Relapsed ovarian high-grade serous carcinoma with long-term survival associated with synchronous primary squamous cell carcinoma of the colon

Karla Sladoljev,[1] Ena Perin,[1] Ani Mihaljević Ferrari,[2] Marko Klarić,[3] Alemka Brnčić-Fischer,[3] Senija Eminović,[4] Danijela Vrdoljak-Mozetič,[5] Emina Babarovic[6]

Keywords: High-grade serous ovarian cancer (HGSOC), recurrence, squamous cell carcinoma (SCC) of the colon, immunohistochemistry, treatment

Abstract

High-grade serous ovarian cancer (HGSOC) is the most common and also the most aggressive subtype of ovarian cancer while squamous cell carcinoma (SCC) of the colon is an extremely rare histologic subtype of all colonic malignancies with poor prognosis.

Here we report a unique case of synchronous primary SCC of the colon and second recurrence of HGSOC in a patient with 15-years survival. Our patient developed two recurrent HGSOCs with disease-free survival time of five and nine years, respectively. The second recurrence of HGSOC was associated with the synchronous primary SCC of the ascending colon and was further complicated with the patient's development of platinum resistance. Awareness of this unusual occurrence should emphasize the need for adequate sampling of tumor tissue in patients with relapsing ovarian cancer. Reports of more cases of SCC of the colon would possibly help to establish appropriate management modality and strategies for treatment.

[1]School of Medicine University of Rijeka, University of Rijeka, Croatia
[2]Clinical Department of Radiotherapy and Oncology, Rijeka University Hospital Centre, School of Medicine, University of Rijeka, Croatia
[3]Clinical Department of Obstetrics and Gynecology, Rijeka University Hospital Centre, School of Medicine, University of Rijeka, Croatia
[4]Department of Pathology, School of Medicine, Rijeka University Hospital Centre, School of Medicine, University of Rijeka, Croatia
[5]Department of Cytology, Rijeka University Hospital Centre, University of Rijeka, Croatia
[6]Department of Pathology, University Hospital Centre, School of Medicine, University of Rijeka, Croatia

Introduction

Ovarian cancer is the most lethal malignancy of the female reproductive tract and high-grade serous ovarian cancer (HGSOC) is the most common and also the most aggressive histologic subtype.[1]

Please cite this paper as: Sladoljev K, Perin E, Ferrari AM, Klarić M, Brnčić-Fischer A, Eminović S, Vrdoljak-Mozetič D, Babarovic E. Relapsed ovarian high-grade serous carcinoma with long-term survival associated with synchronous primary squamous cell carcinoma of the colon. Proc Obstet Gynecol. 2018;8(2): Article 6 [9 p.]. Available from: http://ir.uiowa.edu/pog/ Free full text article.

Corresponding author: *Emina Babarović, Department of Pathology, Rijeka University School of Medicine, Brace Branchetta 20, 51000 Rijeka, Croatia, Telephone: +385 (0)51 325 822; Fax: +385 (0)51 325 810; email: esinozic@gmail.com*

Financial Disclosure: The authors report no conflict of interest.

Colon cancer is the second most commonly diagnosed cancer in females worldwide, but squamous cell carcinoma (SCC) of the colon is an extremely rare histologic subtype representing ~ 0.1% of all colonic malignancies.[2] As a result, clear management guidelines and optimal regimen for the treatment of colon SCC have not been determined.

Here we report an unusual case of synchronous primary SCC of the colon and second recurrence of HGSOC in a patient with 15-year survival.

Case report

A 53-year-old G4P2 postmenopausal woman underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, infracolic omentectomy with multiple peritoneal biopsies in November 2002 because of ovarian cancer. Histological diagnosis was HGSOC (Figure 1A and 1B) and based on pathological findings the disease was staged pT2bN0M0, FIGO IIB. Postoperative treatment consisted of chemotherapy with six cycles of taxol and carboplatin. Upon completion of the chemotherapy, the patient subjectively felt well and without clinical evidence of disease. She was further advised to have regular follow-up examinations every three months at the Gynecologic Oncology Outpatient Department (OPD). Five years following initial diagnosis the patient was asymptomatic, but increased CA-125 levels prompted a Positron Emission Tomography and Computed Tomography (PET-CT) scan of the whole-body with fluorodeoxyglucose (FDG). The scans showed markedly hypermetabolic field and high activity of the disease in the left lower pelvic area without any other FDG avid areas; so the patient was referred for second-look surgery. Intraoperatively, a tumor mass of the sigmoid mesocolon measuring four cm in diameter was revealed. The whole tumor mass was extirpated followed by an appendectomy and additional peritoneal biopsies. Histological examination of the tumor confirmed recurrence of the HGSOC; all other specimens were negative for the disease. Postoperatively, the patient received chemotherapy with six cycles of taxol and carboplatin. Regular follow–ups in OPD were performed and the patient was well with no clinical evidence of the disease, but 14 years following initial diagnosis increased CA-125 levels were detected. Re-evaluation of whole body PET-CT scan with FDG showed high metabolic activity in the wall and adjacent adipose tissue of the ascending colon, multiple smaller peritoneal infiltrates and a few enlarged mesenteric lymph nodes. Once again the patient underwent surgery, specifically supracolic omentectomy and radical right hemicolectomy. Intraoperatively, a solid nodule in the mesentery of the ascending colon, measuring five cm in the greatest dimension and numerous grey nodes and plaques of the omentum and serosal surface of the intestines were found. This time it was not possible to remove all tumor nodes and the residual tumor mass was 0.5 cm. Microscopic examination showed that all serosal and omental nodes and plaques were tumorous tissue of the same morphology of high-grade serous carcinoma with a dominant papillary, and to a lesser extent, glandular and nested architecture (Figure 1C).

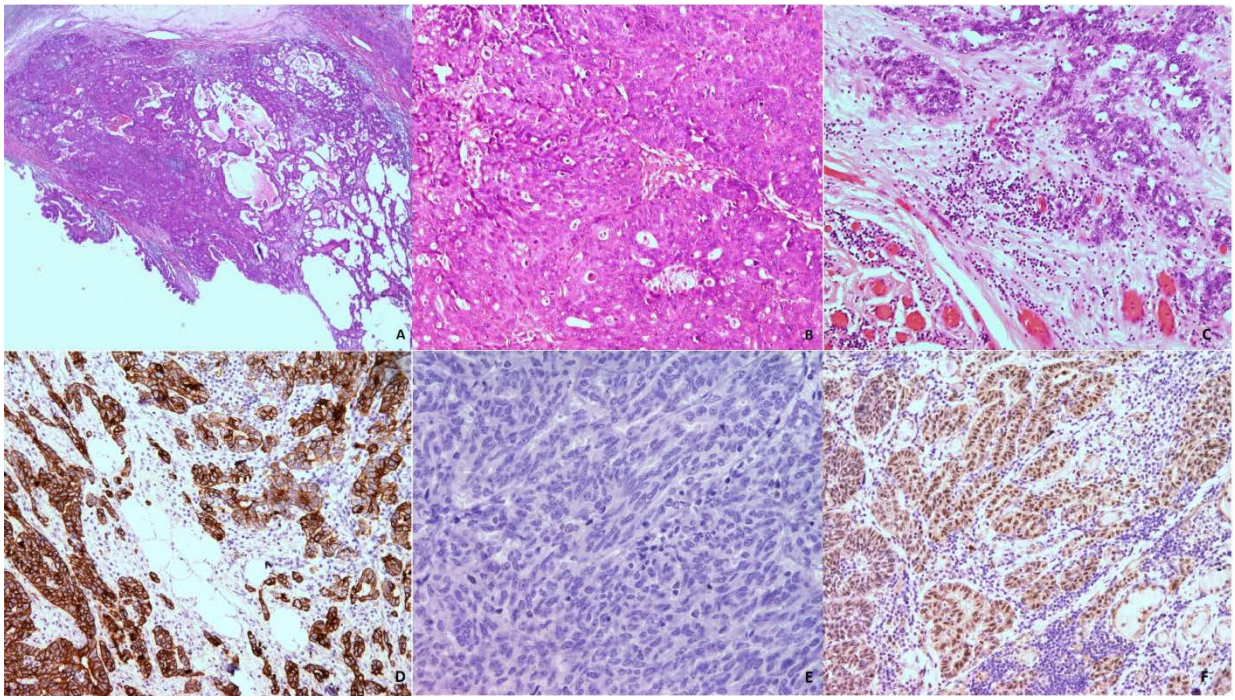

Figure 1. Microscopic features and immunohistochemical characteristics of the resected primary ovarian tumor and serosal metastatic infiltrates of the second recurrence of high- grade serous ovarian carcinoma.

Primary high-grade serous carcinoma of the ovary with glandular, papillary (HE, 20x, A) and solid architecture, severe cytological atypia and increased number of mitotic figures (HE, 100x, B). Microscopic features of the serosal metastatic infiltrates of the second recurrence of HGSOC (HE, 100x, C). Immunohistochemical staining for CK 7 showed diffuse and strong positivity of tumor cells, 100x (D). Immunohistochemical staining for p53 showed a complete absence of nuclear staining with 0% of positive nuclear staining, 200x (E). Immunohistochemical staining for WT1 showed diffuse nuclear staining of tumor cells, 100x (F).

Additionally, 6 out of 14 lymph nodes isolated from adjacent adipose tissue of the small and large intestine, were all infiltrated by HGSOC. Immunohistochemically, tumor cells of primary ovarian tumor and serosal metastatic infiltrates were both CK7 and WT1 diffusely positive and p53 showed a complete absence of nuclear staining with 0% of positive nuclear staining (Figure 1D-F). Therefore, we concluded that it was the same tumor and we set the diagnosis of second recurrence of the HGSOC. As opposed to that, the largest tumor mass in the wall of ascending colon was morphologically and immunohistochemically different. Histologically, the tumor was poorly differentiated composed of cohesive nests of large polygonal cells with abundant eosinophilic cytoplasm and sparsely conspicuous intercellular bridges, but without keratin formation (Figure 2A and 2B).

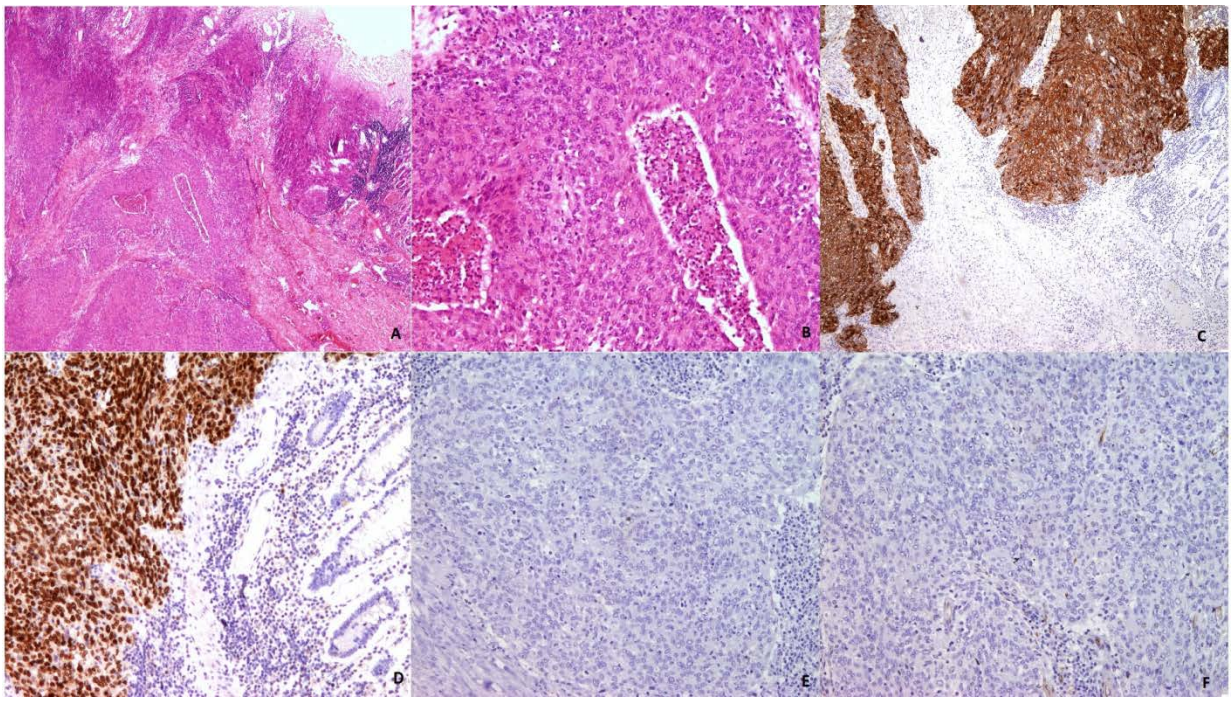

Figure 2. Histological and immunohistochemical characteristics of the resected primary squamous cell carcinoma of the colon.

Primary colon carcinoma that ulcerated mucosa and infiltrate colonic wall with normal mucosa of the colon on the upper right (HE, 20x, A). Morphology of the resected tumor composed of cohesive nests of large polygonal cells with abundant eosinophilic cytoplasm, cytological atypia, rare apoptotic bodies and and foci of necrosis in the center of the nests (HE, 100x, B). Immunohistochemical staining for CK5/6 showed diffuse and strong positivity of tumor cells, 40x (C). Immunohistochemical staining for p63 showed diffuse nuclear staining of tumor cells, 100x (D). Immunohistochemical staining for CK 7 showed a complete absence of staining in tumor tissue, 100x (E). Immunohistochemical staining for WT1 showed showed a complete absence of staining in tumor tissue, 100x (F).

The tumor ulcerated mucosa and deeply infiltrated all layers of the colonic wall with extension to adjacent adipose tissue. A panel of immunohistochemical markers was performed. Tumor tissue was diffusely and strongly positive for CK5/6 and p63; while CK7, CK20, WT1, GATA3 and uroplakin were all diffusely negative (Figure 2C-F). Whole body PET-CT scan with FDG excluded distant metastasis so the diagnosis of a synchronous primary SCC of the colon and relapsed HGSOC was made. Primary colon cancer was staged pT4aN0M0. The patient had no complications during the postoperative course so additional chemotherapy treatment with six cycles of paclitaxel and carboplatin was advised. During chemotherapy, serum levels of CA-125 increased from 14.6 IU/mL; 78 IU/mL to 281.5 IU/mL respectively. After the fourth cycle of chemotherapy, a re-evaluation of whole body PET-CT scan with FDG was performed and disease progression was revealed. Pathological, very intense metabolism of FDG in paracaval, interaortocaval and

paraaortic lymph nodes and serosal surface of rectosigmoid area was observed. Considering the dual pathology it was difficult to know the origin of this disease progression. However, according to the metastatic spread, we have concluded that this is probably a progression of HGSOC. Due to the development of platinum resistance and a worsening of the patient's physical condition the planned chemotherapy scheme was interrupted and mono chemotherapy with topotecan was continued. The patient received four cycles of topotecan. After the fourth cycle of mono chemotherapy the patient developed neurological side effects and enterocolitis, but the serum CA-125 level was decreasing and regular abdominal ultrasound examinations, CT and MR of the brain did not reveal signs of progression. So at that moment the disease of our patient was stable and we decided to continue with a fifth cycle of topotecan. During the fifth cycle of mono chemotherapy neurological side effects got worse and the patient's physical condition abruptly and significantly deteriorated, so further mono chemotherapy with topotecan was interrupted. Abdominal CT and pelvic MR scans revealed disease progression with peritoneum thickening and retroperitoneal tumor masses. Considering the overall poor medical condition of the patient options of hormone therapy versus basic support care were discussed with the patient and her family, and they opted for hormone therapy. We started with Nolvadex which the patient tolerated very poorly, so after one month we replaced it with Anastrozole. The patient developed severe obstructive jaundice due to progression of the disease and eventually passed away 25 months after the last surgery and 15 years and 9 months after the first diagnosis of HGSOC.

Discussion

Here we report an interesting case of a HGSOC patient with 15-year survival. Our patient developed two recurrent HGSOCs with five and nine years disease-free survival time. The second recurrence of HGSOC was associated with a synchronous primary SCC of the ascending colon and was further complicated by the patient′s development of platinum resistance. FIGO stage and volume of residual disease after surgical staging for patients with advanced disease are universally accepted prognostic factors. Initial FIGO stage of our patient was IIB. Stage II tumors are uncommon and represent an intermediate group, which, depending on other factors, can vary widely in terms of survival and cure rates.[3] According to the SEER registry and other studies, long term survival of women with HGSOC is low and only ~30 % have a 10–year survival.[1,4-6] Our patient underwent BRCA1/2 germline mutations testing which was negative.[7-9] In addition to that p53 immunohistochemical analysis showed complete lack of expression in tumor cells which correlates with a TP53 null mutation.[10,11] Our patient was BRCA1/2 negative and had a TP53 null mutation both portend a poor prognosis, but surprisingly the initial prognosis of our patient was relatively good.[7,8,11] Our initial therapeutic approach and treatment of the first recurrence was optimal cytoreductive surgery and six cycles of platinum-based chemotherapy. The second recurrence of HGSOC was

associated with the synchronous primary SCC of the ascending colon, which made our management of the patient even more challenging.

It is well known that cancer survivors may be susceptible to developing second primary malignancies.[12] Risk factors for multiple primary tumors include hereditary cancer syndrome, as well as constitutional and environmental factors. None were detected in our patient. Late toxic effects of radiotherapy and chemotherapy also contribute to the increased risk for a second primary malignancy. Our patient did not received any radiotherapy in the past, but chemotherapeutic agents administered for her treatment could cause DNA damage and that may lead to the development of a subsequent neoplasm. Treatment-related secondary malignancies are well documented in the literature[13,14], but SCC of the colon is an extremely rare type of colonic malignancy, that has not yet been described as such.[3,15] A relationship between adenocarcinoma of the colon and ovarian carcinoma has been reported in many studies and this association has been attributed to hormonal factors, low parity and diet. Secondary colon adenocarcinoma was related with prior radiotherapy treatment of patients with ovarian cancer.[12-14]

Williams et al. in 1979 established diagnostic criteria for colon SCC with rectal involvement.[16] Those criteria included: exclusion of other primary SCC or possible metastasis, careful proctoscopy to exclude proximal extension of anal squamous cell carcinoma and lack of a fistulous tract lined by squamous epithelium. In our case, the patient had a fistula-free cancer of the ascending colon. The location of the tumor excludes the proximal extension of anal squamous cell carcinoma and after excluding distant metastasis by whole body PET-CT scan using FDG, the diagnosis of primary colon SCC was made.

The etiology and pathogenesis of SCC of the colon are not fully understood, although it seems that squamous metaplasia is the principal process of tumorigenesis. Etiological factors might be chronic inflammation and irritation. The most important prognostic factor is disease stage. There are currently no reliable data regarding the survival of these patients, but as reported by Frizelle et al. SCC patients with stage III-IV disease have a poorer prognosis compared with those patients with adenocarcinoma of the colon.[2] The treatment of colon SCC is mainly surgical, but in terms of chemotherapy and treatment planning, due to its rarity, currently there is no standard regimen. Various treatment regimens have been reported, which included 5-fluorouracil [5FU]/mitomycin C, 5FU, 5FU/cisplatin, capecitabine/cisplatin, capecitabine, raltitrexed/oxaliplatin and S-1 and gemcitabine.[15,17,18] We performed radical right hemicolectomy and primary colon SCC was staged as pT4aN0M0; while all other metastatic nodules and lymph nodes were infiltrated by HGSOC. So, we assumed that the colon cancer was completely resected. When in a patient, two active malignancies are diagnosed at the same time; it is challenging to find an anticancer therapy strategy that covers both cancer types without increased toxicity and without negative impact on the overall outcome. Due to the lack of clear management

guidelines for this type of colon cancer and the residual tumor mass of HGSOC, our therapy approach was chemotherapy with paclitaxel and carboplatin. Our treatment plan was further complicated by the patient's development of platinum resistance and subsequent disease progression. Platinum resistance is defined as tumor progression during or within six months after completion of prior platinum therapy; these patients usually receive a non-platinum single agent regimen as second line treatment. Most common chemotherapeutic choices include docetaxel, pegylated liposomal doxorubicin, gemcitabine or topotecan, but there is currently no standard chemotherapy for recurrence. Our therapeutic choice at this point was single agent regimen with topotecan to which the patient responded satisfactorily at the beginning, but after that the patient experienced severe side effects and subsequently rapid progression of the disease.

In conclusion, long-term survival cases for both types of malignancies are rarely reported, proving its poor prognosis, and therefore making this case even more challenging and interesting. Awareness of this unusual occurrence should emphasize the need for adequate sampling of tumor tissue in patients with relapsing ovarian cancer. Reports of more cases of SCC of the colon would possibly help to establish appropriate management modality and strategies for treatment.

References

1. Wright JD, Chen L, Tergas AI, Patankar S, Burke WM, Hou JY, Neugut AI, Ananth CV, Hershman DL. Trends in relative survival for ovarian cancer from 1975 to 2011. Obstet Gynecol. 2015 Jun;125(6):1345-52. https://doi.org/10.1097/AOG.0000000000000854 PubMed PMID: 26000505; PubMed Central PMCID: PMC4484269.

2. Frizelle FA, Hobday KS, Batts KP, Nelson H. Adenosquamous and squamous carcinoma of the colon and upper rectum: a clinical and histopathologic study. Dis Colon Rectum. 2001 Mar;44(3):341-6. https://doi.org/10.1007/BF02234730 PubMed PMID: 11289278.

3. Seidman JD, Cosin JA, Wang BG, Alsop S, Yemelyanova A, Fields A, Boice CR, Zaino RJ. Upstaging pathologic stage I ovarian carcinoma based on dense adhesions is not warranted: a clinicopathologic study of 84 patients originally classified as FIGO stage II. Gynecol Oncol. 2010 Nov;119(2):250-4. https://doi.org/10.1016/j.ygyno.2010.07.002 Epub 2010 Jul 31. PubMed PMID: 20673974.

4. Akeson M, Jakobsen AM, Zetterqvist BM, Holmberg E, Brännström M, Horvath G. A population-based 5-year cohort study including all cases of epithelial ovarian cancer in western Sweden: 10-year survival and prognostic factors. Int J Gynecol Cancer. 2009 Jan;19(1):116-23. https://doi.org/10.1111/IGC.0b013e3181991b13 PubMed PMID: 19258952.

5. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007 Jan-Feb;57(1):43-66. https://doi.org/10.3322/canjclin.57.1.43 PubMed PMID: 17237035.

6. Dao F, Schlappe BA, Tseng J, Lester J, Nick AM, Lutgendorf SK, McMeekin S, Coleman RL, Moore KN, Karlan BY, Sood AK, Levine DA. Characteristics of 10-year survivors of high-grade serous ovarian carcinoma. Gynecol Oncol. 2016 May;141(2):260-263. https://doi.org/10.1016/j.ygyno.2016.03.010 Epub 2016 Mar 11. PubMed PMID: 26968641; PubMed Central PMCID: PMC4844793.

7. Bowtell DD, Böhm S, Ahmed AA, Aspuria PJ, Bast RC Jr, Beral V, Berek JS, Birrer MJ, Blagden S, Bookman MA, Brenton JD, Chiappinelli KB, Martins FC, Coukos G, Drapkin R, Edmondson R, Fotopoulou C, Gabra H, Galon J, Gourley C, Heong V, Huntsman DG, Iwanicki M, Karlan BY, Kaye A, Lengyel E, Levine DA, Lu KH, McNeish IA, Menon U, Narod SA, Nelson BH, Nephew KP, Pharoah P, Powell DJ Jr, Ramos P, Romero IL, Scott CL, Sood AK, Stronach EA, Balkwill FR. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. Nat Rev Cancer. 2015 Nov;15(11):668-79. https://doi.org/10.1038/nrc4019 PubMed PMID: 26493647; PubMed Central PMCID: PMC4892184.

8. Dong F, Davineni PK, Howitt BE, Beck AH. A BRCA1/2 Mutational Signature and Survival in Ovarian High-Grade Serous Carcinoma. Cancer Epidemiol Biomarkers Prev. 2016 Nov;25(11):1511-1516. https://doi.org/10.1158/1055-9965.EPI-16-0286 Epub 2016 Aug 5. PubMed PMID: 27496093.

9. Domchek SM, Aghajanian C, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, Mitchell G, Fried G, Stemmer SM, Hubert A, Rosengarten O, Loman N, Robertson JD, Mann H, Kaufman B. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. Gynecol Oncol. 2016 Feb;140(2):199-203. https://doi.org/10.1016/j.ygyno.2015.12.020 Epub 2015 Dec 23. PubMed PMID: 26723501; PubMed Central PMCID: PMC4992984.

10. Yemelyanova A, Vang R, Kshirsagar M, Lu D, Marks MA, Shih IeM, Kurman RJ. Immunohistochemical staining patterns of p53 can serve as a surrogate marker for TP53 mutations in ovarian carcinoma: an immunohistochemical and nucleotide sequencing analysis. Mod Pathol. 2011 Sep;24(9):1248-53. https://doi.org/10.1038/modpathol.2011.85 Epub 2011 May 6. PubMed PMID: 21552211.

11. Shahin MS, Hughes JH, Sood AK, Buller RE. The prognostic significance of p53 tumor suppressor gene alterations in ovarian carcinoma. Cancer. 2000 Nov 1;89(9):2006-17. https://doi.org/10.1002/1097-0142(20001101)89:9<2006::AID-CNCR18>3.3.CO;2-Z PubMed PMID: 11064359.

12. Coyte A, Morrison DS, McLoone P. Second primary cancer risk - the impact of applying different definitions of multiple primaries: results from a retrospective population-based cancer registry study. BMC Cancer. 2014 Apr 18;14:272. https://doi.org/10.1186/1471-2407-14-272 PubMed PMID: 24742063; PubMed Central PMCID: PMC4005906.

13. Sánchez de Cos Escuín J, Rodríguez López DP, Utrabo Delgado I, Gallego Domínguez R, Sojo González MA, Hernández Valle M. Disease Recurrence and Second Tumors in Long-term Survivors of Lung Cancer. Arch Bronconeumol. 2016 Apr;52(4):183-8. https://doi.org/10.1016/j.arbres.2015.07.013 Epub 2015 Nov 11. PubMed PMID: 26558321.

14. Soerjomataram I, Coebergh JW. Epidemiology of multiple primary cancers. Methods Mol Biol. 2009;471:85-105. https://doi.org/10.1007/978-1-59745-416-2_5 PubMed PMID: 19109776.

15. Lyttle JA. Primary squamous carcinoma of the proximal large bowel. Report of a case and review of the literature. Dis Colon Rectum. 1983 Apr;26(4):279-82. https://doi.org/10.1007/BF02562498 PubMed PMID: 6839899.

16. Williams GT, Blackshaw AJ, Morson BC. Squamous carcinoma of the colorectum and its genesis. J Pathol. 1979 Nov;129(3):139-47. https://doi.org/10.1002/path.1711290306 PubMed PMID: 529012.

17. Nahas CS, Shia J, Joseph R, Schrag D, Minsky BD, Weiser MR, Guillem JG, Paty PB, Klimstra DS, Tang LH, Wong WD, Temple LK. Squamous-cell carcinoma of the rectum: a rare but curable tumor. Dis Colon Rectum. 2007 Sep;50(9):1393-400. https://doi.org/10.1007/s10350-007-0256-z PubMed PMID: 17661147.

18. Zhao S, Guo J, Sun L, Lv J, Qiu W. Gemcitabine-based chemotherapy in colon squamous cell carcinoma: A case report and literature review. Mol Clin Oncol. 2017 Apr;6(4):561-565. https://doi.org/10.3892/mco.2017.1178 Epub 2017 Mar 1. PubMed PMID: 28413669; PubMed Central PMCID: PMC5374950.