

ORIGINAL RESEARCH

The incidence and clinical outcomes following prophylactic risk-reducing salpingo-oophorectomy in BRCA mutation carriers: a single-center retrospective study

Tuğçe Sırma¹ , Konul Mehdiyeva¹ , Lena Türeyici¹ , Gürdeniz Serin² ,
Gökтуğ Aydoğan² , Aslı Ece Solmaz³ , Haluk Akın³ , Ahmet Aydın Özşaran¹ ,
Mustafa Coşan Terek¹ , Levent Akman¹ , Nuri Yıldırım^{1,*} 

¹Department of Obstetrics and Gynecology, Division of Gynecological Oncology, Ege University Faculty of Medicine, 35100 İzmir, Turkey

²Department of Pathology, Ege University Faculty of Medicine, 35100 İzmir, Turkey

³Department of Genetics, Ege University Faculty of Medicine, 35100 İzmir, Turkey

***Correspondence**

nuri.yildirim@ege.edu.tr
(Nuri Yıldırım)

Abstract

Background: The aim of this study was to determine the incidence of Secretory cell outgrowth (SCOUT), p53 signature, serous tubal intraepithelial lesion (STIL), serous tubal intraepithelial carcinoma (STIC) and occult invasive cancer (OC) in patients with (*BRCA1* and/or (*BRCA2*) pathogenic variants and to evaluate clinical outcomes and the risk of developing primary peritoneal carcinoma (PPC) in the follow-up period. **Methods:** This study is a single center retrospective clinical study. We evaluated 63 patients with *BRCA* mutations. The treatment approach was prophylactic risk-reducing salpingo-oophorectomy (RRSO) according to Sectioning and Extensively Examining the Fimbriated end of the fallopian tube (SEE-FIM) protocol and immunohistochemical staining. The patients had proven *BRCA1-2* variants, but had no personal history of ovarian, peritoneal or fallopian tube cancer and there was no preoperative sign of malignancy. **Results:** Out of 63 patients, 29 women were identified as carrying a mutation in the *BRCA1* gene, while 33 were identified as carrying a mutation in the *BRCA2* gene. One patient had both a *BRCA1* and *BRCA2* mutation. The mean age at surgery was 45.9 years (range, 34 to 71 years). In total, 10 (15.8%) SCOUTs, 4 (6.3%) p53 signatures and 3 (4.7%) STILs were observed. One patient with isolated STIC was detected which was identified in both *BRCA1* and *BRCA2* mutations and did not undergo restaging surgery or adjuvant chemotherapy. After diagnosis of STIC at RRSO, PPC did not develop during 23 months. **Conclusions:** The STIC and STIL, which are precancerous lesions, were observed with RRSO by applying SEE-FIM protocol. In addition, the subsequent period did not demonstrate any occurrences of PPC. Further studies are required to investigate the management of these precancerous lesions and OC, due to the rarity of STIC lesions and the low number of case series.

Keywords

BRCA; Risk-reducing salpingo-oophorectomy; Serous tubal intraepithelial carcinoma

1. Introduction

Epithelial ovarian cancer (EOC) is the primary reason of mortality in gynecological malignancies, with a 5-year survival rate of 47% [1]. The most prevalent histological type is high-grade serous carcinoma (HGSC), accounting for 70–80% of cases [2]. It is estimated that approximately 10% of ovarian carcinomas, particularly HGSC, are attributable to hereditary factors [2]. It is well known that more than 90% of all hereditary EOC cases are related to *BRCA* pathogenic variants [3]. The risk of occurring EOC is 36–53% for *BRCA1* mutation carriers and 11–25% for *BRCA2* mutation carriers [4]. It is estimated that approximately 50% of HGSC cases are associated with a defect in Homologous Recombination, which primarily

depends on the function of the *BRCA1-2* DNA repair proteins. In recent years, there has been significant attention on the utilisation of poly (ADP)-ribose polymerase (PARP) inhibitor drugs, such as olaparib, niraparib and rucaparib, in the context of maintenance therapy following the response to platinum-based chemotherapy as a first-line treatment. These studies have demonstrated a notable prolongation in survival rates for patients diagnosed with homologous recombination deficiency (HRD), particularly those with a mutation in the *BRCA1* or *BRCA2* genes [5]. Current findings indicate that high-grade serous ovarian carcinomas have the potential to originate from the fallopian tube [6]. The most effective method of prevention is a timely risk-reducing salpingo-oophorectomy (RRSO),

which has been shown to reduce the risk of EOC by up to 96% [7]. In accordance with the guidelines established by the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO), the recommendation for the administration of RRSO is between 35 and 40 years of age, subsequent to the completion of childbearing in *BRCA1* mutation carriers [8]. In patients with a pathogenic variant in the *BRCA2* gene, causing later onset of ovarian cancer, RRSO may be postponed until 40–45 years of age [8]. The principal pathological findings documented in cases of prophylactic removal of adnexa are serous tubal intraepithelial lesions (STIL), serous tubal intraepithelial carcinoma (STIC) and occult invasive cancer (OC) [9]. STIC is a precursor lesion mostly appears in the distal part of the fallopian tube and fimbria and leads to the occurring of HGSC [3, 10]. The STIC, STIL and OC are determined by applying the Sectioning and Extensively Examining the Fimbriated end of the fallopian tube (SEE-FIM) protocol. This protocol has been applied in the patients with *BRCA* pathogenic variants by resection and transversal sectioning of the fimbria and remanig tube at 2–3 mm intervals [9]. Prior to the development of STIC, detected by the SEE-FIM protocol, three precursor lesions, characterised by Secretory cell outgrowth (SCOUT), p53 signature and STIL, were hypothesised to play potential roles in the pathogenesis. As demonstrated in earlier research, the incidental identification of these precursor lesions does not appear to be linked to primary peritoneal or ovarian cancer during follow-up [9, 11–13]. The incidence of OCs varies from 1.9 to 5.6%, and the incidence of STICs varies from 0.8 to 9.8% at the time of the RRSO in patients with *BRCA* mutation carriers [9, 14–16]. Conversely, in a large cohort study conducted in the Netherlands, the results of RRSO conducted on 2557 patients with *BRCA* mutations were evaluated [17]. The study identified a low proportion ($n = 28$, 1.0%) of asymptomatic patients with HGSC; nonetheless, the data concerning the remaining patients remains unclear [17]. However, the clinical impact of STIC is not yet fully understood.

The goal of this paper was to ascertain the prevalence of pre-cancerous lesions, Secretory cell outgrowth (SCOUT), p53 signature, serous tubal intraepithelial lesion (STIL), serous tubal intraepithelial carcinoma (STIC) and occult invasive cancer (OC), in patients with pathogenic variants of the *BRCA1* and/or *BRCA2* genes. Additionally, the study aspire to evaluating clinical outcomes and the risk of developing primary peritoneal carcinoma (PPC) in the follow-up period.

2. Materials and methods

2.1 Study design

We carried out a retrospective analysis of 63 patients with *BRCA* mutation who underwent RRSO at the Department of Gynecological Oncology of Ege University, İzmir, between January 2021 and November 2024. Patients who fulfilled the inclusion criteria and were enrolled in the study had proven germline variants in the *BRCA1-2* and were referred by the Department of Genetics and General Surgery. A comprehensive review of the medical records of all patients was conducted for parity, personal history of breast cancer and family his-

tory of breast and/or ovarian cancer, *BRCA* mutation status, tamoxifen use, menopausal status and age at RRSO and was obtained from electronic hospital database and patient files. Preoperative pelvic examination, transvaginal ultrasonography (TVUSG) and serum Cancer Antigen 125 (CA-125) levels were performed in all cases to exclude the suspicion of cancer. All women completed childbearing. Patients were excluded from the study if there were suspected or known gynecological cancer, no confirmed pathogenic *BRCA* variants.

The RRSO with hysterectomy procedure was performed by laparotomy, laparoscopic or vaginal approach after the whole upper abdomen and pelvis had been explored. Peritoneal washing for cytology (using approximately 50 mL of normal saline) was performed with or without omental and peritoneal biopsies as standard when technically possible. Frozen section was applied in case of suspicious adnexal mass. It was decided that surgical staging would only be performed in the presence of an OC.

We discussed with the patients about the possible risk of occurring uterine papillary serous carcinoma (UPSC) in the future period based on the previous prospective cohort studies (the risk of UPSC 1.53% to 3.69% and 3% and the risk of all histologic types 4.3%, respectively) [18–20]. All the patients accepted the hysterectomy with RRSO. The RRSO with hysterectomy was performed for all patients. All the patients had not have the history of hysterectomy before.

In case the pathology result was STIL or STIC and OC after RRSO, patients were followed up with pelvic examination, TVUSG and CA-125 levels every 6 months.

2.2 Histopathological and immunohistochemical examination

From 2021, both ovaries and tubes of all cases undergoing RRSO were examined following the SEE-FIM protocol by expert gynecological pathologists. The protocol ensures the production of multiple 2- to 3-mm longitudinal sections of the resected bilateral adnexa, which are then subjected to microscopic evaluation for the purpose of detecting OC and STIC [21, 22]. Surgical tissue samples were fixed in 10% buffered formalin, then embedded in paraffin, and finally cut into 4 μm -thick sections. Routine staining with haematoxylin and eosin (H&E) was then performed [23], and immunohistochemical staining for p53 and Ki67 was subsequently carried out [9]. Invasive carcinomas are defined as carcinomas diagnosed in the absence of preoperative clinical evidence of malignancy. Such findings are characterised by a negative physical examination, transvaginal ultrasound and normal serum CA-125 levels. These are detected in prophylactic salpingo-oophorectomy specimens and are poorly differentiated carcinomas with a predominant serous histotype [24]. The term of STIC is defined by the combination of three features. Firstly, the presence of an atypical cell morphology, which is characterised by nuclear pleomorphism, an increased nuclear/cytoplasmic ratio, loss of polarity and the absence of ciliated cells. Secondly, there is an aberrant expression of the p53 protein, which can be characterised as either strong diffuse expression or absent/null staining, or other aberrant patterns. Thirdly, there is an increased proportion of Ki67-

positive nuclei (>10%) [9, 25]. The term “STIL” was defined as a lesion characterised by the following features: abnormal p53 staining, variable Mindbomb Homolog-1 (MIB1) labelling, initial architectural atypia, a lack of ciliated cells, an increased nuclear/cytoplasmic ratio, preserved polarity of the epithelium, the absence of striking cellular atypia [25]. The term was also used to include those lesions that fell short of the diagnosis of STIC [25]. A p53 signature manifests as a morphologically unremarkable, unobstructed tract of non-ciliated (secretory) cells, comprising a minimum of 12 cells, accompanied by a pronounced, aberrant immunohistochemical staining for p53, consequent to an underlying gene mutation, and a minimal proliferative index (typically less than 10%) [25]. The Secretory Cell Outgrowth (SCOUT) is considered to be a probable precursor lesion of the p53 signature. This is characterised by the presence of the secretory cells (at least 30 cells) in a nest-like configuration, exhibiting low mitotic activity, pseudostratification with any aberrant expression of p53 immunohistochemically [25].

2.3 Outcomes

The main endpoint of the present study was to ascertain the incidence of p53 signature, STIL, STIC and OC in patients with *BRCA* mutation underwent the SEE-FIM protocol of RRSO specimens, and to evaluate the impact of these pre-cancerous lesions on the clinical outcome.

2.4 Statistical analysis

The statistical analysis was evaluated by utilising the Statistical Package for the Social Sciences (SPSS) Software Package (Windows version 26, IBM Corp., Chicago, IL, USA). Categorical variables were presented with numbers and percentages, while continuous variables were expressed as absolute numbers, mean, median and range.

3. Results

Between January 2021 and November 2024, a total of 63 patients with *BRCA* mutation carriers underwent RRSO were enrolled in this study. It was ascertained that none of the patients had a prior medical history of oophoro- or salpingectomy. Twenty-nine women (46.0%) were *BRCA1*, 33 (52.3%) were *BRCA2*, and 1 (1.5%) was *BRCA10+2* mutation carriers.

Table 1 presents comparisons of the demographic and clinical characteristics of the patients. The mean age at risk-reducing surgery was 45.9 years and the majority of patients were between the ages of 40 and 49. The mean age for *BRCA1* was 48.7 years (range 37–67 years), 48.1 years for *BRCA2* (range 34–71 years) and for *BRCA1+2* mutation carrier, it was 41. The first patient was subjected to RRSO at the age of 67 due to a history of operated breast cancer and a *BRCA1* pathogenic variant. The operation revealed a purely cystic formation measuring approximately 7 cm in diameter, originating from the left adnexa. Furthermore, the patient's CA-125 value was found to be within normal limits. (CA-125: 15 IU/mL). Frozen section reported as benign. The final pathology revealed follicle cyst. The second patient exhibited a *BRCA2* pathogenic variant and a personal and

family history of breast cancer. At the age of 71, RRSO was performed due to the presence of a heterogenous cystic mass containing fatty and calcific areas measuring approximately 5 cm in size, originating from the right adnexa. The CA-125 level was 25 IU/mL. Frozen section reported as benign. The final pathology revealed mature cystic teratoma. At the time of the surgery, 45 women (71.4%) were postmenopausal caused by iatrogenic induced or spontaneous and 18 women (28.5%) were premenopausal. Of the 63 patients, five were nulliparous.

Fifty-three (84.1%) patients had personal history of breast cancer and 2 (3.1%) patients without previous personal history of breast cancer underwent prophylactic bilateral mastectomy before RRSO, while the remaining patients did not have a history of breast cancer in the past (Table 1). The breast cancer history in the family was detected in 11 (37.9%) *BRCA1* mutation carriers, in 14 (42.4%) *BRCA2* mutation carriers and also the patient with both *BRCA1* and *BRCA2* mutation carrier had a family history of breast cancer. A family history of ovarian cancer was only detected in *BRCA1* mutation carriers ($n = 11$, 37.9%). 22 of 63 patients (34.9%) were tamoxifen users (current and former) and 35 had never used tamoxifen or any other medications.

The mean preoperative CA-125 level was 14.2 IU/mL for the patients with *BRCA1* mutation, 14.6 IU/mL for the patients with *BRCA2* mutation and 12.0 IU/mL for the patient with both *BRCA1* and *BRCA2* mutation (Table 1). All patients underwent TVUSG imaging prior to RRSO. Suspicious features were observed in 2 cases (3.1%). The first case was an asymptomatic 61 years old, *BRCA1* carrier, with solid and well-circumscribed measuring 5×6.5 cm mass on the right adnexal mass lobe and CA-125 level was 15 IU/mL. Intraoperatively, the presence of the pelvic kidney was observed. In the second case (52 years old, *BRCA2* carrier), TVUSG demonstrated 3–4 cystic structures within the left ovary and 7×6 cm cyst within right ovary. CA-125 was 33 IU/mL and intraoperatively, suspicious deposits seen in the pouch of Douglas were biopsied and sent for frozen section with the bilateral salpingo-oophorectomy specimen. Frozen section reported as benign. The final pathology revealed follicle cyst and endosalpingiosis. The peritoneal washing was negative for all the patients. Majority of the patients ($n = 33$, 52.3%) underwent total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO) and cytology with or without omental biopsy. The histopathological results of the hysterectomy specimens were reported as chronic cervicitis, leiomyoma, adenomyosis, atrophic endometrium, endometrial polyp, proliferative endometrium and simple endometrial hyperplasia (without atypia).

Table 2 shows the details of histopathologic findings for each groups. In total 10 (15.8%) SCOUTs were detected in our study at the time of the RRSO; 5 of them (17.2%) were *BRCA1* mutation carriers and the remaining patients were (15.1%) *BRCA2* mutation carriers. The p53 signature was observed in 4 (6.3%) patients (*BRCA1*: $n = 2$, 6.8% and *BRCA2*: $n = 2$, 6.0%). Isolated STIL lesions were diagnosed in 3 (4.7%) patients, 2 (6.8%) occurred among women carrying *BRCA1* mutation and the last one (3.0%) with *BRCA2* mutation. Isolated STIC was observed in 1 (1.5%) patient with both *BRCA1* and *BRCA2* carrier had history of breast cancer surgery. At the time of the RRSO, the age was 41 years.

TABLE 1. Clinical features of the patients.

Characteristics	<i>BRCA1</i> carriers (n = 29, 46.0%)	<i>BRCA2</i> carriers (n = 33, 52.3%)	<i>BRCA1+2</i> carriers (n = 1, 1.5%)	Total
Age of RRSO (yr)				
Mean (range)	48.7 (37–67)	48.1 (34–71)	41	45.9 (34–71)
30–39, n (%)	1 (3.4%)	5 (15.1%)	-	6 (9.5%)
40–49, n (%)	17 (58.6%)	15 (45.4%)	1 (100%)	33 (52.3%)
≥50, n (%)	11 (37.9%)	13 (39.3%)	-	24 (38.0%)
Nulliparity				
Yes	5 (17.2%)	-	-	5 (7.9%)
No	24 (82.7%)	33 (100%)	1 (100%)	58 (92.0%)
Menopausal status at RRSO				
Postmenopausal	19 (65.5%)	26 (78.7%)	-	45 (71.4%)
Premenopausal	10 (34.4%)	7 (21.2%)	1 (100%)	18 (28.5%)
Breast cancer history before RRSO	22 (75.8%)	30 (90.9%)	1 (100%)	53 (84.1%)
Family history				
Breast cancer	11 (37.9%)	14 (42.4%)	1 (100%)	26 (41.2%)
Ovarian cancer	11 (37.9%)	-	-	11 (17.4%)
Other cancers	6 (20.6%)	5 (15.1%)	-	11 (17.4%)
Prophylactic mastectomy before RRSO	2 (6.8%)	-	-	2 (3.1%)
Drug use				
None	22 (75.8%)	12 (36.3%)	1 (100%)	35 (55.5%)
TMX	5 (17.2%)	17 (51.5%)	-	22 (34.9%)
Femara	1 (3.4%)	2 (6.0%)	-	3 (4.7%)
Arimidex	1 (3.4%)	1 (3.0%)	-	2 (3.1%)
Herceptin	-	1 (3.0%)	-	1 (1.5%)
Preoperative CA-125 levels (IU/mL)				
<35	28 (96.5%)	31 (93.9%)	1 (100%)	60 (95.2%)
>35	1 (3.4%)	2 (6.0%)	-	3 (4.7%)
Mean level (range)	14.2 (4–68)	14.6 (3–61)	12	14.4 (3–68)
Preoperative pelvic imaging (TVUSG)				
Normal findings	25 (86.2%)	29 (87.8%)	1 (100%)	55 (87.3%)
Abnormal findings (benign)	3 (10.3%)	3 (9.0%)	-	6 (9.5%)
Suspicious findings	1 (3.4%)	1 (3.0%)	-	2 (3.1%)
Type of RRSO				
TLH + BSO + cytology	11 (37.9%)	8 (24.2%)	1 (100%)	20 (31.7%)
TAH + BSO + cytology ± omental biopsy	14 (48.2%)	19 (57.5%)	-	33 (52.3%)
VH + BSO	4 (13.7%)	5 (15.1%)	-	9 (14.2%)
Robotic hysterectomy + BSO + cytology	-	1 (3.0%)	-	1 (1.5%)
Peritoneal cytology	-	-	-	-

RRSO: risk-reducing salpingo-oophorectomy; TMX: tamoxifen; CA-125: Cancer Antigen 125; TVUSG: transvaginal ultrasonography; TLH: total laparoscopic hysterectomy; TAH: total abdominal hysterectomy; BSO: bilateral salpingo-oophorectomy; VH: vaginal hysterectomy; BRCA: BReast CAncer.

TABLE 2. Histopathologic findings at RRSO.

	Normal pathology	SCOUT	p53 signature	STIL	STIC	OC
<i>BRCA1</i> (n = 29)	20 (68.9%)	5 (17.2%)	2 (6.8%)	2 (6.8%)	-	-
<i>BRCA2</i> (n = 33)	25 (75.7%)	5 (15.1%)	2 (6.0%)	1 (3.0%)	-	-
<i>BRCA1+2</i> (n = 1)	-	-	-	-	1 (100%)	-
Total (n = 63)	45 (71.4%)	10 (15.8%)	4 (6.3%)	3 (4.7%)	1 (1.5%)	-

SCOUT: secretory cell outgrowth; *STIL*: serous tubal intraepithelial lesion; *STIC*: serous tubal intraepithelial carcinoma; *OC*: occult invasive cancer; *BRCA*: Breast Cancer.

CA-125 level was 12 IU/mL, examination of the pelvis and TVUSG were negative. Restaging surgery was not performed and adjuvant chemotherapy was not given but the patient was followed closely. All the patients were subjected to transvaginal ultrasound scanning and CA-125 level assessment every 6 months and primary peritoneal carcinoma (PPC) did not occur at all. None of the patients were diagnosed OC at the final pathological examination.

4. Discussion

High-grade serous carcinoma represents the most prevalent histological subtype of epithelial ovarian carcinoma, with approximately 10% of cases being associated with mutations in the *BRCA1* and *BRCA2* genes [3]. A significant proportion of HGSC cases are thought to originate in the fallopian tubes [26], with STIC being the precursor lesion, leading to the recommendation of standardised and detailed tubal sampling using the SEE-FIM protocol [27]; the average duration of STIC progression to HGSC is 6.5 years [26]. A variety of pre-neoplastic lesions, including p53 signature and STIL lesions, have been identified on histological examination of the fallopian tubes [27]. The temporal relationship between these lesions and HGSCs remains a subject of debate [27].

In recent study, the mean age at risk-reducing surgery was 45.9 years (range, 34–71 years) which was higher than the international guidelines but this result was similar to that obtained by Lee *et al.* [23], who searched 63 patients with *BRCA* mutation and found that the median age was 46.5 years. Additionally, our study showed that only 5 (7.9%) patients with *BRCA1* mutation carriers were nulliparous which means the majority of women want to undergo risk-reducing surgery after completed childbearing, that's why they may delay surgery. Another possible reason is concern about negative hormonal influence, quality of life and health [23].

In light of the most recent findings on the association between STICs and HSGCs among patients who had pathogenic variants in *BRCA1-2* genes [9], previous trials have indicated that the incidence of STIC in cases of *BRCA1-2* mutations ranges from 0.8 to 2.3% [14, 15]. Additionally, the incidence of HGSCs was about 1–2.5% [15, 17]. In the present result, the incidence of isolated STIC was 1.5%, which shows resemblance to previous studies which had in a similar regarding the number of included patients [3, 9, 14, 28, 29].

It is evident that the potential risk of developing PPC arising from the STIC in carriers of the *BRCA1-2* gene is, as yet,

unclear [9]. In the present result, the STIC lesion was detected in 1 (1.5%) case and was not undergone restaging. The PPC did not occur during follow-up of the 23 month. There have been several studies that support our findings. Similarly, the study by Abay *et al.* [3] showed that 1 (2.0%) patient with *BRCA1* mutation had STIC and did not undergo restaging as well but 8 cycles of chemotherapy were given after RRSO and PPC development was not observed during the 20 months follow-up period. According to these data demonstrated that the short-term follow-up period may not be sufficiently prolonged to allow for the occurrence of PPC in both studies. On the other hand, Saccardi *et al.* [9], in the long-time follow-up period (median 54.5 months), detected STICs in 4 (2.6%) patients. A close monitoring process was implemented for all patients at six-month intervals; however, no patient exhibited the development of PPC. Furthermore, the study published by Kang *et al.* [12] in 2023 revealed that no patient diagnosed with STIC developed PPC about 8 years follow-up period. On the contrary, in a large cohort meta-analysis conducted in the Netherlands, 2519 patients underwent RRSO and were subsequently followed up for a mean period of 13 years [30]. In 19 cases, despite the absence of pathology detected during RRSO, HGSC developed in a mean timeframe of 8 years. Notably, five of the eight patients diagnosed with STIC also developed HGSC at an average of 8 years. In a further meta-analysis encompassing 17 studies with a total sample size of 3121 patients, STIC was observed in 115 patients [7]. In the group with STIC, PPC cancer (n = 15, 13%) developed in a mean of 4.5 years, and similarly in the group without STIC, PPC cancer (n = 12, 0.4%) developed in a mean of 4.5 years. A similar observation was made in a UK study, where 3 patients (0.3%) developed PPC within 4–10 years after RRSO performed in 891 patients [31].

An additional purpose of the current trial was to ascertain the incidence of OC. In the present sample, the presence of OC was not identified. While there have been several studies that contrast to our findings. Kang *et al.* [12] found OC in 4 (3.3%) patients despite no evidence of malignancy on preoperative examination. Abay *et al.* [3] revealed OC was detected only in 1 (2.0%) case. Saccardi *et al.* [9] demonstrated 3 (2.0%) patients had OC, in particular 2 tubal cancers and 1 ovarian cancer, was consistent with those reported by Ricciardi *et al.* [32].

Undoubtedly, following the detection of STIC, the challenge is to determine the most suitable treatment to prevent the po-

tential recurrence or progression of the disease [9]. Following the diagnosis of STIC in RRSO, a plethora of management strategies have been posited. Nevertheless, there remains a paucity of robust evidence to support the efficacy of restaging, chemotherapy or close monitoring [9].

Van der Hoeven *et al.* [33] enrolled combination of 15 studies and demonstrated that 82 patients were diagnosed STIC. Thirteen of them (16.0%) underwent restaging surgery, only 3 of them (4.0%) received chemotherapy and the remaining patients ($n = 36$, 44.0%) followed closely. Recurrence disease occurred in four of the 36 patients who did not receive chemotherapy or undergo staging surgery following their initial RRSO. As a result, this study suggested that chemotherapy or restaging surgery was related to a lower risk of recurrence [33]. Wethington *et al.* [28] observed there was not found difference for the recurrence rate between restaging surgery for the diagnosis of STIC or after follow-up only. 12 patients were diagnosed with isolated STIC. The patients were treated in one of two ways: hysterectomy and omentectomy were performed on seven patients, while lymphadenectomy of the pelvic or para-aortic regions was carried out on 11 patients. It is noteworthy that adjuvant chemotherapy was not given to all patients. During a follow-up period of 28 months (range, 16–44 months), the recurrence rate was found to be similar in both groups, with no statistically significant difference observed. In other research published by Ricciardi *et al.* [32], the isolated STIC lesions were observed in 7 cases, of whom four did not undergo restaging surgery. Notably, adjuvant chemotherapy was not given to all patients. After a 30-month (9–84) follow-up period, oncological outcomes were found to be similar between the two groups.

Although there have been reports of an increased risk of pelvic peritoneal cancer in patients diagnosed with STIC, it is important to note that this risk also exists in patients with benign pathology [3]. Zakhour *et al.* [34] included 257 patients with *BRCA* mutation underwent RRSO. They observed 9 cases of STIC with an incidence rate of 3.5%, and 2 of which were pelvic serous carcinoma. Conversely, three patients with benign pathology progressed to serous carcinoma of the pelvis. These findings are in line with previous literatures, Minig *et al.* [35], and Powell *et al.* [36] observed one patient with normal histopathological findings developed PPC. Another endpoint of Minig's study only one patient had positive cytology among 3 patients diagnosed STIC and surgical staging was performed in this patient. None of these 3 patients went on to develop PPC while followed up [35]. Powell *et al.* [37] conducted a study in which patients diagnosed with STIC were divided into three distinct groups: staging surgery, adjuvant chemotherapy and no treatment. In this study, only three out of seventeen patients received chemotherapy, while only nine out of seventeen patients underwent surgical staging. However, the outcomes were favourable for all patients diagnosed with STIC, regardless of whether they received chemotherapy, operated or not treated [37].

In addition to STIC, three other lesions must be considered: p53 status, SCOUT and STIL. As these lesions have only been recognised in recent times, further research is required to ascertain their clinical significance. It is also possible that they may play a role in the pathogenesis of EOC [11].

There are several strengths of the current study including (1) uniform SEE-FIM protocol was used for all cases (2) all RRSO specimens were examined by expert gynecological pathologists (3) A rigorous selection process was employed to identify suitable patients. Only patients with pathogenic variants in *BRCA1-2* genes and negative sign of cancer by TVUSG screening were chosen. Notwithstanding the aforementioned strengths, it is important to acknowledge the limitations of the present study, which are inherent to its retrospective nature, a single center, not a randomized trial, short period of follow-up, small number of cases.

5. Conclusions

Overall, no significantly different outcomes or reduced rates of subsequent PPC after RRSO were reported in the main trials that compared restaging surgery, adjuvant chemotherapy or close follow-up in patients with STIC [9]. It should be remembered that there is still a risk of occurring PPC. In conclusion, on the basis of the result of our study and on the evidence of previous publications, the implementation of a prolonged follow-up in patients detected with the isolated STIC should be thought as a possible strategy for management. Undeniably, larger prospective case series with adequate patients and longer follow-up can define the advantages of RRSO in order to establish more certain recommendations and to define management.

AVAILABILITY OF DATA AND MATERIALS

The data underpinning the finding of this study can be obtained from the corresponding author, NY, upon a reasonable request.

AUTHOR CONTRIBUTIONS

NY—project development; management/editing. TS—data collection; data analysis; manuscript writing. AAÖ—management/editing. MCT—management/editing. LA—management/editing. LT—data collection. KM—data collection; data analysis. AES—data collection; data analysis. HA—management/editing. GS—pathologic examination; data analysis. GA—pathologic examination; data analysis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the institutional Ethics Committee of Ege University Faculty of Medicine (approval number: 25-2T/45). Consents were obtained from all participants included in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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