Bilateral serous tubal intraepithelial carcinoma associated with high-grade serous carcinoma of the peritoneum: evidence for transcoelomic tumor spread by extended lymph node evaluation

Hermann Brustmann, MD, PhD[1]

Keywords: High-grade serous carcinoma, serous tubal intraepithelial carcinoma, STIC, intraluminal exfoliation, peritoneum, transcoelomic spread, pelvic lymph nodes

Abstract

Serous tubal intraepithelial carcinoma (STIC) is now considered a putative precursor lesion of most extrauterine high-grade serous carcinomas (HGSC). It is frequently reported in high-risk women and women with advanced-stage serous carcinoma. This case study reports a serous high-grade carcinoma (HGSC) consisting of a bilateral STIC with a focus of stromal invasion in the left tube, and a peritoneal HGSC. The grossly normal-appearing tubes including the fimbriated ends were sectioned following the SEE-FIM protocol. In both tubes, tumor aggregates were exfoliated extensively to the tubal lumens. The neoplastic epithelia in any location were diffusely positive for p53 in strong nuclear patterns. Pelvic lymph nodes were negative for tumor on serial sections and keratin 7 immunohistochemistry, and there was no evidence of lymphatic vessel involvement. The lack of any evidence of lymphovascular invasion and regional lymph node metastases supports the interpretation of intraluminal and transcoelomic spread, and may be taken as evidence of dissemination of tubal neoplastic cells by exfoliation in this case. The biology of transcoelomic spread is reviewed in this manuscript.

[1]Department of Pathology, Landesklinikum Baden-Moedling, Austria

Introduction

Recently, attention has been drawn to the junction between the fimbrial mucosa and the tubal serosa as well as to the junction between the fimbrial mucosa and the ovarian surface epithelium as the location of origin of some forms of epithelial ovarian cancer.[1-3] Serous tubal intraepithelial carcinoma (STIC) has been identified in the fallopian tubes of prophylactic salpingo-oophorectomies of BRCA mutation carriers with a predilection for the fimbriae in about 90% of cases.[2,4] STIC is now considered a putative precursor lesion of most extrauterine high-grade serous carcinomas (HGSC). It is frequently reported in high-risk women and women with advanced-

Please cite this paper as: Brustmann, H.. Bilateral serous tubal intraepithelial carcinoma associated with high-grade serous carcinoma of the peritoneum: evidence for transcoelomic tumor spread by extended lymph node evaluation. POG in Press. 2018 December; Article 3 [10 p.]. Available from: https://ir.uiowa.edu/pog_in_press/ Free full text article.

Corresponding author: *Dr. Hermann Brustmann, Department of Pathology, Landesklinikum Baden-Moedling, Waltersdorfer Straße 75, A-2500 Baden, Austria. Tel: +43-2252-9004-14700, Fax: +43-2252-9004-49355; e-mail: ddrbrustmann@hotmail.com, alternative e-mail: hermann.brustmann@baden.lknoe.at .*

Financial Disclosure*: The authors report no conflict of interest.*

Copyright: © 2018 Brustmann. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

stage serous carcinoma.[5,6]

This case study reports HGSC associated with a bilateral STIC at the fimbrial ends and infundibular regions of the fallopian tubes, and local stromal invasion in the left tube, with a primary presentation with ascites and consequent peritoneal biopsy showing peritoneal HGSC, followed by Wertheim´s operation including pelvic lymphadenectomy. Extensively examined pelvic lymph nodes were negative for tumor, and there was no evidence of lymphatic vessel involvement. Thus, this case may provide evidence for a contiguous spread of tumor cells from a STIC by exfoliation and transcoelomic spread to the peritoneal surface.

Case Report

A 42 year old woman presented with increasing abdominal circumference lasting for five days. She complained of flank pain and hematuria. Her familial history was unremarkable. She was para 2, had a tubal ligation 15 years ago, was postmenopausal for four years and was treated for adnexitis three months prior. Serologically, inflammatory parameters were elevated. On physical examination, transvaginal ultrasound showed moderate free fluid in the abdominal cavity, but uterus and adnexa were unremarkable. The value of CA125 was elevated to 682.1 kU/L.

On computed tomography, nodular consolidations of the omentum were noted. There were no signs of bulky lymphadenopathy. Diagnostic paracentesis yielded bloody fluid. On cytological examination, three dimensional papillary clusters with significant nuclear polymorphism, hyperchromasia, and nucleoli were noted. The nuclei were placed eccentrically in the cytoplasm which showed some vacuolization. These findings were interpreted as malignant cells consistent with a papillary serous adenocarcinoma, a primary lesion of the peritoneum or the female genital tract. A subsequent core biopsy of the omental mass revealed HGSC. On immunohistochemistry, the tumor was strongly positive for WT1 and p53, consistent with a tubo-ovarian or peritoneal primary. A diagnostic laparoscopy followed by subsequent laparotomy was performed. The abdominal situs revealed a greater omentum abnormally thickened by grayish white tumor masses in diffuse and nodular configurations, consistent with an omental cake, while small stipple-like tumor deposits were seen on the bladder peritoneum. Uterus, ovaries and fallopian tubes were grossly unremarkable. A frozen section from the omental biopsy confirmed the previously diagnosed HGSC. The surgical report noted no infiltration of the omental tumor into the greater curvature of the stomach or transverse colon, and the omental cake was resected completely. There was no tumor involvement noted in the liver or spleen. The preliminary surgical diagnosis was suspicious for a primary peritoneal carcinoma. Peritoneal lavage yielded carcinoma cells. Surgical therapy included hysterectomy, bilateral salpingo-oophorectomy, and resection of the omentum majus and the peritoneal tumor deposits as well as pelvic lymphadenectomy. The latter was done for optimal staging since the site of the primary tumor was uncertain prior to surgery, and there was no evidence of

suspicious lymph nodes from either surgery or imaging. No visible tumor was left at the end of the operation. The patient gave written consent to the use of her case for this study.

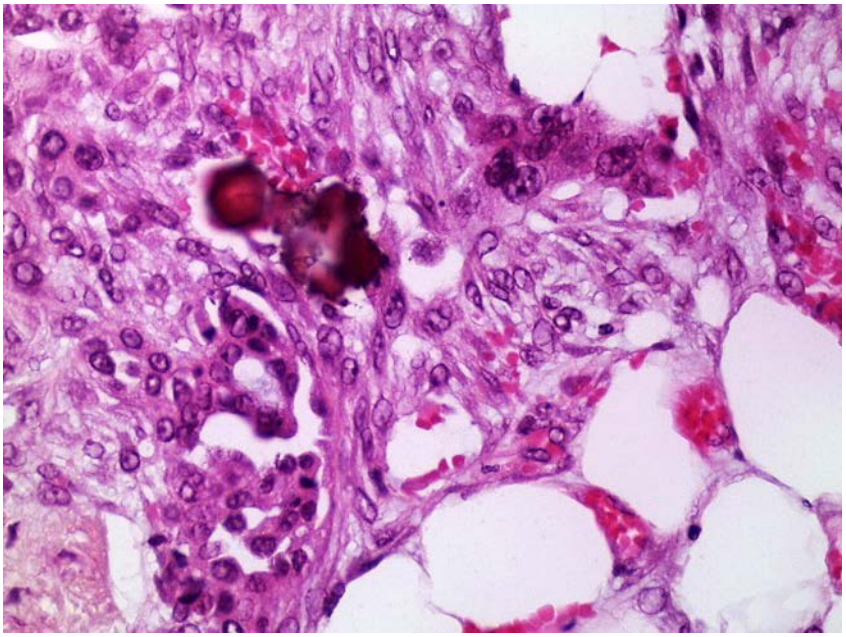

Figure 1.

Histologically, the omental tumor displayed a mixed architecture of solid nests, abortive tubuli, and papillary structures associated with occasional psammoma bodies (Figure 1). Small tumor nests were noted in optically clear spaces, consistent with micropapillary growth patterns. Areas of hemorrhagic tumor necrosis as well as an interstitial round cell inflammatory infiltrate were seen. There was high-grade nuclear pleomorphism, with variation in size. The nuclear chromatin was coarse with patchy nuclear clearings. Large nucleoli were observed frequently. There was no evidence of mucin as demonstrated by PAS-Alcian stain. Immunohistochemically, the tumor was diffusely positive for cytokeratin 7, p53 in strong diffuse nuclear patterns, and p16. The tumor cells were immunonegative for cytokeratin 20, calretinin, estrogen receptor, CEA, and TTF1. The rate of proliferation by Ki-67 was at 80%. Mitoses with frequently atypical configurations were a common finding, with about 40 figures in 10 high power fields (X400), as were apoptotic bodies. Small tumor deposits were noted at the uterine and fallopian tube serosa bilaterally. PAX8 immunostaining showed typical nuclear reactivity of the omental lesion as well as the STICs. Since morphology and immunoprofiles of the STICs, omental and peritoneal lesions were consistent with serous high grade neoplasia, no further immunostains were performed (e.g.,

SATB2 for colorectal carcinoma which is CD20 positive in the vast majority of cases)

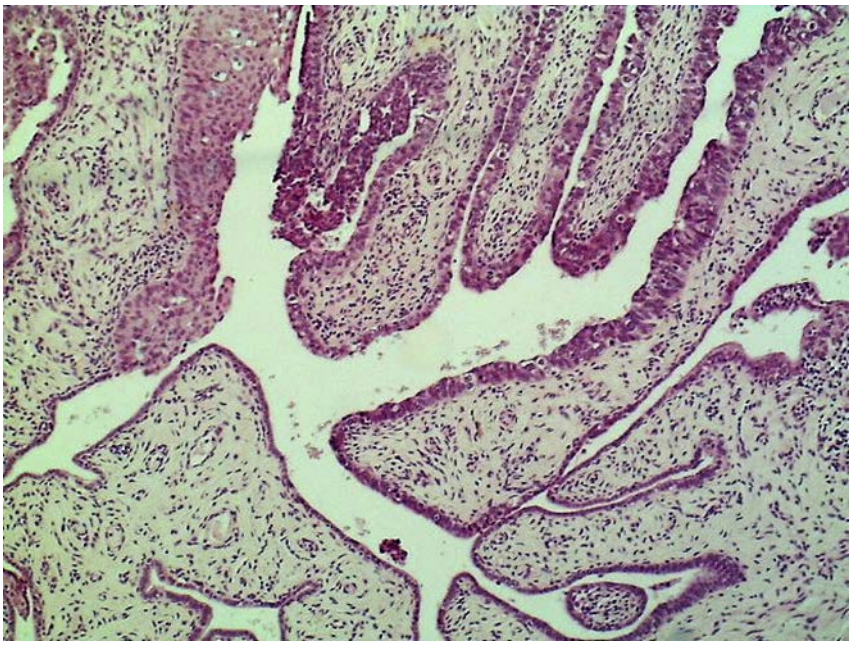

Figure 2.

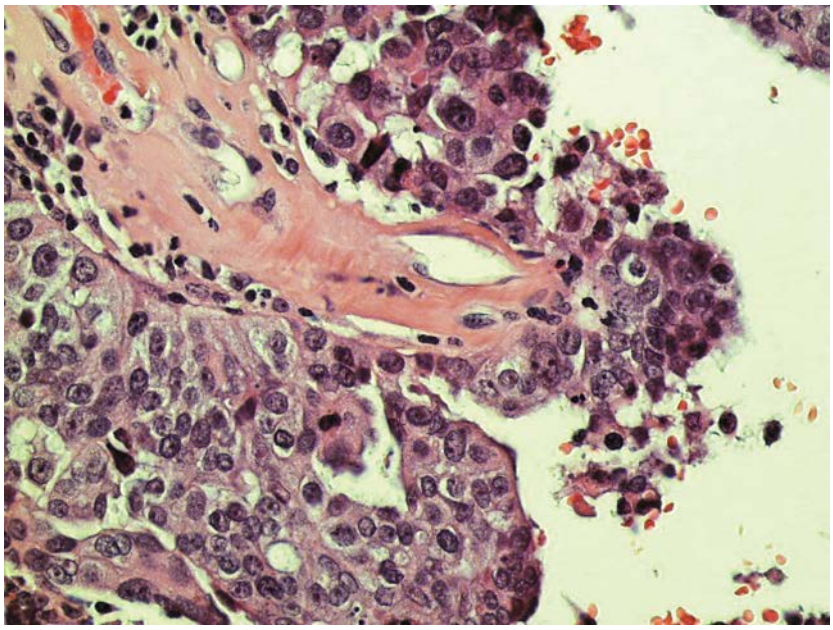

Figure 3.

The normal- appearing tubes, including the fimbriated ends, were sectioned extensively following the SEE-FIM protocol.[7] Both tubes were embedded completely; the fimbriated ends were sectioned longitudinally. Cross sections of the tubes were cut at approximately 3 mm intervals along the horizontal axis, the fimbriated ends were amputated and sectioned parallel to the long axis at 2 mm intervals. Histologically, the tubal mucosa was unremarkable in most of the slides. However, neoplastic proliferations were observed at the infundibular regions and the fimbrial ends of both tubes. These epithelia were characterized by marked nuclear atypia with hyperchromasia, irregular outlines, increased size, exhibited stratification and crowding, loss of polarity, tufting, papillary growth patterns, and high nuclear-to-cytoplasmic ratios (Figures 2,3). They appeared comparable to the above described tumor masses morphologically as well as immunohistochemically by the antibodies described above. In particular, there was diffuse and strong nuclear p53 expression and Ki67 indices were high (Figure 4).

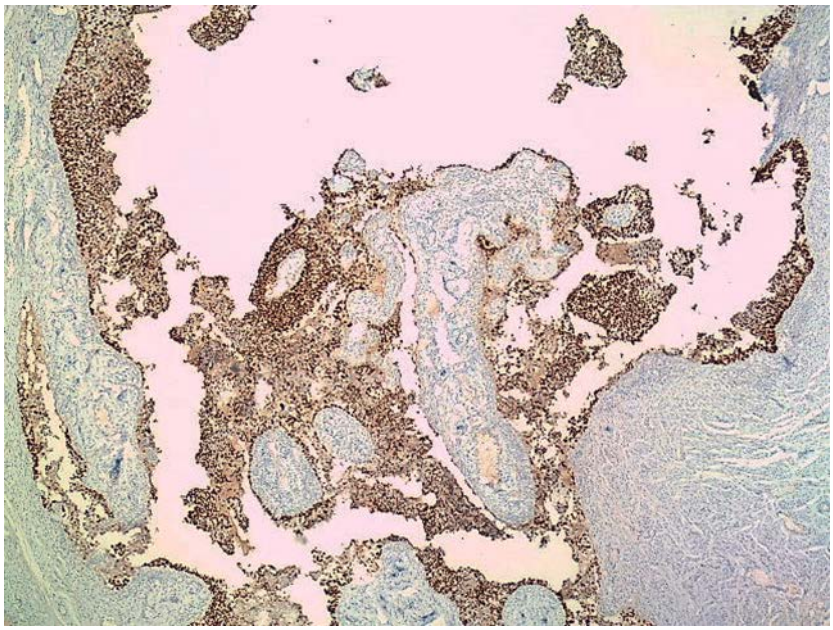

Figure 4.

Occasional psammoma bodies were noted. In the infundibulum of the left tube, a small neoplastic focus of about 1mm diameter infiltrated into the tubal lamina propria. In both tubes, tumor aggregates were detached to the tubal lumens extensively (Figures 4,5).

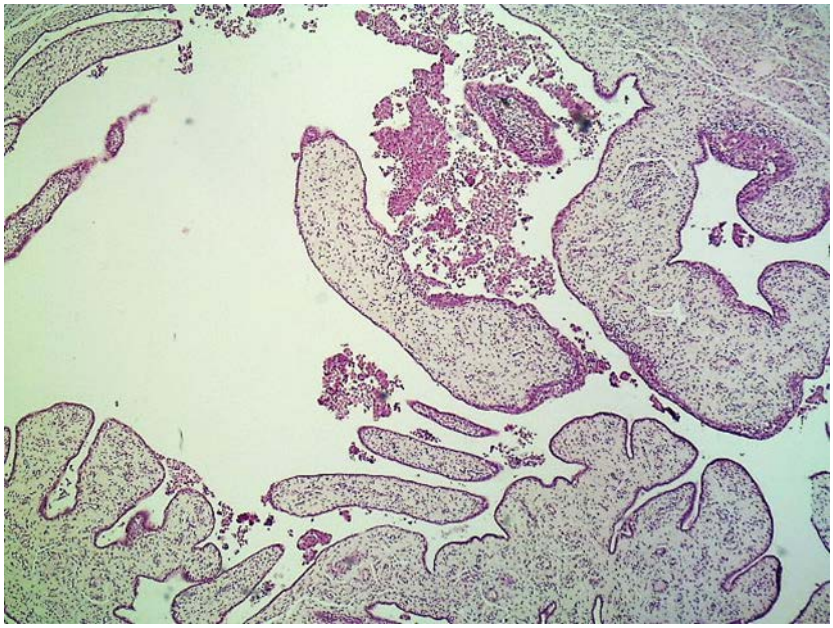

Figure 5.

There was no evidence of lymphovascular invasion, as confirmed by CD31 immunostaining, consistent with L/V0 for staging purposes. CD31 is a sensitive marker for vascular and lymphatic endothelia that is used routinely in our laboratory. Another option would be the use of D2-40, a specific and sensitive marker for just lymphatic endothelia. However, this antibody was not applied in this case since there was no evidence of involvement of any endothelial lined spaces by tumor cells. In total, 27 regional lymph nodes were submitted for histology, sectioned in 2 mm intervals, investigated in serial sections including cytokeratin 7 immunohistochemistry, and all were found to be free of tumor metastases, micrometastases, or isolated tumor cells. Additionally, the ovaries were microscopically free of tumor. A final diagnosis of a bilateral STIC associated with a unilateral focus of invasive tubal HGSC and peritoneal HGSC was rendered. The author interpreted these findings as consistent with a primary lesion in the fallopian tubes, and a stage of FIGO IIIC was assigned.

The patient received six cycles of chemotherapy (Taxol/Carboplatin/Avastin) and is on maintenance Avastin. There is no sign of tumor recurrence 25 months out from surgery.

Genetic testing was not performed secondary to financial concerns.

Discussion

The origin of most non uterine HGSC in the fallopian tubes due to germline BRCA 1/2 mutations is well recognized in the recent literature.[8] Additionally, sporadic cases of non-uterine HGSC have been shown to arise in the

fallopian tube fimbria in the majority of cases, providing further evidence for the tubal origin of these neoplasms.[8] To this end, the diagnostic potential of complete examination of the fallopian tubes to identify such STICs has been emphasized.[9]

This case study does not just add another case of STIC to the literature. Rather, it attempts to consider and discuss a bilateral STIC with unilateral tube wall infiltration and associated peritoneal HGSC, without evidence of lymphovascular space involvement and regional lymph node metastases. Foci of lamina propria infiltration in STIC cases have been recognized previously.[8] Bilateral STICs are mentioned in different studies.[8,10] However, bilaterality is observed in a minority of cases only. The question has been raised whether STIC could represent a secondary metastatic spread from nongynecologic sites. Rabban et al. reported on tumors metastasizing to the fallopian tube mucosa with a predominance of adenocarcinomas and most frequent primaries in the colon and breast, potentially resembling STIC.[11] Rare metastases originated from lymphomas, neuroendocrine carcinomas, and mesotheliomas. They pointed to a frequent expression of p53 as a potential diagnostic pitfall in such lesions. In the present case, the immunohistochemical, histochemical and morphologic profile as described above is consistent with a HGSC.

Bilateral tubal STIC with unilateral focally invasive HGSC associated with peritoneal disease also needs to be investigated for a mutual relationship. Kuhn et al. investigated *TP53* mutations in STIC and concurrent pelvic HGSC.[12] Their findings support a clonal relationship of these entities, and demonstrate the utility of p53 immunostaining as a surrogate for *TP53* mutation in the histological diagnosis of STIC. They emphasized the importance of appreciation of a diffuse strong staining that correlates with a missense mutation, whereas complete absence of staining correlates with null mutations. A positive staining was recorded by =60% of reactive nuclei. Important for the study at hand is the observation that multiple STICs were generally p53 positive.[12]

This case was finally interpreted as bilateral STIC with peritoneal metastatic spread. This decision was made based on previous studies. Kuhn et al. reported that the vast majority of STICs showed shortened telomeres, one of the earliest molecular changes in carcinogenesis.[13] The majority of corresponding HGSC showed longer telomeres. The authors interpreted these findings as a further support to the proposal that STICs are precursors of HGSC. Bashashati et al. found *TP53* to be the only somatic mutation consistently present in all samples of the HGSC that they investigated using spatial mutational profiling. They also noted that the fallopian tube lesion was ancestral based on phylogenetic mapping.[14] Based on *TP53* sequencing, Singh et al.[15] suggested that STIC can even metastasize to the contralateral adnexa without peritoneal involvement.

The spread of the tubal lesion in this case to the peritoneal surface and omentum majus needs further consideration. Tumor cell clusters of different sizes were noted in the lumina of both tubes. They appear as a result of

intraluminal shedding from the epithelial neoplasia, with the same immunohistochemical features as the latter and the omental tumor (p53, Ki67 indices). Bijron et al. previously reported that intraluminal shedding of STIC cells is common and a likely route of abdominal spread.[16] STIC, intraluminal tumor cells, and abdominal metastases displayed an identical immunohistochemical profile and *TP*53 mutation. While Bijron et al. only discussed STICs, the case at hand had a focus of invasive disease, leaving a possibility of lymphatic spread. However, the lack of any evidence of lymphovascular invasion and regional lymph node metastases supports the interpretation of transcoelomic spread of tubal neoplastic cells by exfoliation. Comprehensive lymph node examination is needed to exclude a lymphatic pathway of tumor spread. Other recent research has recommended surgical staging including lymphadenectomy in cases of STIC.[17] Nasser et al. considered lymphangiosis carcinomatosa and lymph node metastases as evidence of a STIC as precursor lesion in their case of peritoneal HGSC. Taken together, there is evidence for the possibility of several pathways for peritoneal spread in STIC.[18]

Conclusion

On the basis of the criteria and studies discussed above, this author made a pragmatic decision as to the primary site, as proposed previously.[16] The site of the primary lesion was assigned as tubal rather than peritoneal in the presence of a bilateral STIC and a locally invasive carcinoma in the absence of signs of lymphatic invasion, suggesting transcoelomic dissemination of metastasizing tumor cells. To the best of the author´s knowledge, this is the first report applying an extensive protocol to all investigated lymph nodes with serial sections and cytokeratin 7 immunohistochemistry to exclude evidence of lymphatic spread.

References

1. Auersperg N. The origin of ovarian carcinomas: a unifying hypothesis. Int J Gynecol Pathol. 2011 Jan;30(1):12-21. https://doi.org/10.1097/PGP.0b013e3181f45f3e PubMed PMID: 21131839.

2. Medeiros F, Muto MG, Lee Y, Elvin JA, Callahan MJ, Feltmate C, Garber JE, Cramer DW, Crum CP. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. Am J Surg Pathol. 2006 Feb;30(2):230-6. https://doi.org/10.1097/01.pas.0000180854.28831.77 PubMed PMID: 16434898.

3. Seidman JD, Zhao P, Yemelyanova A. "Primary peritoneal" high-grade serous carcinoma is very likely metastatic from serous tubal intraepithelial carcinoma: assessing the new paradigm of ovarian and pelvic serous carcinogenesis and its implications for screening for ovarian cancer. Gynecol Oncol. 2011 Mar;120(3):470-3. https://doi.org/10.1016/j.ygyno.2010.11.020 Epub 2010 Dec 14. PubMed PMID: 21159368.

4. Kindelberger DW, Lee Y, Miron A, Hirsch MS, Feltmate C, Medeiros F, Callahan MJ, Garner EO, Gordon RW, Birch C, Berkowitz RS, Muto MG, Crum CP. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. Am J Surg Pathol. 2007 Feb;31(2):161-9. https://doi.org/10.1097/01.pas.0000213335.40358.47 PubMed PMID: 17255760.

5. Vang R, Shih IeM, Kurman RJ. Fallopian tube precursors of ovarian low- and high-grade serous neoplasms. Histopathology. 2013 Jan;62(1):44-58. https://doi.org/10.1111/his.12046 PubMed PMID: 23240669.

6. Nik NN, Vang R, Shih IeM, Kurman RJ. Origin and pathogenesis of pelvic (ovarian, tubal, and primary peritoneal) serous carcinoma. Annu Rev Pathol. 2014;9:27-45. https://doi.org/10.1146/annurev-pathol-020712-163949 Epub 2013 Aug 5. PubMed PMID: 23937438.

7. Mingels MJ, van Ham MA, de Kievit IM, Snijders MP, van Tilborg AA, Bulten J, Massuger LF. Müllerian precursor lesions in serous ovarian cancer patients: using the SEE-Fim and SEE-End protocol. Mod Pathol. 2014 Jul;27(7):1002-13. https://doi.org/10.1038/modpathol.2013.212 Epub 2013 Dec 6. PubMed PMID: 24309326.

8. Gilks CB, Irving J, Köbel M, Lee C, Singh N, Wilkinson N, McCluggage WG. Incidental nonuterine high-grade serous carcinomas arise in the fallopian tube in most cases: further evidence for the tubal origin of high-grade serous carcinomas. Am J Surg Pathol. 2015 Mar;39(3):357-64. https://doi.org/10.1097/PAS.0000000000000353. PubMed PMID: 25517954.

9. Morrison JC, Blanco LZ Jr, Vang R, Ronnett BM. Incidental serous tubal intraepithelial carcinoma and early invasive serous carcinoma in the nonprophylactic setting: analysis of a case series. Am J Surg Pathol. 2015 Apr;39(4):442-53. https://doi.org/10.1097/PAS.0000000000000352 PubMed PMID: 25517955.

10. Przybycin CG, Kurman RJ, Ronnett BM, Shih IeM, Vang R. Are all pelvic (nonuterine) serous carcinomas of tubal origin? Am J Surg Pathol. 2010 Oct;34(10):1407-16. https://doi.org/10.1097/PAS.0b013e3181ef7b16 Erratum in: Am J Surg Pathol. 2010 Dec;34(12):1891. PubMed PMID: 20861711.

11. Rabban JT, Vohra P, Zaloudek CJ. Nongynecologic metastases to fallopian tube mucosa: a potential mimic of tubal high-grade serous carcinoma and benign tubal mucinous metaplasia or nonmucinous hyperplasia. Am J Surg Pathol. 2015 Jan;39(1):35-51. https://doi.org/10.1097/PAS.0000000000000293 Erratum in: Am J Surg Pathol. 2015 May;39(5):727. PubMed PMID: 25025442.

12. Kuhn E, Kurman RJ, Vang R, Sehdev AS, Han G, Soslow R, Wang TL, Shih IeM. TP53 mutations in serous tubal intraepithelial carcinoma and concurrent pelvic high-grade serous carcinoma--evidence supporting the clonal relationship of the two lesions. J Pathol. 2012 Feb;226(3):421-6. https://doi.org/10.1002/path.3023 Epub 2011 Dec 23. PubMed PMID: 21990067; PubMed Central PMCID: PMC4782784.

13. Kuhn E, Meeker A, Wang TL, Sehdev AS, Kurman RJ, Shih IeM. Shortened telomeres in serous tubal intraepithelial carcinoma: an early event in ovarian high-grade serous carcinogenesis. Am J Surg Pathol. 2010 Jun;34(6):829-36. https://doi.org/10.1097/PAS.0b013e3181dcede7 PubMed PMID: 20431479; PubMed Central PMCID: PMC4778420.

14. Bashashati A, Ha G, Tone A, Ding J, Prentice LM, Roth A, Rosner J, Shumansky K, Kalloger S, Senz J, Yang W, McConechy M, Melnyk N, Anglesio M, Luk MT, Tse K, Zeng T, Moore R, Zhao Y, Marra MA, Gilks B, Yip S, Huntsman DG, McAlpine JN, Shah SP. Distinct evolutionary trajectories of primary high-grade serous ovarian cancers revealed through spatial mutational profiling. J Pathol. 2013 Sep;231(1):21-34. https://doi.org/10.1002/path.4230 PubMed PMID: 23780408; PubMed Central PMCID: PMC3864404.

15. Singh N, Gilks CB, Wilkinson N, McCluggage WG. Assessment of a new system for primary site assignment in high-grade serous carcinoma of the fallopian tube, ovary, and peritoneum. Histopathology. 2015 Sep;67(3):331-7. https://doi.org/10.1111/his.12651 Epub 2015 Mar 31. PubMed PMID: 25640750.

16. Bijron JG, Seldenrijk CA, Zweemer RP, Lange JG, Verheijen RH, van Diest PJ. Fallopian tube intraluminal tumor spread from noninvasive precursor lesions: a novel metastatic route in early pelvic carcinogenesis. Am J Surg Pathol. 2013 Aug;37(8):1123-30. https://doi.org/10.1097/PAS.0b013e318282da7f PubMed PMID: 23648462.

17. Schneider S, Heikaus S, Harter P, Heitz F, Grimm C, Ataseven B, Prader S, Kurzeder C, Ebel T, Traut A, du Bois A. Serous Tubal Intraepithelial Carcinoma Associated With Extraovarian Metastases. Int J Gynecol Cancer. 2017 Mar;27(3):444-451. https://doi.org/10.1097/IGC.0000000000000920 PubMed PMID: 28187099.

18. Nasser S, Arsenic R, Lohneis P, Kosian P, Sehouli J. A case of primary peritoneal carcinoma: evidence for a precursor in the fallopian tube. Anticancer Res. 2014 Jan;34(1):407-12. PubMed PMID: 24403495.