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ORIGINAL ARTICLE

Evaluation of SEE-FIM (Sectioning and Extensively Examining the FIMbriated End) Protocol in Identifying Fallopian Tube Precursor Lesions in Women with Ovarian Tumors

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About the Author

Dr. Swati Arora has been a sincere and hardworking student. She has put superlative efforts in this study. Throughout the research period, she has shown her dedication and interest toward the study. Her work can be seen in other publications, which includes an original article published in a renowned international journal and two case reports published in indexed journals. During her post graduation period also, she was keen and curious to learn new things. She possesses good communication skills. Her clinical knowledge was also commendable. She also holds quality of being skeptical.

Abstract

Background Studies of prophylactic salpingo-oophorectomies in high-risk population led to incidental finding of precursor lesions in the fimbrial end of fallopian tube rather than the ovary. Early detection of these precursor lesions can be helpful in the prevention of ovarian tumors, and the presence of these lesions can be more efficiently studied by applying Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) protocol.

Aim To study precursor lesions of fallopian tubes associated with ovarian tumors by applying SEE-FIM protocol.

Materials and methods Sixty specimens of hysterectomy with bilateral salpingo-oophorectomy, clinically diagnosed as ovarian tumor (study group), were examined by SEE-FIM protocol. Specimens without ovarian tumor were taken as the control group, and same protocol was applied on them. Histological changes in fallopian tube were grouped either as tubal intraepithelial carcinoma (TIC), tubal intraepithelial lesion (TIL), only stratification and negative for any changes.

Results Out of 60 cases in the study group, 10.00% (6/60) cases showed TIC, 38.34% (23/60) cases revealed TIL, 23.33% (14/60) cases showed changes of stratification and the rest were negative for any changes. Among these 60 cases,

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there were 7 cases of high-grade serous carcinoma, 5 (71.43%) of them showed changes of TIC. In the control group, out of 60 cases, none showed TIC changes, TIL was noted in 6.66% (4/60) cases, changes of stratification were seen in 26.67% (16/60) cases and the rest were negative for any changes.
Conclusion SEE-FIM protocol maximizes the examination of fimbrial end and is helpful in identifying precursor lesions of ovarian epithelial tumors.

Keywords SEE-FIM protocol · Fimbrial end · Ovarian tumors · TIC

Introduction

Ovarian cancer is one of the leading causes of death due to gynecologic malignancies and the fifth most common cause of cancer deaths in women. Five year survival rate is greater than 95% for stage I tumors, in contrast to 15–30% for advanced stage disease with spread beyond the ovary (stage III/IV) [1].

Unfortunately, the majority of women with ovarian cancer, including those with the most common subtype high-grade serous carcinoma (HGSC), are diagnosed at an advanced stage. This could be attributed to the lack of effective screening tools for early detection of ovarian cancer in high-risk and general populations [2].

Serous carcinomas are the most lethal form of pelvic epithelial cancers due to their propensity for serosal organ involvement and rapid peritoneal spread. Studies of prophylactic salpingo-oophorectomies in women with BRCA1/2 mutation have identified the fallopian tube as a source of early serous carcinoma [3].

This study was carried out to know the histological changes in fallopian tubes associated with ovarian tumors by applying SEE-FIM (Sectioning and Extensively Examining the FIMbriated end) protocol and thus aimed at identification of precursor lesions that could be useful for early detection and prevention of these carcinomas.

Materials and Methods

Source of Data

The present study included specimens of hysterectomy with bilateral salpingo-oophorectomy received at the histopathology section, Department of Pathology, BLDEU'S Shri B.M Patil Medical College, Hospital and Research Centre, Vijayapur.

Duration of the study was 1 year and 8 months from November 1, 2013, to June 30, 2015.

Patients who underwent hysterectomy with bilateral salpingo-oophorectomy having clinical diagnosis of ovarian tumor, which turned out to be surface epithelial tumors (benign, borderline and malignant serous/mucinous/endometrioid/clear cell/Brenner tumor), were included in the study, whereas ovarian tumors which, on histopathology, turned out to be germ cell tumors, sex cord stromal tumors and metastatic tumors and also ovarian tumors coexistent with primary fallopian tubal/breast/endometrial and cervical tumors were excluded from the study.

Methods of Collection of Data

All patients who underwent hysterectomies with bilateral salpingo-oophorectomy having clinical diagnosis of ovarian tumor (*study group*), received in histopathology section at Department of Pathology, were included in the study.

Specimens of hysterectomy with bilateral salpingo-oophorectomy, done for other indications apart from ovarian tumor, were taken as the *control group*.

In all these cases, detailed examination of fallopian tubes was done by applying *SEE-FIM protocol*. This protocol entailed amputation of each fimbria at the infundibulum, longitudinal sectioning of the fimbria to allow maximal exposure of them and extensive cross-sectioning of the remainder of the tube at 2–3-mm intervals (Figs. 1, 2, 3).

Sections were placed in labeled cassettes, tissue processing and embedding in paraffin blocks was done, and sections of 3–5 micron thickness were prepared, which were stained with routine hematoxylin & eosin (H&E).

Detailed examination of bilateral fallopian tubes was done and classified according to the following group of changes:

- Tubal intraepithelial carcinoma (TIC)—in this entity, entire epithelium is replaced by malignant cells.

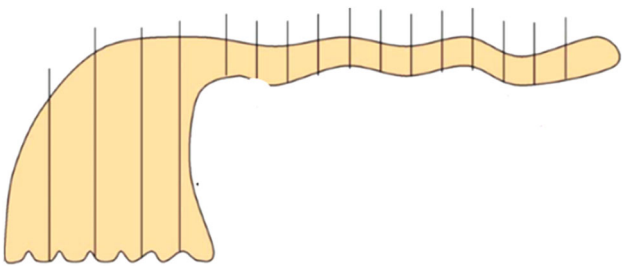

Fig. 1 Protocol for Sectioning and Extensively Examining the FIMbriated End (SEE-FIM) of the fallopian Tube [4]

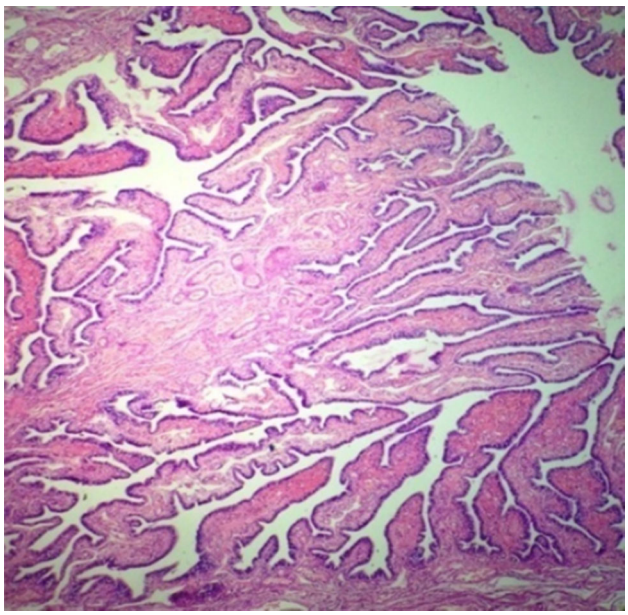

Fig. 2 Photomicrograph of fallopian tube, grossed according to SEE-FIM protocol (H&E stain ×40)

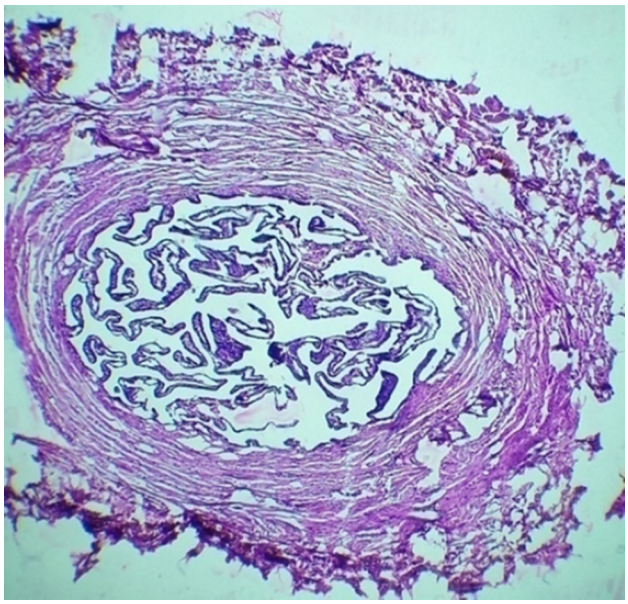

Fig. 3 Photomicrograph of cross section of fallopian tube (H&E stain ×40)

- Tubal intraepithelial lesion (TIL)—includes stratification with nuclear hyperchromasia, overcrowding and mild atypia.
- Only stratification
- Negative for any changes

Histological changes in bilateral fallopian tubes were noted, and overall change was assigned based on the higher morphological feature. Usefulness of SEE-FIM protocol in identifying fallopian tube precursor lesions was evaluated.

Table 1 IHC Scoring

Percentage of stained cells (%)	Score
0	0
1–10	1
10–50	2
50–100	3

Immunohistochemical staining for Ki67 and p53 was performed on the samples of fallopian tube tissue in the cases where histopathological diagnosis of TIC has been made. Scoring was done according to the percentage of the cells stained as shown in Table 1 [5].

Cases with either moderate to strong expression of p53 in $> 75\%$ of the cells or complete absence of p53 staining (0% cells stained) in foci of histological atypia and with high Ki67 staining regions ($\geq$ 10% positively stained cells) were categorized as STIC [6].

Statistical Analysis

Data were analyzed using percentage of various histological changes and diagrammatic presentation.

Results

In the present study, the age range of the study group was 25–70 years and of control group was 28–61 years. Mean age of women with ovarian tumor was 44 years, and median age was 45 years. Mean and median age for ovarian carcinoma was 51 and 48 years, respectively. Mean age of women with HGSC was 51 years.

In the present study, there were 51 cases of benign ovarian tumors (36 benign serous cystadenoma, 3 benign serous cystadenofibroma, 10 benign mucinous tumor and 2 benign Brenner tumor), 1 case of borderline ovarian tumor and 8 cases of malignant ovarian tumor (7 cases of serous carcinoma and 1 case of bilateral mucinous carcinoma). The 7 cases of ovarian serous carcinoma (3 involving right ovary, 1 in left ovary and 3 cases bilateral) were graded as low or high grade depending on the nuclear atypia and mitotic rate, and it was found that all the serous carcinoma cases belonged to the high grade.

Out of the total 60 cases of ovarian tumors, 6 (**10.00%**) cases showed changes of TIC in fallopian tubes; 3 were in ipsilateral side and 3 were bilateral (Figs. 4, 5, 6), 23 (38.34%) cases revealed TIL (Fig. 7), 14 cases (23.33%)

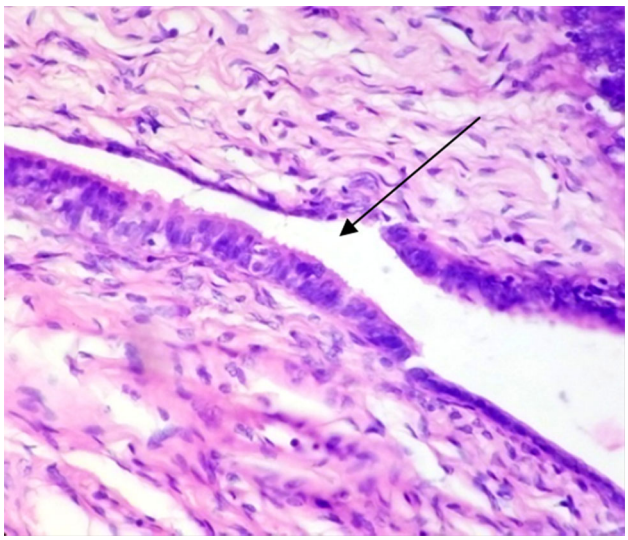

Fig. 4 Photomicrograph of TIC, showing nuclear stratification, overcrowding and atypia (H&E stain ×100)

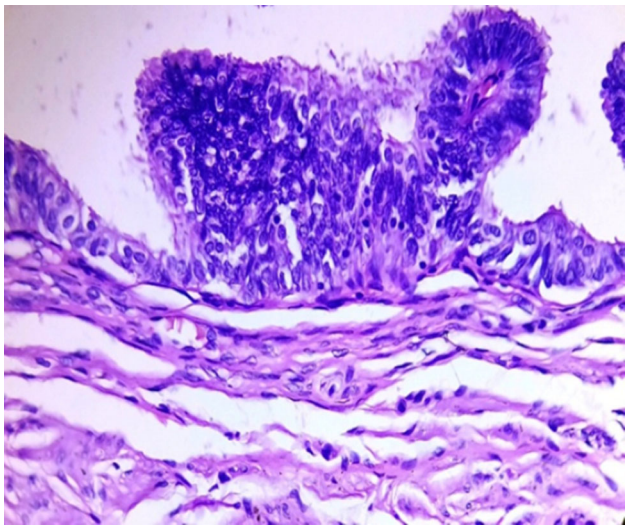

Fig. 5 Photomicrograph of TIC, showing nuclear overcrowding, stratification, loss of polarity and prominent nucleoli (H&E stain ×400)

showed changes of stratification, and 17 (28.33%) were negative for any changes in the tubes (Table 2). Among the 51 cases of benign tumors, none of them had TIC in their tubes. Only one case of borderline tumor was there in our study which was also not positive for TIC. Malignant ovarian tumors were 8 in number, and out of them, 6 (5 HGSC and 1 mucinous adenocarcinoma) were positive for TIC in respective tubes (Table 3).

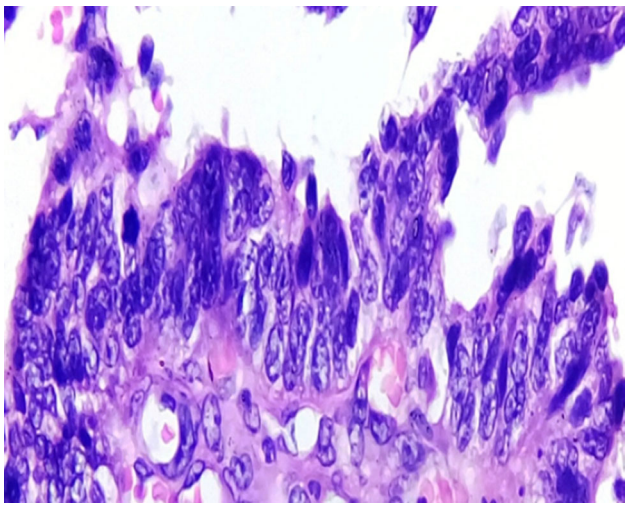

Fig. 6 Photomicrograph of TIC, showing nuclear stratification and hyperchromasia with loss of polarity (H&E stain ×400)

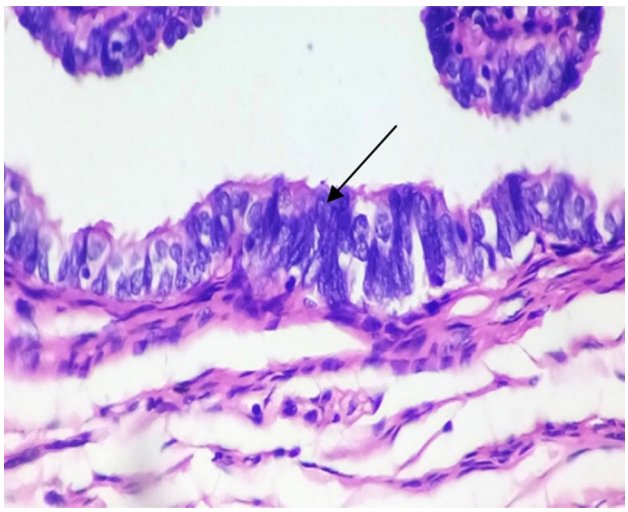

Fig. 7 Photomicrograph of TIL, showing nuclear stratification and mild atypia (H&E stain ×400)

Results of Immunohistochemistry (IHC)

IHC staining for p53 and Ki67 was done in the 6 cases where histopathological diagnosis of TIC was made (Figs. 8, 9). Table 4 shows the scores of IHC staining.

Histological changes in bilateral fallopian tubes were also studied in specimens without ovarian tumor (control group). Indications for bilateral salpingo-oophorectomy in these specimens were fibroid, DUB, PID, chronic cervicitis, bleeding PV, endometrial hyperplasia/carcinoma, carcinoma cervix. Histological changes of TIC were not seen in any of the 60 cases in the control group. In total, 4 cases showed TIL, which were noted in cases where bilateral

Table 2 Distribution of changes in study group

Sl. no.	Changes seen	No. of cases	Percentage (%)
1	TIC	6	10.00
2	TIL	23	38.34
3	Only stratification	14	23.33
4	Negative for any changes	17	28.33
	Total	60	100

Table 3 Distribution of TIC in ovarian tumors

Tumors	No. of cases	TIC positive cases
Benign	51	0
Borderline	1	0
Malignant	8	6
Total	60	6

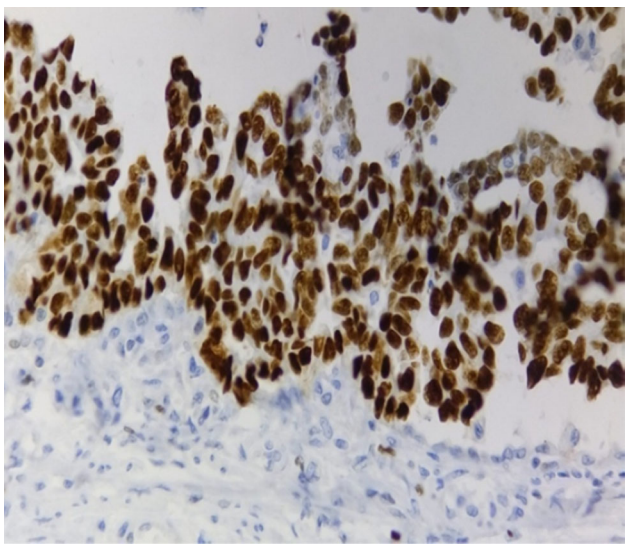

Fig. 8 Photomicrograph of fallopian tube showing p53 positivity in $> 75\%$ of the cells, score = 3. ($\times$400)

salpingo-oophorectomy was done because of PID and fibroid. Stratification change was noted in 16 cases, and the rest of the cases (40 cases) had no changes in their fallopian tubes (Table 5).

Discussion

Ovarian cancer is the most lethal gynecological cancer, with the commonest subgroup being epithelial ovarian carcinomas (EOCs). Examination of prophylactic salpingo-oophorectomy specimens in BRCA mutation carriers

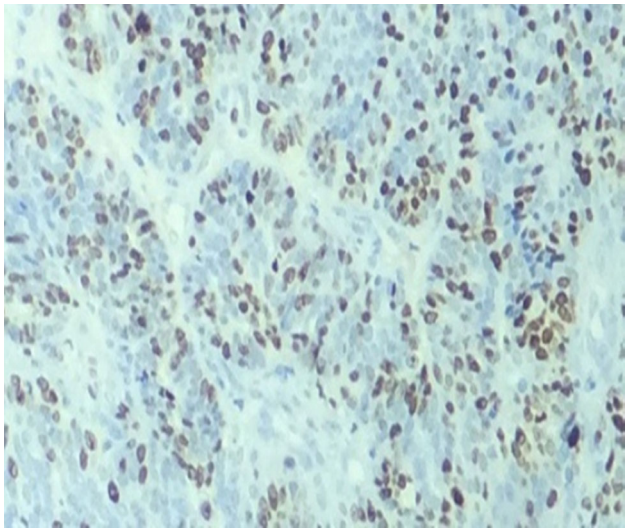

Fig. 9 Photomicrograph of fallopian tube showing positivity for MIB-1(Ki67) in $> 10\%$ of the cells, score = 2. ($\times$100)

Table 4 Scores of IHC staining

Sl. no.	CASES (HPR no.)	Scoring for p53	Scoring for Ki67
1	1826/14	3	2
2	2886/14	3	2
3	4047/14	3	2
4	416/15	3	2
5	1300/15	3	2
6	1585/15	3	3

revealed precursor lesions in the form of early serous malignancies (STICs) in fallopian tube, rather than involving the ovarian surface or within ovarian cortical inclusion cysts [2]. These unexpected findings in high-risk women led to the development of a specialized protocol; SEE-FIM protocol, which was found to be helpful in identifying the occult tubal lesions [7].

In the present study, 60 specimens of hysterectomy with bilateral salpingo-oophorectomy were evaluated for the presence of tubal changes in the study and control groups. Out of 60 cases in the study group, TIC was observed in 10.00% (6/60) cases, TIL in 38.34% (23/60) cases, changes of stratification seen in 23.33% (14/60) of the cases, and 28.33% (17/60) were negative for any changes in the tubes. There were 7 cases of HGSC, and 5 (71.43%) of them showed TIC and the rest 2 showed TIL. Kindelberger et al. [3] found STIC in 66.67% and Przybycin et al. [8] in 60.61% of the HGSC cases. Mingles et al. [9] found STIC in 42.59% cases, Tang et al. [10] found 18.75% cases and

Table 5 Distribution of changes according to the indications for BSO in the control group

Sl. no.	Indication for bilateral salpingo-oophorectomy	Tubal changes				Total
		TIC	TIL	Only stratification	Negative for any changes	
1	Fibroid, fibroid with PID/DUB	0	3	3	12	18
2	PID	0	1	5	14	20
3	DUB, DUB with adenomyosis	0	0	4	8	12
4	Chronic cervicitis	0	0	2	2	4
5	Bleeding PV	0	0	0	2	2
6	Endometrial hyperplasia/carcinoma	0	0	2	1	3
7	Carcinoma cervix	0	0	0	1	1
	Total (%)	0 (0.00%)	4 (6.66%)	16(26.67%)	40 (66.67%)	60 (100%)

Table 6 Percentage (%) of STIC in various studies

Studies	Study population	No. of cases of ovarian serous carcinoma	No. of cases of STIC	Percentage (%) of STIC in serous carcinoma cases (%)
Kindelberger et al. [3]	55	30	20	66.67
Przybycin et al. [8]	37	33	20	60.61
Mingles et al. [9]	54	54	23	42.59
Tang et al. [10]	46	32	6	18.75
Maeda et al. [11]	52	12	6	50.00
Present study	60	7	5	71.43

Maeda et al. [11] found STIC in 50.00% of the cases (Table 6).

There were no changes of STIC in borderline serous tumor cases as observed in our study which is in concordance with the study by Tang et al. [10]

In the present study, we found one case of mucinous adenocarcinoma, which showed changes of TIC in the tubes. Studies done by Przybycin et al. [8] and Maeda et al. [11] obtained 1 and 3 cases of mucinous carcinoma, respectively, but the tubes did not harbor TIC in both the studies.

In the present study, 60 cases of hysterectomy with bilateral salpingo-oophorectomy, done for indications apart from ovarian tumor, were taken as the *control group* and same protocol was applied on them. But none of the cases showed changes of TIC.

However, four cases in the control group were harboring changes of TIL and 16 cases harboring changes of stratification.

This can be attributed to factors like inflammation, menstruation, ovulation, OCP use, breastfeeding and parity. All these factors have an impact on the microenvironment of fallopian tube leading to the above-mentioned histological changes [1].

In conclusion, despite the location of surface epithelial tumors in the ovaries, the precursor lesions have never been identified in the ovarian tissue. In fact, examination of salpingo-oophorectomy specimens in high-risk women revealed precursor lesions in the fimbrial end of fallopian tube, namely serous tubal intraepithelial carcinoma (STIC). On this discovery, SEE-FIM protocol was designed, which entailed on increasing the surface area of the fimbria available for examination and thus increase the possibility of detecting the precursor lesions.

In the present study, we evaluated this protocol to identify the precursor lesions and observed that **10.00%** (6/60 cases) of the ovarian tumors harbored TIC and **71.43%** (5/7 cases) of the HGSC had STIC.

The changes noted in the fimbrial end of the fallopian tube, in cases of ovarian epithelial tumors, were possible because of strict adherence to SEE-FIM protocol, which helped in evaluation of the tube for the presence of various precursor lesions especially in the fimbrial end.

The data implicating fimbrial end of fallopian tube as the site of origin of high-grade serous carcinoma are further a proof of usefulness of SEE-FIM protocol in identifying fallopian tube precursor lesions in women with ovarian epithelial tumors and its therapeutic use in early detection, treatment and prevention of this highly lethal disease.

Compliance with Ethical Standards

Conflict of interest Authors have no conflict of interest to declare.

Ethical Statement This is a research involving human participants. Ethical clearance certification was taken from the authorized body.

References

1. Tone AA, Salvador S, Finlayson SJ, et al. The role of the fallopian tube in ovarian cancer. Clin Adv Hematol Oncol. 2012;10:296–306.
2. Li J, Fadare O, Xiang L, Kong B, Zheng W. Ovarian serous carcinoma: recent concepts on its origin and carcinogenesis. J Hematol Oncol [Internet]. 2012 [cited 2015 Oct 8];5:1–11. Available from: http://www.jhoonline.org/content/5/1/8. Accessed 8 Oct 2015.
3. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: evidence for a causal relationship. Am J Surg Pathol. 2007;31:161–9.
4. Crum CP, Drapkin R, Miron A, et al. The distal fallopian tube: a new model for pelvic serous carcinogenesis. Curr Opin Obstet Gynecol. 2007;19:3–9.
5. Giurgea LN, Ungureanu C, Mihailovici MS. The immunohistochemical expression of p53 and Ki67 in ovarian epithelial borderline tumors. Correlation with clinicopathological factors. Rom J Morphol Embryol. 2012;53:967–73.
6. Visvanathan K, Vang R, Shaw P, et al. Diagnosis of serous tubal intraepithelial carcinoma based on morphologic and immunohistochemical features: a reproducibility study. Am J Surg Pathol. 2011;35:1766–75.
7. Kurman RJ, Shih IM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—shifting the paradigm. Hum Pathol. 2011;42:918–31.
8. Przybycin CG, Kurman RJ, Ronnett BM, et al. Are all pelvic (nonuterine) serous carcinomas of tubal origin? Am J Surg Pathol. 2010;34:1407–16.
9. Mingels MJJM, Ham MA, Kievit IM, et al. Mullerian precursor lesions in serous ovarian cancer patients: using the SEE-Fim and SEE-End protocol. Mod Pathol. 2014;27:1002–13.
10. Tang S, Onuma K, Deb P, et al. Frequency of serous tubal intraepithelial carcinoma in various gynecologic malignancies: a study of 300 consecutive cases. Int J Gynecol Pathol. 2012;31:103–10.
11. Maeda D, Ota S, Takazawa Y, et al. Mucosal carcinoma of the fallopian tube coexists with ovarian cancer of serous subtype only: a study of Japanese cases. Virchows Arch. 2010;457:597–608.