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Original Article

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Clinical outcome and pattern of care for isolated or incidental serous tubal intraepithelial carcinoma: a multicenter retrospective cohort study

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ABSTRACT

Objective: Serous tubal intraepithelial carcinoma (STIC), a potential precursor of high-grade serous carcinoma, is associated with subsequent carcinomas development. This study aimed to identify cases of STIC and serous tubal intraepithelial lesions (STIL) and examine clinical outcomes and patterns of care in *BRCA1/2* mutations carriers undergoing risk-reducing salpingo-oophorectomy (RRSO), as well as patients with incidental STIC/STIL after benign gynecologic surgery.
Methods: This retrospective study was conducted at six institutions to examine patients with isolated STIC/STIL. Demographic, adjuvant treatment, and follow-up data were collected from the date of implementation of Sectioning and Extensively Examining the Fimbriated end protocol, which varied from 2006 to 2015, until December 2022.
Results: We analyzed the data of 1,119 women who underwent RRSO and were carriers of *BRCA1/2* mutations. The detection rate of isolated STIC/STIL was 1.70%. No patient with STIC/STIL received adjuvant chemotherapy or staging operations. The institutions used different surveillance intervals and methods, with the most common being a 3–6 month interval (11 of 19 patients) and gynecological sonography (17 of 19 patients). All patients remained with no evidence of disease (NED) throughout the follow-up period (2–121 months). Additionally, we analyzed data from five women with incidental STIC/STIL diagnosed after benign gynecological surgery; one woman underwent staging surgery. During the follow-up period (3–46 months), all patients remained in NED.
Conclusion: While patient monitoring after STIC/STIL detection may be considered due to the minimal risk of carcinoma, excessive concern may not be necessary. Furthermore, adjuvant chemotherapy should be considered only with caution.

Keywords: Serous Ovarian Neoplasms; Carcinoma in Situ; Genes, BRCA1; Genes, BRCA2; Prophylactic Surgical Procedures; Salpingo-oophorectomy

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Synopsis
A multicenter retrospective study analyzed data on serous tubal intraepithelial carcinoma/lesion (STIC/STIL). The study found a 1.70% detection rate for STIC/STIL among BRCA1/2 mutation patients. Subsequent carcinomas did not develop during follow-up despite patients not receiving adjuvant chemotherapy or staging surgery.

INTRODUCTION

Ovarian cancer is the most life-threatening gynecological cancer. Approximately 90% of ovarian cancers are of the epithelial origin, with high-grade serous carcinoma (HGSC) being the most common subtype. Ovarian cancer exhibits only a few recognizable early symptoms, posing challenges for its early detection. Consequently, many patients are diagnosed at an advanced stage, leading to poor prognosis and a high mortality rate. Despite the ongoing emphasis on the importance of early ovarian cancer detection, no effective screening test is available [1-4].

Unlike cervical and endometrial cancers, which have well-known precursor lesions, the origin of ovarian cancer is not fully understood. Previously, it was believed that ovarian HGSC originates within the ovary itself [5,6]. However, in 2001, Piek et al. [7] investigated the development of precancerous lesions by examining fallopian tube samples from women who carry *BRCA1* mutations, which predispose them to developing ovarian cancer. The study discovered dysplastic lesions with high Ki67 positivity and p53 overexpression compared to that in morphologically normal epithelium. Based on this study, Piek et al. [8] hypothesized that ovarian serous carcinomas originate from the epithelium of the fallopian tube. This hypothesis is supported by several studies that have identified serous tubal intraepithelial carcinoma (STIC) as a potential precursor lesion of the fallopian tubes [6,9].

Medeiros et al. [10] introduced a pathological technique of the Sectioning and Extensively Examining the Fimbriated end (SEE-FIM) protocol for evaluating the fallopian tubes and fimbriae. This protocol has improved the detection rate of early tubal carcinomas in high-risk patient populations. Since the introduction of the protocol, several studies have investigated the clinical outcomes and significance of STIC. Some case reports and retrospective studies have reported no evidence of subsequent carcinoma after STIC detection during the follow-up period [11-14]. However, a recent meta-analysis revealed that patients with STIC have a hazard ratio of 33.9 for peritoneal carcinoma (PC) development during follow-up compared to patients without STIC (95% confidence interval [CI]=15.6–73.9; p<0.001). Furthermore, the study reported that women with STIC have a cumulative risk of 10.5% for PC development at 5 years (95% CI=6.2–17.2) and 27.5% at 10 years (95% CI=15.6–43.9) [15]. Therefore, the European Society for Medical Oncology and European Society of Gynecological Oncology recommend that “peritoneal restaging should be considered in cases of incidentally detected, apparently isolated STIC lesions” owing to its potential precursor role in ovarian cancer and its association with the risk of subsequent carcinoma (level of evidence IV, strength of recommendation B) [16]. However, the current National Comprehensive Cancer Network guidelines do not offer any established management options for STIC, except for surgical staging or chemotherapy if invasive cancer is suspected [17].

Currently, clinicians face challenges in strategizing treatment plans in real-life clinical situations because of ambiguous and insufficient guidelines for STIC management after risk-reducing salpingo-oophorectomy (RRSO). Therefore, there is an ongoing unmet need for clear and concise guidelines on adjuvant treatment and surveillance of STIC to ensure that patients receive optimal care. To achieve a consensus among clinicians regarding appropriate adjuvant treatment and surveillance of STIC and serous tubal intraepithelial lesions (STIL), outlining the clinical course of the disease in patients to identify differences in clinical patterns of practice and determine clinical outcomes is essential. Hence, this study aimed to investigate the detection rate of STIC/STIL in Korea and identify the clinical outcomes and patterns of care for STIC/STIL across various institutions.

MATERIALS AND METHODS

1. Study design and population

This multicenter retrospective cohort study included women with isolated STIC/STIL. Patient data were collected from six institutions, consisting of five tertiary hospitals in Seoul, South Korea (Asan Medical Center [AMC], Ewha Womans University Medical Center - Mokdong Hospital [EUMC], Samsung Medical Center [SMC], Seoul National University Hospital [SNUH], and Severance Hospital), along with the National Cancer Center (NCC), a specialized institute for cancer research and treatment under the Ministry of Health and Welfare of South Korea. Eligible patients were women identified as *BRCA1/2* mutation carriers through *BRCA* genetic testing and were diagnosed with histologically isolated STIC/STIL through RRSO. Patient records were collected based on the date of RRSO, considering any variations in the protocol introduction at each institution from the date of implementation of the SEE-FIM protocol until December 2022 (data collection from 2013 at AMC, 2012 at EUMC, 2016 at SMC, 2008 at SNUH, 2015 at Severance Hospital, and 2006 at NCC). *BRCA1/2* mutations included likely pathogenic variants detected through *BRCA* gene testing. Furthermore, data were collected from women who received an incidental histological diagnosis of STIC/STIL after undergoing benign gynecological surgery without knowledge of their *BRCA1/2* mutation status. Women who had been diagnosed with pelvic carcinoma (including ovarian, fallopian tube, uterine, or PCs) before STIC diagnosis or RRSO were excluded.

2. Diagnostic criteria for STIC/STIL

The SEE-FIM protocol was used to analyze the fallopian tubes for the diagnosis of STIC/STIL. The diagnostic process for STIC/STIL followed the protocol of each hospital. Although there was no central pathology review, each of the six participating institutions adhered to the diagnostic criteria based on the WHO classification of female genital tumors [18]. Each institution performed morphological assessment and immunohistochemical staining for p53 and Ki-67. STIC was diagnosed when abnormal morphological features such as a high nuclear-cytoplasmic ratio, nuclear enlargement, pleomorphism, hyperchromasia, absence of ciliated cells, loss of polarity with or without epithelial stratification, and occasional mitotic figures were observed, together with a mutant expression of p53 immunostaining (pattern of null or overexpression in more than 80%) and increased Ki-67 immunostaining in more than 10% of cells [18-20]. Cases that did not fully meet these diagnostic criteria may be diagnosed as STIL [18,21-23]. Therefore, the diagnosis of STIL may be ambiguous with the diagnosis of STIC and may vary slightly between different pathologists. However, it is essential that the results of p53 immunohistochemical staining show a mutant pattern.

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3. Data collection and statistical methods

We collected demographic and clinical data, including age at diagnosis, body mass index (BMI), childbirth history, menopausal status, medical history, familial medical history, *BRCA* gene test date and results, surgical details, histopathological findings, CA-125 levels, and imaging test results. We also collected data on adjuvant treatment, including staging surgery, pathological and cytologic results, chemotherapy history, as well as surveillance details such as follow-up period, interval, method, patients' last status, development of subsequent PC, blood test results, CA-125 levels, and imaging findings. One physician reviewed the collected patient data from each institution to determine patients' eligibility for the study.

Statistical analyses were conducted using SPSS statistical software (version 26.0 for Windows; SPSS Inc., IBM® Corp., Armonk, NY, USA). Continuous variables are presented as means and ranges for descriptive analysis. Categorical variables are presented as absolute numbers and percentages. The follow-up period was defined as the time from the completion of STIC treatment until the occurrence of a subsequent carcinoma or the last outpatient follow-up.

4. Ethic statement

This multicenter, retrospective cohort study was approved by the Institutional Review Board (IRB) of all participating institutions. The requirement for obtaining informed consent from individual participants was waived by the IRB, and data from all institutions were collected as de-identified data. This study adhered to the ethical standards set by the Institutional Committee on Human Experimentation and complied with the principles outlined in the Declaration of Helsinki.

RESULTS

1. Isolated STIC/STIL in RRSO specimens

We analyzed 1,119 women who underwent RRSO and were carriers of *BRCA1/2* mutations. The number of RRSO cases was as follows: 349/10 years at AMC, 88/11 years at EUMC, 107/7 years at SMC, 82/8 years at SNUH, 250/8 years at Severance Hospital, and 243/17 years at NCC. Among them, 19 patients were diagnosed with STIC or STIL based on RRSO pathology, resulting in a detection rate of isolated STIC/STIL at 1.70%. The detection rates of STIC/STIL at each institution were as follows: 2.29% at AMC, 1.14% at EUMC, 0.37% at SMC, 0% at SNUH, 1.20% at Severance Hospital, and 1.23% at NCC. **Table 1** displays the baseline characteristics of patients diagnosed with isolated STIC/STIL. The mean age at diagnosis was 53.4 years, and the median BMI was 24.8 kg/m^2. Overall, 89.4% of the patients had a history of multiparity, and 57.9% were postmenopausal. Among the 19 women, 18 had a history of breast cancer, and two had a history of thyroid or gastric cancers other than ovarian/tubal/peritoneal cancer. Thirteen patients harbored *BRCA1* mutation, whereas six had *BRCA2* mutation. Five patients had a second-degree familial history of breast cancer, whereas six had a second-degree family history of ovarian cancer or PC. Before RRSO, baseline workups were conducted, including gynecological sonography, CA-125 testing, and abdominal-pelvic computed tomography (APCT) for 19, 13, and 3 patients, respectively. No abnormality was observed in any patient during the baseline workups (data not shown).

Table 2 presents the operative details and pathological findings of RRSO in patients with isolated STIC/STIL. RRSO was performed laparoscopically in almost 90% of the cases, with robot-assisted laparoscopy in one case and laparotomy in the other. Only one

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Table 1. Baseline characteristics of patients with isolated serous tubal intraepithelial carcinoma

Variables	Total (n=19)
Age at diagnosis (yr)	53.37 (38–75)
BMI (kg/m^2)	25.09 (19.30–31.33)
Parity	
Nulliparity	2 (10.5)
Multiparity	17 (89.4)
Menopausal status	
Premenopausal	8 (42.1)
Postmenopausal	11 (57.9)
Past history of breast cancer	18 (94.7)
Past history of other cancer*	2 (10.5)
Germline BRCA mutation	
BRCA1	13 (68.4)
BRCA2	6 (31.6)
Family history of cancer within second-degree relatives	
Breast cancer	5 (26.3)
Ovarian/tubal/peritoneal cancer	6 (31.6)
Preoperative evaluations before RRSO	
CA-125	13 (68.4)
GY sonography	19 (100.0)
APCT	3 (15.8)

Values are presented as mean (range) or number (%).
APCT, abdominopelvic computed tomography; BMI, body mass index; GY, gynecological; IQR, interquartile range; RRSO, risk-reducing salpingo-oophorectomy.
*The history of other cancer included thyroid and stomach cancer.

Table 2. Operative details and pathological findings in patients with isolated STIC

Variables	Total (n=19)
Operative methods	
Laparoscopy	17 (89.5)
Robotic-assisted	1 (5.3)
Laparotomy	1 (5.3)
Accompanied procedures	
Hysterectomy	1 (5.3)
Cytology of peritoneal washing	
None	11 (57.9)
Done	8 (42.1)
Pathology*	
STIC	15 (78.9)
STIL	4 (21.1)

Values are presented as number (%).
STIC, serous tubal intraepithelial carcinoma; STIL, serous tubal intraepithelial lesion.
*All identified cases of STIC and STIL were unilateral lesions.

patient underwent RRSO with concomitant hysterectomy for other reasons. Cytology was not performed at the time of RRSO in 57.9% of the patients, and all reported cytology results were negative in the remaining 42.1%. The pathologic report for RRSO revealed 15 cases of isolated unilateral STIC and 4 cases of unilateral STIL without other histological malignancies.

Table 3 presents individual details and surveillance information for each patient diagnosed with an isolated STIC/STIL. None of the patients with STIC/STIL underwent aggressive adjuvant treatment, such as staging surgery or chemotherapy. The follow-up interval ranged from 3–6 months for 11 of the 19 patients, with some being followed-up every 6–12 months from the second year after diagnosis. Gynecological sonography was the preferred method of follow-up for 17 patients, whereas CA-125 testing was performed in 14 patients. APCT was used in only two patients. The follow-up time for six patients was less than 1 year, ranging from

Table 3. Detailed information about adjuvant treatment and follow-up after isolated STIC/STIL diagnosis at RRSO

No.	Institution	Age (yr)	BRCA mutation	Initial CA-125 (U/mL)	Operative procedures	Pathology	Peritoneal washing	Adjuvant treatments	FU interval	FU evaluations	FU duration (last status)
1	A	64	1	NA	L/S BSO	STIC, unilateral	Negative	Observation	3–6 mo	CA-125, GY sono, APCT	24 mo (NED)
2	B	48	2	9.3	L/S BSO	STIC, unilateral	NA	Observation	3–6 mo	CA-125, GY sono	121 mo (NED)
3	B	46	1	13.1	L/S BSO	STIC, unilateral	NA	Observation	3–6 mo	CA-125, GY sono	121 mo (NED)
4	B	51	1	8.5	Open BSO	STIC, unilateral	NA	Observation	3–6 mo for 1 yr → 6–12 mo	CA-125, GY sono	68 mo (NED)
5	B	49	1	12.8	L/S BSO	STIL, unilateral	NA	Observation	≤3 mo for 1 yr → 3–6 mo	CA-125, GY sono	48 mo (NED)
6	B	47	1	18.9	L/S BSO	STIL, unilateral	NA	Observation	≤3 mo for 1 yr → 3–6 mo	CA-125, GY sono	69 mo (NED)
7	B	53	1	11.8	Robot BSO	STIL, unilateral	NA	Observation	3–6 mo	CA-125, GY sono	29 mo (NED)
8	B	57	1	14.9	L/S BSO	STIC, unilateral	NA	Observation	3–6 mo	CA-125, GY sono	27 mo (NED)
9	B	67	2	NA	L/S BSO	STIL, unilateral	NA	Observation	3–6 mo	CA-125, GY sono	6 mo (NED)
10	C	67	1	NA	L/S BSO	STIC, unilateral	Negative	Observation	3–6 mo for 2 yr → 6–12 mo	GY sono	44 mo (NED)
11	C	53	1	NA	L/S BSO	STIC, unilateral	NA	Observation	3–6 mo	GY sono	18 mo (NED)
12	C	44	1	NA	L/S BSO	STIC, unilateral	NA	Observation	6–12 mo	APCT	10 mo (NED)
13	C	48	1	NA	L/S BSO	STIC, unilateral	NA	Observation	≤3 mo	GY sono	8 mo (NED)
14	D	44	2	8.2	L/S BSO	STIC, unilateral	Negative	Observation	3–6 mo for 1 yr → 6–12 mo	GY sono	45 mo (NED)
15	D	38	2	11.7	L/S BSO	STIC, unilateral	Negative	Observation	3–6 mo for 1 yr → 6–12 mo	CA-125, GY sono	44 mo (NED)
16	D	44	1	20.9	L/S BSO	STIC, unilateral	Negative	Observation	6 mo	CA-125, APCT	6 mo (NED)
17	E	54	2	7.5	L/S BSO	STIC, unilateral	Negative	Observation	≤3 mo for 1 yr → 3–6 mo	CA-125, GY sono	70 mo (NED)
18	E	65	2	11.0	L/S BSO	STIC, unilateral	Negative	Observation	≤3 mo	CA-125, GY sono	2 mo (NED before FU loss)
19	E	75	1	31.0	TLH BSO	STIC, unilateral	Negative	Observation	≤3 mo	CA-125, GY sono	2 mo (NED before FU loss)

APCT, abdominopelvic computed tomography; FU, follow-up; GY, gynecological; L/S BSO, laparoscopic bilateral salpingo-oophorectomy; NA, not available; NED, no evidence of disease; RRSO, risk-reducing salpingo-oophorectomy; sono, sonography; STIC, serous tubal intraepithelial carcinoma; STIL, serous tubal intraepithelial lesion; TLH, total laparoscopic hysterectomy.

2–10 months. The remaining patients were followed up for 18–121 months. No subsequent carcinoma and death related to STIC/STIL were detected during the follow-up period.

2. Incidental STIC/STIL in benign gynecological surgery specimens

During gynecological surgery for benign diseases of the uterus and ovaries, five women were incidentally diagnosed with STIC or STIL without prior knowledge of their *BRCA1/2* mutation status. One case was reported in the EUMC, and four cases were reported in the SMC. Of the five women, four were diagnosed with STIC and one with STIL. **Table 4** presents the individual details. Preoperative CA-125 testing information was available for two patients, both of whom had normal results. Bilateral salpingectomy was performed in all patients; however, in two cases, the ovaries were not removed. Most patients underwent follow-up after diagnosis. However, one patient underwent additional baseline workups, including a *BRCA1/2* genetic testing, CA-125 testing, APCT, magnetic resonance imaging, and positron emission tomography, as well as staging surgery, which involved laparoscopic bilateral oophorectomy, partial omentectomy, and multiple peritoneal biopsies. Surgical pathology

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Table 4. Detailed information regarding adjuvant treatment and follow-up after incidental STIC/STIL diagnosis after benign gynecological surgery

No.	Institution	Age (yr)	Initial CA-125 (U/mL)	Operative procedures (indication)	Pathology	Peritoneal washing	BRCA mutation	Adjuvant treatments	FU interval	FU evaluations	FU duration (last status)
1	A	52	NA	Robot TH BS (myoma)	STIC, unilateral	NA	1	Baseline evaluation,* staging surgery†	3–6 mo	CA-125, APCT	3 mo (NED before FU loss)
2	C	84	22.8	SubTH BSO (ovarian cyst)	STIC, unilateral	NA	NA	Observation	-	-	FU loss
3	C	49	7.3	LAVH BSO (myoma, ovarian cyst)	STIC, unilateral	NA	NA	Observation	3–6 mo for 1 yr → 6–12 mo	APCT	46 mo (NED)
4	C	59	NA	L/S BSO (ovarian cyst)	STIC, unilateral	NA	NA	Observation	6–12 mo	GY sono	10 mo (NED before FU loss)
5	C	47	NA	TLH RSO LS LOC (NA)	STIL, unilateral	NA	NA	Observation	6–12 mo	GY sono	37 mo (NED)

APCT, abdominopelvic computed tomography; FU, follow-up; GY, gynecological; L/S BSO, laparoscopic bilateral salpingo-oophorectomy; LAVH, laparoscopically assisted vaginal hysterectomy; NA, not available; NED, no evidence of disease; RSO LS LOC, right salpingo-oophorectomy, left salpingectomy and left ovarian cystectomy; sono, sonography; STIC, serous tubal intraepithelial carcinoma; STIL, serous tubal intraepithelial lesion; SubTH BSO, subtotal hysterectomy and bilateral salpingo-oophorectomy; TH BS, total hysterectomy and bilateral salpingectomy.
*Baseline evaluations included APCT, pelvic magnetic resonance imaging, and positron emission tomography.
†The staging procedure involved laparoscopic bilateral oophorectomy, partial omentectomy, and multiple peritoneal biopsies. The histological results showed no pathological lesions.

and further evaluation revealed normal results (data not shown). However, *BRCA1* mutation was detected in the *BRCA1/2* mutation test. Consequently, the patient was referred to a genetic medicine consultation center for further evaluation. Two patients were followed up at 3–6month intervals, whereas the other two were followed up at 6–12 months intervals. The follow-up evaluation methods included CA-125 testing, APCT, or gynecological sonography. During the follow-up period, ranging from 3–46 months, no case of subsequent carcinoma and death related to STIC/STIL were identified, except for one patient who did not undergo follow-up after surgery.

DISCUSSION

Our study found that the detection rate of isolated STIC/STIL during RRSO was approximately 1.70%. The detection rate of isolated STIC/STIL in each institution ranged from 0% to 2.29%. The detection rate of STIC without STIL was 1.34%. These findings are consistent with the low STIC detection rates reported in previous studies [24-27]. This wide range is attributable to the rarity of STIC. Wethington et al. reported that the incidence of isolated STIC is 2% [27]. Vaughan et al. [26] estimated the incidence of STIC in patients with *BRCA1/2* mutations to range from 0.6% to 6%.

Although STIC has attracted the interest of many researchers over the past two decades, limited research information has been reported owing to the rarity of the disease. Given this scarcity of information, clinicians may wonder whether additional staging surgery or adjuvant treatment is necessary to reduce the likelihood of subsequent carcinoma development after STIC detection. They may also question the appropriate follow-up duration, surveillance method, and recurrence rate of subsequent carcinoma after STIC detection in real-life clinical situations in Korea.

Various studies have reported on subsequent carcinoma development in patients with STIC, depending on whether adjuvant therapy was administered. **Table 5** presents an overview of the previously published literature on STIC/STIL. Agoff et al. [11] and Rush et al. [28] reported three and nine cases of STIC, respectively. In these studies, two and four patients who received

Table 5. Overview of previously published studies of isolated STIC/STIL

Study (type)	Pathology (No. of cases)	Age (range, yr)	BRCA status (No. of cases)	Cytology (No. of cases)	Adjuvant treatment (No. of cases)		FU evaluations (interval) [No. of cases]	FU duration (range, mo)	Subsequent carcinoma (No. of cases)
					Staging surgery	Adjuvant chemotherapy			
Agoff et al. [11] (case-series)	STIC (3)	47–74	BRCA1/2 (1/1), UK (1)	Neg (2), Pos (1)	NR	Done (2), ND (1)	NR	30–48	NED
Carcangiu et al. [12] (case-series)	STIC (3)	NR	BRCA1 (3)	ND (1), Neg (2)	ND (3)	ND (3)	GY exam, CA-125, TVS (twice a year)	7–87	NED (3)
Callahan et al. [13] (retrospective)	STIC (3)	44–66	BRCA1/2 (1/2)	Neg (2), Pos (1)	Done (2), ND (1)	Done (3)	NR	NR	NR (3)
Wethington et al. [27] (retrospective)	STIC (12)	39–77	BRCA1/2 (5/5), UK (2)	Neg (11), Pos (1)	Done (8), ND (4)	ND (12)	CA-125, imaging testing (NA)	16–44	NED (11), death due to another cancer (1)
Blok et al. [29] (retrospective)	STIC (4)	46–71	BRCA1/2 (3/1)	NR (2), Neg (2)	ND (4)	ND (4)	NR	2–135	PC (2)
Stanciu et al. [24] (retrospective)	STIC (7)	NR	BRCA1/2 (3/3), UK (1)	Neg (7)	ND (7)	ND (7)	NR	NR	PC (2)
	STIL (2)		NR	NR	NR	NR			NR
Rush et al. [28] (prospective)	STIC (9)	37–65	BRCA1/2 (6/2), WT (1)	Neg (2), Pos (7)	NR	Done (4), ND (5)	NR	6–228	NED (9)
Saccardi et al. [14] (retrospective)	STIC (4)	43–52	BRCA1/2 (3/1)	Neg (4)	ND (10)	ND (10)	CA125, GY sono, pelvic exam (every 6 mo for 5 yr, then, annually)	27–106	NED (10)
	STIL (6)	40–51	BRCA1/2 (4/2)	Neg (6)				12–82	
Patrono et al. [25]* (review)	STIC (67)	37–77	BRCA1/2 (36/21), BRCA1 or 2 (5), BRCA2UV (1), UK (4)	Neg (54), Pos (7), ND (1), NR (5)	Done (53), ND (14)	Done (11), ND (45), NR (11)	NR	2–150	PC (3)
Van der Hoeven et al. [31] (review)	STIC (82)	36–77	BRCA1/2 (53/28), NA (1)	Neg (41), Pos (4), NR (37)	Done (13), ND (16), NR (53)	Done (3), ND (31), NR (48)	NR	7–138, NR (46)	PC (4)
Ruel-Laliberté et al. [30] (review, meta-ana.)	STIC (99)	Mean 54±9.39	BRCA1 or 2 (83), WT (13), UK (3)	NR	Done (28)	Done (7)	NR	1–150	PC (9)
Our study (multi-center, retrospective)	STIC (15)	38–75	BRCA1/2 (10/5)	Neg (8), ND (7)	ND (19)	ND (19)	CA-125 [14], TVS [17], APCT [3] (≤3 mo [6], 3–6 mo [12], 6–12 mo [1])	2–121	NED (19)
	STIL (4)	47–67	BRCA1/2 (3/1)	ND (4)				6–69	

FU, follow-up; GY, gynecological; HGSOC, high-grade serous ovarian carcinoma; Meta-ana., meta-analysis; NA, not available; ND, not done; NED, no evidence of disease; Neg, negative; NR, no record; PC, peritoneal carcinoma; Pos, positive; sono, sonography; STIC, serous tubal intraepithelial carcinoma; STIL, serous tubal intraepithelial lesion; UK, unknown; UV, unclassified variant; WT, wild type.
*This study reported cases of isolated STIC found in RRSO specimens and incidental STIC found in nonprophylactic surgical specimens. Only cases of isolated STIC in RRSO specimens are included in the table.

adjuvant chemotherapy (taxol/carboplatin for three or six cycles, respectively) did not develop additional carcinomas. Stanciu et al. [24] conducted a retrospective study of 300 consecutive RRSO cases over 9 years and found that two of seven patients with STIC who did not receive additional treatment developed PC. Similarly, Blok et al. [29] reported subsequent PC in two of four patients with STIC who were followed up without further treatment. These findings may suggest that additional adjuvant treatment following a STIC diagnosis may offer the benefit of reducing the likelihood of subsequent carcinoma. However, caution is necessary when interpreting the potential benefits of adjuvant treatment, as studies on the clinical course of STIC were conducted on a small scale or have reported limited outcomes.

To provide a comprehensive overview of small-scale studies on the clinical outcomes of STIC, Ruel-Laliberté et al. [30] conducted a meta-analysis involving 99 patients across 14 articles, reporting inconsistent and varied adjuvant treatment options and indications. They found that patients who did not undergo surgical staging had a 14.5% risk of developing subsequent carcinoma. Similarly, a systematic review by Van der Hoeven et al. [31] reported a heightened

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risk of recurrence in patients who did not undergo staging procedures or who did not receive chemotherapy after the initial diagnosis of STIC during RRSO.

In contrast, our study demonstrated that none of the 19 patients with isolated STIC/STIL after RRSO developed subsequent carcinomas during a follow-up period of 2–121 months. Notably, none of these patients received aggressive adjuvant treatment, such as staging surgery or chemotherapy. Although this was a retrospective cohort study, it included a larger number of STIC cases than the previous studies owing to its multicenter design. Our findings are comparable to those of Carcangiu et al. [12] and Saccardi et al. [14], who reported no subsequent PC in their smaller cohorts of patients with STIC who did not receive adjuvant chemotherapy. Variations in the clinical outcomes of STIC across various studies may be attributed to the differences in study design, analysis methods, or patients' ethnicities. Therefore, the development of subsequent carcinoma may be significantly lower, at least in real-world clinical situations in Korea. It can be concluded that additional adjuvant treatments following a diagnosis of STIC are not strongly recommended and should be approached only after careful consideration.

Establishing appropriate surveillance guidelines through consensus among medical professionals may be crucial to predict and improve clinical outcomes in patients with STIC/STIL. However, studies on the optimal duration and methods of surveillance following STIC detection are limited. Furthermore, no studies have directly investigated the differences in clinical practice patterns among clinicians. The available reports offer only limited information regarding the methods used and the intervals between surveillance during the post-STIC detection period. In a retrospective cohort study including patients with *BRCA1/2* mutations who underwent RRSO, Saccardi et al. [14] reported four cases of STIC and six cases of STIL. The authors conducted surveillance every 6 months for the first 5 years, which included CA-125 testing, gynecologic pelvic examinations, and transvaginal/transabdominal ultrasound. Similarly, Carcangiu et al. [12] conducted an annual surveillance in three STIC cases, which included CA-125 testing, gynecological examination, and transvaginal ultrasound performed twice per year.

Our study examined the patterns of care in terms of surveillance methods and intervals after detecting 19 STIC cases across different institutions. Most clinicians preferred short-term surveillance within 6 months of STIC detection, whereas some opted for annual surveillance within 1–2 years. Most patients underwent CA-125 testing and gynecologic sonography for surveillance, whereas APCT was used infrequently. Despite variations in surveillance intervals and methods, all institutions performed regular monitoring. It can be inferred that most clinicians in Korea consider surveillance necessary due to the possibility of subsequent carcinoma development. The methods and intervals used were not significantly different from those reported in previous studies [12,14]. Although clinicians have not yet reached a consensus on the appropriate surveillance protocols, our findings can be used as minimal evidence to determine surveillance methods and intervals after STIC detection.

Our study reported five cases in which STIC/STIL was incidentally discovered during benign gynecologic surgery. However, determining the exact detection rate of incidental STIC/STIL in the general female population is not feasible, unlike in patients with *BRCA* mutations or a family history of breast or ovarian cancer. This is because many salpingectomy samples obtained to manage benign diseases may not undergo the SEE-FIM protocol, potentially leading to missed STIC detection. The administration of adjuvant therapy, surveillance

evaluation tools, and follow-up intervals after incidental STIC/STIL diagnosis varied across institutions. Interestingly, in the only case in which *BRCA* genetic testing and staging surgery were performed after an incidental STIC diagnosis, a *BRCA1* mutation was discovered. Considering that the results of *BRCA* genetic testing provide valuable information relevant to individuals' healthcare, even in healthy patients, we cautiously recommend additional *BRCA* mutation testing to provide patients with additional prognostic information in cases where STIC/STIL is incidentally diagnosed following a benign gynecological surgery.

Our study had some limitations. The study was conducted retrospectively across multiple institutions; therefore, it is challenging to exclude the effects of inaccuracies, the absence of data, and other sources of bias. To mitigate these limitations, a single physician reviewed all data for consistency and appropriateness. Second, the diagnostic process for STIC/STIL using SEE-FIM relied on each hospital's protocol rather than on a central review by a representative institution. This implies that deviations in the diagnosis of STIC/STIL by institutions cannot be completely ruled out. This is a typical limitation inherent to retrospective study designs in which not all samples could be collected because samples from all patients who had undergone surgery in the past were not preserved. It is also important to note that the STIC data collected in this study were limited to six institutions, which may not provide a comprehensive analysis of patients with STIC in Korea. Consequently, these findings may not be fully representative of the clinical outcomes of STIC in Korea. However, a significant number of patients with STIC may have been included in this study, as the participating institutions were tertiary hospitals with large numbers of patients or institutions specializing in cancer research and treatment under the South Korean Ministry of Health and Welfare. Therefore, future studies should include larger cohorts. Finally, this study included cases of follow-up failure and a short follow-up period. Therefore, limited accurate information is available regarding the clinical course of disease in patients with STIC/STIL with a short follow-up. Continuous studies on these individuals are necessary.

However, this retrospective multicenter cohort study was conducted to address the rarity of STIC/STIL. We investigated the detection rate of STIC/STIL in women who underwent RRSO and identified their clinical outcomes. Additionally, we presented the clinical data of patients who were incidentally diagnosed with STIC after benign gynecological surgery. Furthermore, we examined whether there were differences in clinical practices for surveillance processes among clinicians in real-world situations and whether these changes affected STIC/STIL patient outcomes.

Our study indicates that the detection rate of STIC/STIL in Korea is low. Furthermore, no subsequent carcinoma development was observed during the follow-up period across all institutions, even in the absence of adjuvant treatment, and regardless of variations in follow-up intervals and surveillance methods. Given the potential risk of subsequent carcinoma that cannot be entirely ruled out, patient monitoring may be considered. However, excessive concern and surveillance regarding subsequent carcinoma may be unnecessary, and adjuvant treatments should be approached with caution. Further data from prospective cohort or observational studies are needed to assess the validity of adjuvant treatments.

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