CASE REPORT

Nagoya J. Med. Sci. **85**. 814–821, 2023
doi:10.18999/nagjms.85.4.814

A case of simultaneous breast cancer and ovarian cancer based on a hereditary breast and ovarian cancer syndrome

Saki Kotaka[1], Hiroaki Yasui[1], Hirofumi Tsubouchi[1], Masahiko Mori[1], Haruru Kotani[2], Akiyo Yoshimura[2], Akira Ouchi[3], Masataka Okuno[3], Koji Komori[3], Yasuhiro Shimizu[3] and Shiro Suzuki[1]

[1]*Department of Gynecologic Oncology, Aichi Cancer Center Hospital, Nagoya, Japan*
[2]*Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan*
[3]*Department of Gastroenterological Surgery, Aichi Cancer Center Hospital, Nagoya, Japan*

ABSTRACT

We experienced a relatively rare case of synchronous breast and ovarian cancer in a patient with hereditary breast and ovarian cancer syndrome (HBOC). Here, we report the usefulness of laparoscopic examination to determine the subsequent treatment strategy in cases of suspected concurrent multiple carcinomas. Our patient was diagnosed with breast cancer following detection of a right breast mass. She was diagnosed with HBOC as she was found to be harboring a germline pathogenic variant of breast cancer susceptibility gene 1 (*BRCA1*). Preoperative images suggested the presence of neoplastic masses in the abdominal cavity, and the possibility of metastatic peritoneal dissemination of breast cancer or concurrent overlapping of gynecological malignancies was considered. We decided to employ laparoscopic examination, and if simultaneous overlapping of cancers was suspected, we planned to further evaluate whether primary debulking surgery (PDS) for gynecological cancer was possible or not. Laparoscopy revealed the presence of ovarian cancer with neoplastic lesions on the bilateral ovaries and disseminations in the pelvic and abdominal cavities. The total predictive index was 0; therefore, PDS was considered feasible. We performed a total mastectomy, followed by laparotomy, and optimal surgery was achieved. The final diagnosis was simultaneous stage IIB invasive ductal breast carcinoma and stage IIIC high-grade serous ovarian carcinoma. In this case of suspected concurrent multiple carcinomas, laparoscopy was beneficial for decision-making regarding subsequent surgical treatment. We believe that the use of laparoscopy will enable simultaneous surgery for breast cancer and ovarian cancer to become one of the treatment strategies in the future.

Keywords: hereditary breast and ovarian cancer syndrome, breast cancer susceptibility gene 1, laparoscopic examination, predictive index

Abbreviations:
HBOC: hereditary breast and ovarian cancer syndrome
BRCA: breast cancer susceptibility gene
PDS: primary debulking surgery
NAC: neoadjuvant chemotherapy

Received: November 9, 2022; accepted: November 21, 2022
Corresponding Author: Saki Kotaka, MD
Department of Gynecologic Oncology, Aichi Cancer Center Hospital,
1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan
Tel: +81-52-762-6111, Fax: +81-52-764-2963, E-mail: 321d014@m.mie-u.ac.jp

INTRODUCTION

In carriers of the breast cancer susceptibility gene 1 (*BRCA1*) mutation and hereditary breast and ovarian cancer syndrome (HBOC), the reported cumulative risk of breast cancer at age 80 years is 72% and the risk of ovarian cancer at age 80 years is 44%.[1] Although breast cancer and ovarian cancer can occur simultaneously, especially in HBOC patients, this is rare and there is no well-established treatment strategy.

We experienced the case of a relatively young HBOC patient who was diagnosed with breast cancer and in whom concurrent overlapping ovarian cancer was suspected. This patient underwent laparoscopic examination followed by mastectomy and primary debulking surgery (PDS). Here, we report and discuss this case with the intention that it will be of help in treating similar cases in the future.

CASE PRESENTATION

The patient was 40 years old, 0 pregnancy. In terms of family history, her father had leukemia, her mother had ovarian cancer, and her maternal grandmother had colon cancer.

She was aware of a right breast mass and presented it to the clinic. A large, 2.5 cm mass was found in the right mammary gland, and a needle biopsy showed invasive ductal carcinoma. Immunohistochemistry results were negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor type 2, ie, triple negative breast cancer. Genetic examination was performed, and a germline pathogenic *BRCA1* variant was found, leading to the diagnosis of

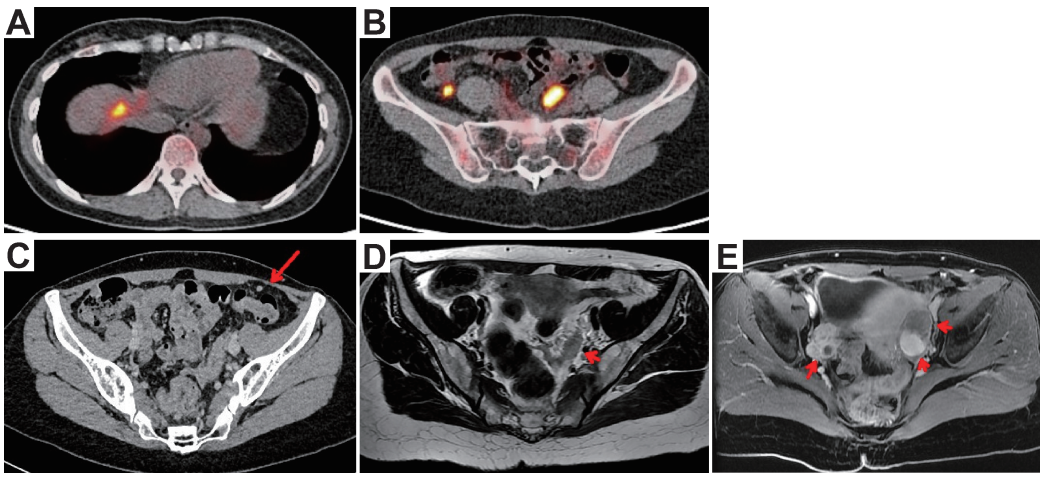

Fig. 1 Positron emission tomography/computed tomography (PET-CT), contrast-enhanced CT, and magnetic resonance imaging (MRI) before surgery

Fig. 1A: PET-CT findings suggest the peritoneal dissemination in the right diaphragm.

Fig. 1B: PET-CT findings suggest the peritoneal dissemination in the right para-colonic area and the tumor at the left side of rectum.

Fig. 1C: Contrast-enhanced CT findings suggest the peritoneal dissemination in the peritoneum of abdominal cavity.

Fig. 1D: MRI, such as T2-emphasized imaging findings, suggest a tumor at the left side of rectum.

Fig. 1E: MRI, such as contrast fat-suppression T1-weighted imaging findings, suggest tumors in bilateral adnexal regions.

HBOC. Positron emission tomography/computed tomography (PET-CT), contrast-enhanced CT, and magnetic resonance imaging (MRI) were conducted and revealed multiple neoplastic lesions in the abdominal cavity, including the right diaphragm, right para-colonic area, left adnexal region, and left side of rectum, which implied peritoneal dissemination (Fig. 1A-1E). Gynecological examinations, including bimanual testing and transvaginal ultrasound examination, showed no significant findings, and both cervical cytology and endometrial histology showed no malignant findings. We confirmed an elevated CA-125 level of 259.5 U/mL by blood examination.

Based on the abovementioned findings, it was possible that the peritoneal disseminations were intraperitoneal metastases of breast cancer or an overlapping of advanced ovarian cancer. We determined that an intraperitoneal observation by laparoscopy and intraoperative rapid pathological diagnosis would be useful in differentiating whether the peritoneal disseminations were breast cancer metastases or ovarian neoplasms. If the intraoperative rapid histological diagnosis indicated metastasis of breast cancer, the patient would be considered to have stage IV breast cancer. Conversely, if peritoneal dissemination from ovarian cancer was suspected, we could evaluate using a predictive index to determine whether PDS is possible or not. The predictive index is a method to assess whether optimal cytoreduction is possible in advanced ovarian cancer cases by evaluating the presence of omental cake, peritoneal carcinosis, diaphragmatic carcinosis, mesenteric retraction, bowel infiltration, stomach infiltration and liver metastasis.[2] If the predictive index score was less than 8, we planned to perform PDS for gynecological cancer immediately after mastectomy and sentinel lymph node biopsy for breast cancer.

Through laparoscopic review, there was only a small amount of ascites in the pelvic cavity (Fig. 2A), neoplastic lesions in the bilateral adnexa (Fig. 2B, 2C), and a disseminated tumor lesion on the right diaphragm that appeared to be greater than 2 cm in size (Fig. 2D, 2E).

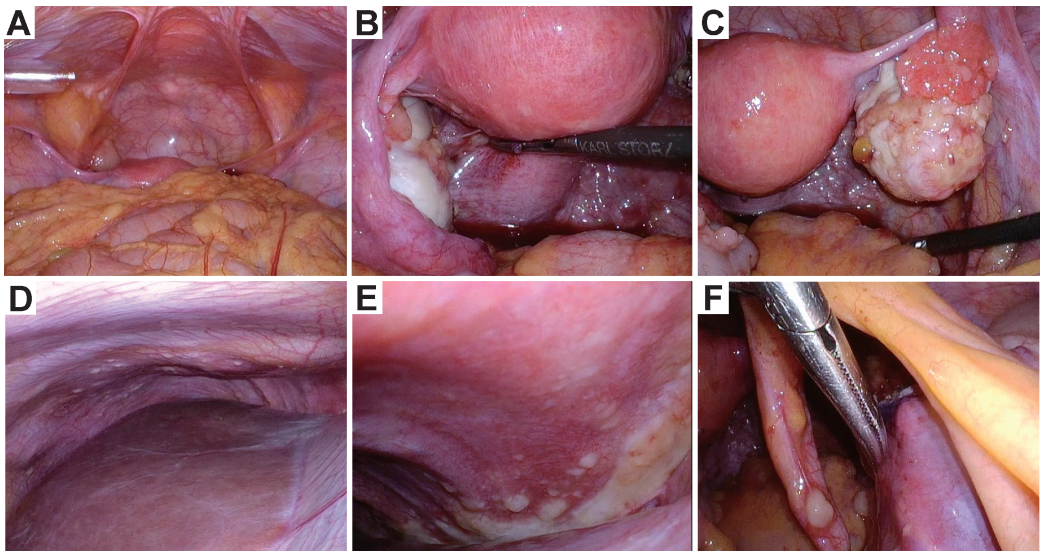

Fig. 2A–F Intraoperative photographs of laparoscopy
Fig. 2A: Whole view of the pelvic cavity.
Fig. 2B: The left adnexal area.
Fig. 2C: The right adnexal area.
Fig. 2D: The right diaphragm surrounding the liver.
Fig. 2E: The right diaphragm close to falciform ligament of the liver.
Fig. 2F: The appendix.

Numerous small nodules existed on the peritoneum in the pelvic cavity as well as on the surface of the sigmoid colon and the appendix (Fig. 2F). Assuming ovarian cancer, the patient was considered stage IIIC, an advanced stage of ovarian cancer by the International Federation of Gynecology and Obstetrics classification 2014. The right ovary and the right fallopian tube, which had minimal adhesion to the surrounding tissue, were easy to extract laparoscopically and were submitted for intraoperative rapid tissue diagnosis. The result was adenocarcinoma, and there were no findings confirming breast cancer metastases. Thus, the intra-abdominal findings were consistent with ovarian cancer. The predictive score was calculated as 0; therefore, the patient underwent mastectomy followed by laparotomy to achieve PDS.

The largest tumor lesion was 9 cm in length on the right diaphragm, and it had invaded the diaphragmatic muscle layer and could not be treated by peritoneal resection alone; therefore, open thoracotomy and partial full-thickness resection of the right diaphragm was required. The tumor on the left side of the rectum had invaded the rectum and required proctectomy with left inferior hypogastric plexus resection. Finally, the patient underwent right mastectomy, sentinel lymph node biopsy (negative result), right diaphragmectomy, resection of disseminated foci (pelvic and abdominal), appendectomy, type B radical hysterectomy[3] due to tumor invasion to left retroperitoneal cavity, bilateral salpingo-oophorectomy, proctectomy, left external iliac lymph node biopsy, and temporary loop ileostomy. Small-seeded metastases of 1 mm in diameter remained on the peritoneum. Thus, the patient was judged to have undergone an optimal surgery, which is extremely close to a complete surgery. The operative time was 11 hours and 35 minutes, and blood loss was 650 g. The right pelvic visceral plexus was completely preserved. However, there was a neurogenic bladder as a postoperative complication. Although a right pleural effusion was observed in the thoracic cavity due to the right diaphragmatic excision, breathing and circulation were maintained without drainage of the effusion. The patient was finally discharged on the 23rd postoperative day.

Histopathological examination denoted an invasive ductal carcinoma stage IIB (pT2N1miM0) (Fig. 2G) and a high grade serous ovarian carcinoma stage IIIC (pT3cN1aM0) (Fig. 2H). Homologous recombination deficiency (HRD) was sequenced using right ovarian cancer. HRD was positive with a genomic instability score of 45 and the same mutation detected as the germline pathogenic variant previously in *BRCA1* was found. We performed adjuvant chemotherapy with paclitaxel, carboplatin, and bevacizumab, followed by adjuvant radiotherapy for breast cancer and

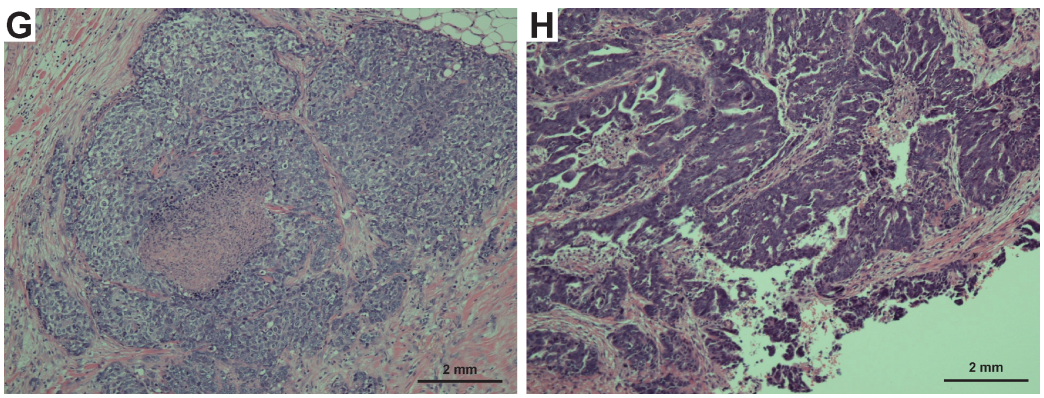

Fig. 2G, H Histopathological images with hematoxylin-eosin staining
Fig. 2G: Histopathological images with hematoxylin-eosin staining of the right breast tumor.
Fig. 2H: Histopathological images with hematoxylin-eosin staining of the right ovarian tumor.

maintenance therapy in combination with olaparib and bevacizumab for ovarian cancer.[4] The first chemotherapy was started 35 days after surgery. We scheduled colostomy closure and contralateral risk-reducing mastectomy simultaneously at 9 months after operation.

DISCUSSION

In this case report, we described our experience of a relatively rare case of concurrent breast cancer and advanced ovarian cancer in a patient with HBOC. In *BRCA1* mutation carriers, the cumulative risk of breast cancer begins to increase around age 26, with a cumulative risk of 24% at age 40, and the incidence rate reaches a relative plateau between the ages of 31–40 years. In terms of ovarian cancer, it has also been reported that the cumulative risk of developing ovarian cancer begins to increase in the late 30s but remains low until age 40, and the cumulative risk of developing ovarian cancer at age 40 is still 2%.[1] Therefore, the risk of breast cancer is much higher than that of ovarian cancer in HBOC patients. There is a paper to study on patients diagnosed with double primary breast and ovarian cancer. When we use the data, we could calculate the conditional probability of patients with synchronous breast and ovarian cancer among patients who were first diagnosed primary breast, and the probability was almost 0.05%.[5] Although there are several studies on *BRCA* germline mutation carriers diagnosed with synchronous breast cancer and ovarian cancer,[6-10] a case of concurrent breast and advanced ovarian cancer at a young age (40 years or younger) is considered extremely rare.

Generally, ovarian cancer is difficult to diagnose only by images and should be diagnosed by pathological review using specimens obtained during surgery. In this case, the existence of breast cancer was apparent. Therefore, neoplasms in the abdominal cavity implied two possibilities—breast cancer metastases or concurrent gynecological malignancy, including ovarian cancer. Although it is not a paper to analyze simultaneous breast cancer and the presence of adnexal masses, there is a paper to denote that 13% women with breast cancer who have adnexal or pelvic mass are diagnosed metastatic breast cancer in the pelvic cavity.[11] This result imply that we cannot deny the possibility of breast cancer metastasis when we find the neoplastic masses in the abdominal cavity. According to a review article,[12] the factors such as *BRCA1/2* mutation and premenopausal younger age increase the possibility of metastatic breast cancer in this case. Review laparoscopy was reported to be useful for guiding selection of primary treatment.[13] Moreover, review laparoscopy was also useful for determining the subsequent treatment strategy in this case in which concurrent overlapping cancers are suspected.

The treatment strategy for breast cancer is different to that of ovarian cancer. Neoadjuvant chemotherapy (NAC) is equivalent to adjuvant chemotherapy for operable breast cancer.[14] In terms of triple negative breast cancer, NAC with a pathological complete response is superior to adjuvant chemotherapy, patients with NAC are likely to undergo breast conserving surgery, and neoadjuvant chemotherapy with residual disease is inferior to adjuvant chemotherapy from the perspective of survival outcomes.[15] On the contrary, survival outcomes in ovarian cancer patients treated by PDS or NAC-interval debulking surgery (NAC-IDS) are considered equivalent in advanced ovarian cancer.[16] From the point of view of perioperative complications, there is a tendency that NAC-IDS is selected more frequently than PDS in advanced ovarian cancer. However, the huge problem associated with administering NAC for both cancers followed by surgery is that the regimens of NAC for breast cancer and ovarian cancer are different. This makes it complicated to formulate a treatment plan for concurrent breast and ovarian cancer. The effect of one regimen on another cancer is unknown. Therefore, performing NAC for concurrent breast and ovarian cancer is questionable. Given these reasons, we attempted mastectomy for

breast cancer and PDS for ovarian cancer simultaneously before chemotherapy so as not to miss the timing of debulking surgery for each breast and ovarian cancers.

In *BRCA1/2* mutation carriers, overall survival at 3 years in patients with breast cancer who receive local treatment and NAC or adjuvant chemotherapy is at least 88%,[17] whereas overall survival at 3 years in patients with advanced ovarian cancer who achieved a response after standard therapy is 80%–84%.[18] It was also reported that 75% of patients with synchronous breast and ovarian cancer died due to ovarian cancer.[6] These results suggest that the prognosis of advanced ovarian cancer is poorer than that of breast cancer. There is also one report suggesting that paclitaxel and carboplatin may be alternative adjuvant chemotherapy for operable triple negative breast cancer with *BRCA1/2* mutation from the perspective of disease-free survival compared with cyclophosphamide, epirubicin, and fluorouracil followed by docetaxel (hazard ratio 0.44; 95% confidence interval 0.15–1.31).[19] Thus, in this case, we chose an adjuvant chemotherapy regimen for ovarian cancer.

The predictive index is a method to identify whether the tumor is resectable or not in advanced ovarian cancer cases. It has been reported that patients with a predictive index score of 8 or more will undergo suboptimal surgery with a specificity of 100%.[20] Therefore, PDS should be selected for patients with a predictive index of less than 8 to achieve optimal surgery.

However, we must consider the limitations of this predictive method. Although the predictive index is useful in determining whether optimal surgery is assumed possible for advanced ovarian cancer, it must be emphasized that the predictive index has limitations due to the dissociation between laparoscopic evaluation, abdominal findings at laparotomy, and the final surgical procedures. According to a literature review,[2] mesenteric retraction was not evaluable in 25.8% of cases, suggesting the difficulty of mesenteric retraction by laparoscopic examination. The lowest concordance rate of 82.4% was reported for bowel infiltration evaluation between the implementing and supervising centers, and mesenteric retraction and bowel infiltration are particularly prone to false-negative results and should be evaluated with caution. In fact, in this case there was an assumption that the rectum was difficult to move around despite the absence of Douglas fossa closure. Because the posterior rectal space was not developed from the lateral rectal space at that time, we did not identify the necessity of proctectomy with left inferior hypogastric plexus resection for tumor resection. Moreover, the diaphragmatic carcinomatosis was not also counted as a positive score because liver mobilization was difficult at the time of laparoscopy, and we could not observe the diaphragm completely. However, in laparotomy, detailed observation revealed that the diaphragmatic carcinomatosis had invaded the diaphragmatic muscle layer, and a full-thickness diaphragmatic resection was required. Therefore, the surgery became much more invasive than we expected. Thus, we should carefully evaluate whether optimal surgery by PDS is possible or not when the predictive index score is less than 8.

CONCLUSION

Simultaneous breast cancer and advanced ovarian cancer based in HBOC patients at a young age is rare. Moreover, there is no established algorithm for the treatment of synchronous overlapping cancers. We believe that, in the future, the aggressive utilization of laparoscopy, and if possible, simultaneous breast cancer surgery and PDS for ovarian cancer become one of the treatment strategies for similar cases.

ACKNOWLEDGEMENT

This case report was supported by the following co-authors. HY conceptualized the study and wrote the original draft. HT and MM wrote the original draft. HK and AY supervised the original draft concerning breast cancer. AO, MO, KK, and YS supervised the original draft, concerned diaphragmatic surgery, and gastrointestinal surgery. SS wrote the original draft and supervised the whole study.

CONFLICTS OF INTEREST

None declared.

FUNDING

None declared.

REFERENCES

1 Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA*. 2017;317(23):2402–2416. doi:10.1001/jama.2017.7112.
2 Fagotti A, Vizzielli G, De Iaco P, et al. A multicentric trial (Olympia-MITO 13) on the accuracy of laparoscopy to assess peritoneal spread in ovarian cancer. *Am J Obstet Gynecol*. 2013;209(5):462.e1–462.e11. doi:10.1016/j.ajog.2013.07.016.
3 Querleu D, Morrow CP. Classification of radical hysterectomy. *Lancet Oncol*. 2008;9(3):297–303. doi:10.1016/S1470-2045(08)70074-3.
4 Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med*. 2019;381(25):2416–2428. doi:10.1056/NEJMoa1911361.
5 He XQ, Gao YT, Zhang X, Jiang H. Time Intervals between Double Primary Breast and Ovarian Cancers and Survival Outcomes of Patients with Both Cancers: A SEER Database Analysis. *Biomed Res Int*. 2022;2022:4557346. doi:10.1155/2022/4557346.
6 Tasca G, Dieci MV, Baretta Z, et al. Synchronous and Metachronous Breast and Ovarian Cancer: Experience From Two Large Cancer Center. *Front Oncol*. 2020;10:608783. doi:10.3389/fonc.2020.608783.
7 Dilawari A, Cangiarella J, Smith J, Huang A, Downey A, Muggia F. Co-existence of breast and ovarian cancers in BRCA germ-line mutation carriers. *Ecancermedicalscience*. 2008;2:109. doi:10.3332/ecancer.2008.109.
8 Zahari MM, Chiorean AR, Duma MM, Ungureanu A, Kacso G. Invasive bilateral breast cancer and high grade serous ovarian cancer with BRCA1-germline mutation and brainstem metastasis under PARP inhibitors. *Arch Clin Cases*. 2021;6(3):69–75. doi:10.22551/2019.24.0603.10156.
9 Chan GHJ, Ong PY, Low JJH, et al. Clinical genetic testing outcome with multi-gene panel in Asian patients with multiple primary cancers. *Oncotarget*. 2018;9(55):30649–30660. doi:10.18632/oncotarget.25769.
10 Llinás-Quintero N, Cabrera-Florez E, Mendoza-Fandiño G, Matute-Turizo G, Vasquez-Trespalacios EM, Gallón-Villegas LJ. Synchronous Ovarian and Breast Cancers with a Novel Variant in BRCA2 Gene: A Case Report. *Case Rep Oncol Med*. 2019;2019:6958952. doi:10.1155/2019/6958952.
11 Curtin JP, Barakat RR, Hoskins WJ. Ovarian disease in women with breast cancer. *Obstet Gynecol*. 1994;84(3):449–452.
12 Moore EK, Roylance R, Rosenthal AN. Breast cancer metastasising to the pelvis and abdomen: what the gynaecologist needs to know. *BJOG*. 2012;119(7):788–794. doi:10.1111/j.1471-0528.2012.03314.x.
13 Rutten MJ, van Meurs HS, van de Vrie R, et al. Laparoscopy to Predict the Result of Primary Cytoreductive Surgery in Patients With Advanced Ovarian Cancer: A Randomized Controlled Trial. *J Clin Oncol*. 2017;35(6):613–621. doi:10.1200/JCO.2016.69.2962.
14 Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol*. 2008;26(5):778–785. doi:10.1200/

JCO.2007.15.0235.
15 Xia LY, Hu QL, Zhang J, Xu WY, Li XS. Survival outcomes of neoadjuvant versus adjuvant chemotherapy in triple-negative breast cancer: a meta-analysis of 36,480 cases. *World J Surg Oncol*. 2020;18(1):129. doi:10.1186/s12957-020-01907-7.
16 Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet*. 2015;386(9990):249–257. doi:10.1016/S0140-6736(14)62223-6.
17 Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer. *N Engl J Med*. 2021;384(25):2394–2405. doi:10.1056/NEJMoa2105215.
18 Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2018;379(26):2495–2505. doi:10.1056/NEJMoa1810858.
19 Yu KD, Ye FG, He M, et al. Effect of Adjuvant Paclitaxel and Carboplatin on Survival in Women With Triple-Negative Breast Cancer: A Phase 3 Randomized Clinical Trial. *JAMA Oncol*. 2020;6(9):1390–1396. doi:10.1001/jamaoncol.2020.2965.
20 Fagotti A, Ferrandina G, Fanfani F, et al. A laparoscopy-based score to predict surgical outcome in patients with advanced ovarian carcinoma: a pilot study. *Ann Surg Oncol*. 2006;13(8):1156–1161. doi:10.1245/ASO.2006.08.021.