SEE-FIM method, Classical method, Gynaecological pathology

INTRODUCTION:

Clinical interest in the fallopian tube continues to increase. Recent studies on the carcinogenesis and origin of ovarian carcinoma have suggested tubal epithelium as a source of high-grade serous carcinoma (HGSC) (1-4). Tubal carcinoma has been demonstrated in pathological specimens of *BRCA1* and *BRCA2* mutation carrier women who chose to have prophylactic salpingo-oophorectomy to reduce their risk of ovarian carcinoma (4). In addition to HGSC, low-grade serous carcinomas are thought to originate from the tubal epithelium, and papillary tubal hyperplasia (PTH) is considered a precursor to serous borderline tumours (SBT), non-invasive implants, and endosalpingiosis (4).

The fallopian tube has an indirect role in the pathogenesis of endometrioid and clear cell carcinomas of the endometrium and ovary (3). The presence of simultaneous or incidental lesions in fallopian tubes, the need for determination of their pathogenesis or their precursors, and the effects of fallopian tube metastasis on treatment modalities and on disease stage indicate the importance of fallopian tube sampling techniques (5).There are different approaches for sampling fallopian tubes. The pathology textbook Ackerman-Rosai Surgical Pathology recommends the classical sampling technique including collection of three “ring-shaped” sections from various parts of each tube (6). In *Blaustein’s Pathology of the Female Genital Tract* (7), sampling of entire bilateral fallopian tubes with fimbrial ends is recommended for pelvic serous tumors and prophylactic salphingo-oophorectomies.

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However, for benign diseases and other malignant conditions, collection of at least one sample from each tube is recommended (7). The Association of Directors of Anatomic and Surgical Pathology recommends three sections for tubal carcinomas and at least three sections including isthmus, ampulla, and infundibulum/fimbria for routine cases (8).

In this study, we aimed to compare the classical method and Sectioning and Extensively Examining the Fimbriated End Protocol (SEE-FIM) in detecting microscopic lesions in fallopian tubes wıth gynaecological lesions.

MATERIALS AND METHODS

In the pathology department of our hospital, the SEE-FIM protocol has been used since 2023. Before that, fallopian tubes were sampled using the classical method involving collection of three “ring-shaped” sections from various parts of each tube.

The SEE-FIM protocol includes amputation of each fimbria at the infundibulum, longitudinal sectioning of the fimbria, and extensive cross sectioning of the remaining tube at 2-mm intervals (9).This study was conducted on 1282 patients who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy at our hospital from January 2022 to Jan 2024. The fallopian tubes were sampled by the classical method in 662 cases between Jan 2022 and Feb 2023, and 620 cases performed after 2023 underwent the SEE-FIM protocol. All sample slides were re- examined with light microscopy by two pathologists. Data on the macroscopic evaluations and other clinicopathological examinations were collected by chart review.

Cases were grouped according to the final diagnosis as endometrial carcinoma, non-uterine pelvic malignant tumors (ovarian, peritoneal, and tubal), ovarian borderline tumor and premalignant-benign lesions. Pathological findings of the classical and SEE-FIM protocols were compared between subgroups. Pelvic serous carcinomas (PSCs) were classified as “primary ovarian,” “fallopian tube,” and “primary peritoneal” according to Gynecologic Oncology Group criteria (10).

Serous tubal intraepithelial carcinoma (STIC) was diagnosed as noninvasive tubal epithelium displaying marked nuclear atypia characterized by loss of polarity, increased nuclear/cytoplasmic ratios, increased nuclear size, hyperchromasia, irregular nuclear membranes, and chromatin distribution. In addition, absence of cilia and mitotic figures was

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also characterized as STICs (5). Immunostainings for p53 and Ki-67 were performed to diagnose STIC (11, 12).

p53 signatures are defined as benign-appearing tubal epithelium with strong staining for p53 by immunohistochemistry and a low Ki-67 index (5). Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue sections using a manual polymer detection system with citrate buffer heat-induced epitope retrieval. Pre-diluted ready-to-use primary antibodies were used including p53 and Ki-67. PTH was described as small rounded clusters of tubal epithelial cells and small papillae floating within the tubal lumen, with or without associated psammoma bodies, and demonstration of these findings with at least three papillae. Statistical analysis was done as per requirement using IBM SPSS version 24.Ethical committee approval was obtained before starting study.

RESULTS

This study included a total of 1282 abdominal hysterectomy and salpingo-oophorectomy cases. Benign lesions, malignant neoplasms, and premalignant lesions of the fallopian tubes in each group were evaluated in detail.

Table: Pathological diagnosis and number of cases in each group.

Pathology	Classic method (n=662)	SEE-FIM method (n=620)
Endometrial carcinoma	10	8
Non- uterine pelvic malignant tumours- Ovarian Serous carcinomas	10	8
Ovarian borderline tumours	23	12
Premalignant and benign tumours	629	592

No endometrioid adenocarcinoma was detected in endometrial carcinomas using the classical method and was detected in 1out of 8 endometrioid malignant tumours using the SEE-FIM protocol. Other cases were clear cell carcinoma, undifferentiated tumour and serous carcinoma.

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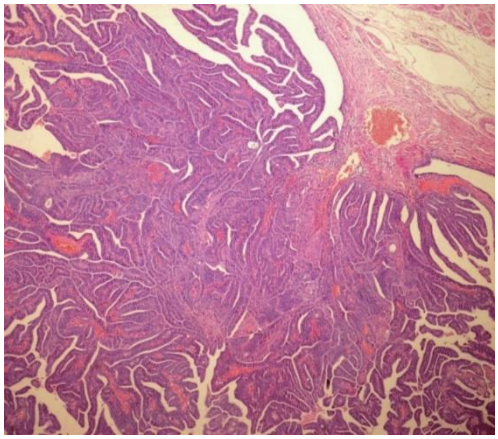

Figure 1: Endometroid carcinoma with tubal invasion.

Out of the non-uterine pelvic malignant tumour cases sampled by the new technique, all 4 were ovarian HGSCs. Serous carcinoma was detected in 1out of 10 non-uterine pelvic carcinoma cases sampled by the classical method and it was ovarian HGSCs .In cases sampled by the new technique, STIC was detected in 2 out of 4 ovarian HGSCs. All lesions were located in fimbrial end (50%).

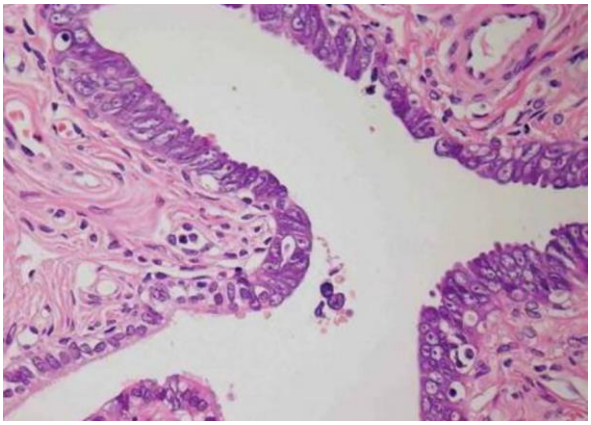

Figure 2: Fallopian tube with serous tubal intraepithelial carcinoma (STIC).

While serous borderline tumour was identified in 1out of 23 ovarian borderline tumours using the classical method, it was detected in 8 of 12 cases in the SEE-FIM group. PTH was shown in 6 out of 8 cases (75%) sampled by the SEE-FIM protocol. One case was bilateral, 3 were diffuse, and 2 were focal lesions. All focal lesions were located in the ampulla and infundibulum. No PTH was seen in the classical method group (0%).Except for serous borderline tumour cases, PTH was not detected by either the classical method or the SEE-FIM protocol.

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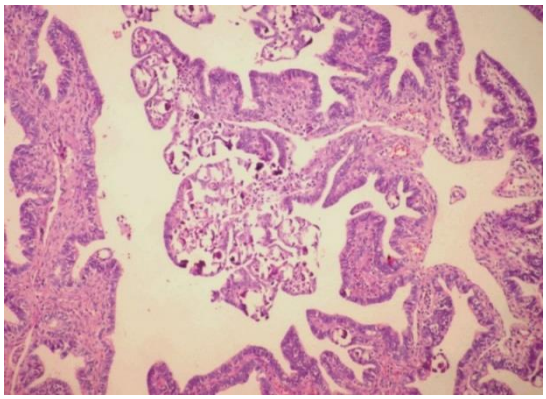

Figure 3: Picture illustrating papillary tubal hyperplasia (PTH)

Out of the 592 benign cases sampled by the new technique, tubal endometriosis and adenomatoid tumour were detected in 14 and 4 cases, respectively. While 10 endometriotic foci were located in the infundibulum, 4 were in the ampulla. Adenomatoid tumours were located in the ampulla and infundibulum, with a mean diameter of 1 cm both at the serosa and subserosa. Neither tubal endometriotic focus nor adenomatoid tumour was identified in any of the 629 cases sampled by the classical method. There was a statistically significant difference between the two techniques regarding the diagnosis of adenomatoid tumour and endometriotic focus ($p = .039$).

DISCUSSION:

Detection of tubal lesions synchronous with endometrial cancer is important in management. Appropriate sampling of the tubes, ovaries, and lymph nodes is crucial in staging and treatment. The correct prognosis estimation is related to detection of tubal lesions in endometrial cancer. In our study, we detected one new tubal infiltrative carcinomas that was not seen by the classical method. As a result, the stage of these case was changed after the detection of the lesion. Culton *et al*. (13) reported synchronous endometrial and fallopian tube tumours in 13 cases. The sizes of the tumours ranged from 0.2 cm to 17.5 cm (14). Kulac and Usubutun (14) compared 100 fallopian tubes sampled by the classical method with 100 fallopian tubes with fimbrial end sampling and reported two invasive and two proliferative lesions that were not seen macroscopically. In our study, the sizes of the tubal lesions were 0.2 cm and 0.3 cm, and they were not detected macroscopically.

Culton *et al*. (13) reported seven of 13 lesions using fimbrial end sampling, and Kulac and Usubutun (14) identified three of four lesions using fimbrial end sampling. In our study

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the lesions was in the fimbrial end. Since tubal lesions can originate from lesions in the endometrium or endometrioid epithelium transformed from the tubal epithelium, studies on tubal lesions are important for determination of origin and pathogenesis of these tumour.

The majority of the non-uterine pelvic carcinomas are serous carcinomas that originate from the ovaries, fallopian tubes, or peritoneum. As non-uterine pelvic carcinomas have poor prognosis, the pathogenesis and origin should be well understood in order to develop new screening methods, new treatment modalities, and improved diagnosis at an early stage. STIC located in fimbria has been demonstrated as the origin of HGSC in recent studies (1-3).

In addition to serous carcinoma, clear cell and endometrioid carcinomas have been thought to originate from endometriotic foci that are assumed to occur through retrograde menstruation (1-3). In our study, we sampled the entire fallopian tubes, and STIC was shown in 2 of 4 cases with HGSCs. The rate was reported as 59%, 52%, and 20% in studies by Przybycin *et al*. (15), Kindelberg *et al*. (16), and Tang *et al*. (17), respectively. In our study, all the cases were ovarian origin and the percentages is 50%. Most lesions were located at the fimbrial end, and this finding is consistent with the other studies. No additional lesions in the fallopian tubes were detected in endometrioid and clear cell carcinoma cases sampled by the new technique. In non-uterine serous pelvic carcinomas sampled by the conventional method, STIC was not identified in one case with HGSC. There were no additional lesions in the tubes in the endometrioid or clear cell carcinoma cases.

Regarding the origin of SBT, Kurman *et al*. (4) reported that all ovarian and extraovarian low-grade serous proliferations originate from spilling and implantation of tubal epithelium in the form of PTH generated due to chronic inflammation. In their study, 20 of 22 cases (91%) with non-invasive and invasive implants were associated with PTH (4). Similarly, Robey and Silva (18) reported that 68% of SBT cases were associated with PTH. Kurman *et al*. (4) reported that PTH is mostly located in the ampulla; while the majority of lesions show a diffuse pattern, they can also be focal. Our study showed a lower percentage (75%) of cases demonstrating an association of PTH with SBT sampled by the new technique. This difference may be due to the smaller number of cases in our study.

The majority of focal lesions were located in the ampulla and infundibulum. The pathogenesis of endometriosis and its association with malignancies remain interesting topics of gynecopathology (19,20). Endometrial tissue can be physiologically seen in the isthmus,

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but there is no enough data on the involvement of other areas. In 592 fallopian tubes sampled by the new technique, we identified 14 endometriotic foci (2%). However, it was not shown in any of the fallopian tubes sampled by the classical method. Adenomatoid tumours are the most common benign neoplasm of the fallopian tubes. Their neoplastic potential and the fact that they can be misdiagnosed as other malignant or benign neoplasms should be considered during the management of these tumours (21). In our study, although we did not detect adenomatoid tumor by the classical method, four adenomatoid tumours were identified by the new technique.

CONCLUSION

There is a chance of misdiagnosing the benign lesions, premalignant lesions, and malignant lesions using the classical method in pathological examination of the fallopian tubes. For this reason, the SEE-FIM protocol should be considered in cases of endometrial cancers, non-uterine pelvic serous cancers, or serous borderline ovarian tumours. The SEE-FIM protocol seems to have advantages for sampling of the entire fallopian tube. However, it may increase the surgical workload if it is used for all routine salpingectomy specimens. For cases with other benign, premalignant, and malignant lesions, at least a detailed examination of the fimbrial end of the fallopian tubes should be undertaken.

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