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RESEARCH ARTICLE

Diagnosis and management of isolated serous tubal intraepithelial carcinoma: A qualitative focus group study

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Abstract

Objective: A Serous Tubal Intraepithelial Carcinoma (STIC) without concomitant invasive carcinoma is occasionally identified and associated with a high risk of subsequent peritoneal carcinomatosis. Management needs optimisation. This study explores professionals' opinions and clinical practices regarding the diagnosis, counselling, treatment and follow-up of isolated STIC to facilitate clinical decision making and optimise the direction of future research. A secondary aim is to assess international clinical guidelines.

Design: Focus group study.

Setting: Four online sessions.

Population: International panel ($n = 12$ countries) of gynaecologists, gynaecologic oncologists, pathologists and medical oncologists ($n = 49$).

Methods: A semi-structured interview guide was used. Two independent researchers analysed transcripts by open and axial coding. Results were organised in domains. Relevant (inter)national guidelines were screened for recommendations regarding isolated STIC.

Main Outcome Measures: Professionals' opinions and clinical practices regarding isolated STIC management.

Results: Regarding pathology, most professionals identified the SEE-FIM protocol as standard of care for high-risk patients, whereas variation exists in the histopathological examination of fallopian tubes in the general population. Confirmation of STIC diagnosis by a specialised pathologist was recommended. Regarding work-up and follow-up after STIC diagnosis, there was variety and discordance. Data on outcomes is limited. As for treatment, chemotherapy and PARP inhibitors were not recommended by most. Eleven guidelines provided limited recommendations.

Conclusions: We identified recommendations and highlighted knowledge gaps in the diagnosis and management of isolated STIC. Moreover, recommendations in clinical guidelines are limited. There is an agreed need for international collaboration for the prospective registration of isolated STIC.

KEYWORDS
fallopian tube, ovarian carcinoma, risk reducing salpingo-oophorectomy, serous tubal intraepithelial carcinoma

See Appendix 1 for Consortium STIC focusgroup.

Serena Negri and Charlotte Fisch contributed equally to this work.

1 | INTRODUCTION

In recent years there has been growing evidence that the majority of extrauterine high-grade serous carcinomas (HGSC) originate from a serous tubal intraepithelial carcinoma (STIC).[1–4] Most frequently this precursor lesion is found in the fimbriated end of the fallopian tubes, in association with an invasive HGSC.[5] Sometimes, a STIC is found isolated. Although the incidence varies between studies, isolated STIC is found in approximately 3% of women with a *BRCA1/2* germline pathogenic variant (PV) undergoing a risk-reducing salpingo-oophorectomy (RRSO)[6,7] and in <0.01% of the general population undergoing salpingectomy for benign indications.[8] Identification of isolated STIC has significant clinical implications as a recent meta-analysis showed a subsequent increased risk of HGSC of the peritoneum (peritoneal carcinomatosis, PC) of 10.5% and 27.5% in *BRCA1/2* PV-carriers 5 and 10 years following a STIC diagnosis at RRSO, respectively.[7] A PC has a poor 5-year survival rate of 26%.[9]

While the malignant potential of isolated STIC is becoming apparent, there are still many uncertainties about diagnosis and management. STICs are rare and often small lesions, therefore they are potentially difficult to diagnose.[10,11] Several diagnostic recommendations have been suggested to validate and uniform the diagnosis of STIC[6,12–15] including the use of Sectioning and Extensively Examining the Fimbriated end (SEE-FIM) grossing protocol and using morphological and immunohistochemical criteria. However, accuracy and reproducibility of this diagnosis remain challenging.[12,16,17] Additionally, after isolated STIC diagnosis, there is no consensus on clinical management in terms of additional surgery, therapy and/or subsequent follow-up. Variation in management exists worldwide and within countries.[18]

To address this clinical gap, we initiated a focus group study comprising an international multidisciplinary panel of professionals. We investigated healthcare professionals' opinions and clinical practices regarding diagnosis, counselling, treatment and follow-up of patients with isolated STIC with the aim of facilitating clinical decisions and providing a foundation for future research. Our secondary aim was to provide an overview of current (inter)national guidelines and their recommendations on isolated STIC.

2 | METHODS

2.1 | Study design

An international qualitative focus group study was conducted with professionals working in the field of ovarian cancer (prevention). We developed online focus groups to assess professionals' opinions and clinical practices in diagnosis, counselling, treatment and follow-up of patients with isolated STIC. Focus groups are considered particularly appropriate for exploratory research because the interaction between participants leads to gaining depth in the discussion and stimulating new ideas.

This qualitative study was carried out following the Consolidated criteria for Reporting Qualitative studies (COREQ) (Table S1).[19]

In addition, we searched existing clinical national and international guidelines. We searched for relevant recommendations regarding diagnosis, counselling, treatment and follow-up of isolated STIC.

This study was not subject to the Dutch 'Medical Research Involving Human Subjects Act', as assessed by the institutional review board of the Radboud University Medical Center (reference nr. 2023/16234).

2.2 | Professionals' recruitment

An international panel of gynaecologists, gynaecologic oncologists, pathologists and medical oncologists currently working in a high-volume/referral centre for ovarian cancer (prevention) and involved in research, were recruited through targeted invitation by e-mail. Recruited professionals were invited to propose professionals that could be eligible to join the study, in a snowball sampling method. Participants were included if they were (i) licensed professionals, (ii) had sufficient English language proficiency and (iii) had access to the online video conference platform Microsoft Teams©. Consent was given for audio- and video recording of the sessions. Per focus group, eight to twelve participants were planned[20,21] balancing clinical background and geographical origin of participants.

2.3 | Data collection

2.3.1 | Focus groups

Participants completed an online questionnaire via the electronic data management system CastorEDC© regarding their professional experience (e.g. years of experience, number of patients/year, number of diagnoses/year and type of centre).

Focus groups were audio- and video recorded via an online video conference platform. They were held as semi-structured interviews, following an interview guide previously prepared by the research team investigating critical aspects in the literature regarding diagnosis, counselling, treatment and follow-up (Interview guide: Appendix S1), but also allowing interaction between participants. The research team consisted of eight members with previous expertise in this research field, who did not participate in the discussion.

At each focus group session three members of the research team were present: one as moderator of the discussion, one as note-keeper and technical support, and others as observers.

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2.3.2 | Guidelines

We consulted national societies of obstetricians and gynaecologists listed on the website of the International Federation of Gynecology and Obstetrics (FIGO)[22] which were founded in a nation with a developed economy, as determined by the United Nations.[23] Additional international collaborative societies were also checked for potential guidelines.

2.4 | Analyses

Focus groups were transcribed and transcripts were independently analysed by two researchers using Atlas.ti (version 23.1.1, Atlas.ti Scientific Software Development GmbH; Berlin, Germany) and applying grounded theory. After reading the interviews, open coding of the first two focus groups was independently performed by the two researchers. Comparable descriptive codes were combined and re-categorised into specific domains. Subsequently, a code book was created. The first two focus groups were re-coded and the last two focus groups were coded, both independently. Finally, the two researchers discussed together their findings until they achieved mutual agreement; in this way, axial codes were defined. Disagreements were discussed with a third researcher until a consensus was reached.

3 | RESULTS

3.1 | Baseline characteristics

Of the 119 professionals who were invited to join the study, 60 expressed interest in participating (positive response rate 50.4%). Four 90-minutes focus groups were organised in April 2023. Forty-nine professionals from twelve different countries joined the sessions (participation rate 81.6%; 11–15 professionals per focus group). The group included 28 gynaecologic oncologists (57%), 5 gynaecologists (10%), 11 pathologists (22%) and 5 medical oncologists (10%). They had a median work experience of 15 years (range 3–34) and 81.6% worked in an academic hospital (Table 1).

TABLE 1 Background characteristics of participants and working experience.

Focus group participants	Total ($n = 49$)
Specialty	
Gynaecologic oncologists	28
Gynaecologists	5
Medical oncologists	5
Pathologists	11
Type of centre working in	
Academic medical centre	40
Non-academic medical centre	9
Referral centre for high-risk patients	48
Continent working in	
Europe (Austria, Germany, Italy, Netherlands, Norway, Poland, Spain, Sweden and the United Kingdom)	36
North America (Canada and the United States)	12
South America (Brazil)	1
Experience in the field, years (range)	15 (3–34)
Gynaecologists and gynaecologic oncologists ($n = 33$)	
Patients seen per year	
At high inherited risk of OC[a] (range)	90 (10–500)
For isolated STIC[a] (range)	2 (0–12)
Risk-reducing procedures per year[a] (range)	30 (10–125)
Opportunistic salpingectomy performed (%)	
Yes	30 (91%)
No	3 (9%)
Medical oncologists ($n = 5$)	
Patients seen per year	
For OC[a] (range)	60 (10–1000)
For isolated STIC[a] (range)	1 (1–10)
Pathologists ($n = 11$)	
Diagnosis per year	
Ovarian cancer[a] (range)	90 (2–750)
STIC (both isolated and concurrent to HGSOC)[a] (range)	20 (2–50)
Risk-reducing tissue examinated per year[a] (range)	25 (12–80)
SEE-FIM protocol performed by pathologist	
Yes	11 (100%)
No	0
SEE-FIM protocol performed for (%)	
All fallopian tubes	2 (18.2%)
RRSO/RRS	6 (54.5%)
RRSO/RRS and OS	1 (9.1%)
RRSO/RRS and malignancies	1 (9.1%)
RRSO/RRS, OS and malignancies	1 (9.1%)

Abbreviations: HGSOC, high-grade serous ovarian cancer; N, number of participants; OC, ovarian cancer; OS, opportunistic salpingectomy; RRS, risk-reducing salpingectomy; RRSO, risk-reducing salpingo-oophorectomy; SEE-FIM, Sectioning and Extensively Examining the FIMbriated end; STIC, Serous Tubal Intraepithelial Carcinoma.

[a]Data are shown as medians.

3.2 | Focus group sessions

At analysis, five domains were identified: pathology, work-up, treatment, follow-up and organisation. A summary of all findings is provided in Table S2.

For each domain, we inferred the most important recommendations on diagnosis, counselling, treatment and follow-up of isolated STIC (Table 2).

3.2.1 | Domain: Pathology

Most professionals agreed that reproducibility in STIC diagnosis is an issue, despite the use of a clinical algorithm

TABLE 2 Recommendations in isolated STIC based on focus group discussions.

Recommendations in isolated STIC	
Pathology	The SEE-FIM protocol should be routinely used in high-risk patients
	In case of isolated STIC, a specialised gynaecologic pathologist should review the case because of moderate reproducibility
	A diagnosis of STIC should be discussed in a multidisciplinary meeting such as a tumour board
	When morphology of the fallopian tube is aberrant, p53 and Ki-67 immunohistochemical staining should be performed
Work-up	Clinical data is needed to understand the role and the extent of staging surgery, clear recommendations/guidelines are needed
	There is a need for clear recommendations/guidelines on additional diagnostics including imaging (ultrasound/CT) and tumour markers (CA125)
	A PET or MRI scan is not recommended
	Germline genetic testing is recommended for patients with isolated STIC and unknown PV status
	Clinical data is needed to determine risk factors for development of peritoneal carcinomatosis after isolated STIC
Treatment	Chemotherapy and PARP-inhibitors are not recommended and should only be considered within clinical trials
Follow-up	Clinical data is needed to learn the advantages and disadvantages of follow-up, clear recommendations/guidelines are needed
Guidelines	The SEE-FIM protocol should be followed in all high-risk patients
	Guidelines on adjuvant imaging/markers, staging, treatment and follow-up should become available based on future international research
Future	There is a need for a longitudinal registration study and international collaboration since STIC diagnosis is rare

and immunohistochemistry. Reproducibility issues were described on all levels: between pathologists, institutions and countries. A potential method to improve this matter was suggested by involving a specialised gynaecologic pathologist in the diagnosis of STIC, central pathology review of specimens and internal validation with colleagues. According to some professionals, international consensus on diagnosis should be reached before further research is undertaken:

> We need to make sure that it's a STIC and not a STIL and not a high-grade serous carcinoma.

Use of the SEE-FIM protocol in high-risk patients was confirmed by most to increase detection rates. As fallopian tube abnormalities are rare in population-level risk patients, some considered only embedding the fimbriated end in these cases while others reported to also use the SEE-FIM protocol.

Aside from variation in STIC diagnosis, the possibility was discussed that STICs differ in regard to their PC risk:

> When we talk about isolated STIC, I don't think that it's one entity. I think it is a multitude of different presentations which may each have a different risk for recurrence.

According to some professionals, there could be morphological characteristics (e.g. papillary architecture, tufting and cell detachment) that might help stratify patients with isolated STIC in terms of future risk of PC, but for now this is subjective and not supported with evidence.

3.2.2 | Domain: Work-up

There was discordance in the necessity for additional diagnostics when isolated STIC is diagnosed. A few professionals considered a CT scan or CA125 measurement, whereas others did not. A rationale to refrain from additional diagnostics for some was that they already assess all high-risk patients preoperatively with imaging and/or CA125. A complete or parcel staging surgery was also considered by many professionals, the lack of data was discussed and most professionals explained not to include a lymphadenectomy (Table S3).

Indication for staging surgery could also be influenced by context, for example, if a patient was initially treated in a non-expert centre, then some professionals would offer staging surgery for a second look.

Many professionals rely on the results of peritoneal washings from the initial surgery, if performed, to decide on the necessity for further management.

Discussion of cases in a multidisciplinary meeting to decide on work-up and follow-up was part of clinical practice for some professionals while others discussed selected patients with STIC or none at all.

In case of STIC at salpingectomy, many agreed on the need for oophorectomy, whereas some would individualise the decision, based on age and presence of a PV. In case of STIC with unknown germline PV status, the majority recommended genetic testing.

3.2.3 | Domain: Treatment

The vast majority of professionals did not recommend chemotherapy in case of isolated STIC, given the lack of data

and the toxicity of the treatment. Only a minority discusses the possibility of chemotherapy with patients:

> You would only expose someone to these treatments with some good evidence on benefits.

PARP-inhibitors were neither administered nor recommended. Some professionals would consider chemotherapy and/or PARP-inhibitors within a clinical trial.

3.2.4 | Domain: Follow-up

Follow-up was not consistently performed. Some offered follow-up once or twice yearly with ultrasound and/or CA125 measurements while others refrained from follow-up and recommended the patient to return in case of symptoms. A minority considered regular CT scans. Some professionals stated that follow-up is not indicated in the current guidelines and many underlined the lack of data:

> I don't have an easy solution on how these patients should be followed; there is just no data.

There were also differing opinions regarding the counselling of patients; some professionals disclose the exact percentage risk of PC from current data, while others tell patients that there is an increased risk without mentioning the exact numbers:

> I think it's fair to tell them the numbers we know.

> We do disclose that there's a lot of uncertainty about this diagnosis, but that there is a risk.

Concern was expressed about the unclear pathogenesis driving the development of PC after STIC diagnosis and whether it should be labelled as recurrence or new primary. One of the pathophysiological mechanisms mostly considered was that PC comes from exfoliated cells from the fallopian tubes:

> I don't know, whether you consider it a recurrence if someone is seven or even ten years down the line, or if it's a new primary.

> If someone has had a diagnosis of STIC and then it goes on to develop a peritoneal carcinoma, is this a new primary peritoneal cancer? Or is it a recurrence of a STIC that was not adequately staged?

3.2.5 | Domain: Organisation

The heterogeneity in management of patients with isolated STIC was a topic often addressed throughout the focus groups:

> Clearly there are differences in treatment policies across different centers, across different countries.

The need for guidelines and a more standardised approach was emphasised by many professionals, as was the need to raise awareness about the importance of isolated STIC diagnosis. Referral to a dedicated gynaecological cancer centre and discussion of cases in a multidisciplinary meeting was recommended to decide on work-up and follow-up.

Regarding future research, most professionals expressed the importance of collaboration and creation of an international registry of STIC cases:

> International collaboration seems really necessary.

> Only then, when we have large numbers, will the truth start to really become clear.

3.3 | Guidelines review

One hundred and thirty-four National societies of obstetricians and gynaecologists were listed on the FIGO website in September 2023.[22] Of these, 35 were founded in a developed economy nation, as determined by the United Nations[23] and were screened for guidelines. Three international collaborative societies were added, as was one society in which three nations (Austria, Germany and Switzerland) collaborate, resulting in 36 societies. All societies and guidelines screened are listed in Table S4. No guidelines were found online for 16 societies. Twenty societies with a total of 35 potentially eligible guidelines were screened for recommendations on diagnosis, counselling, and treatment or follow-up of isolated STIC. Of these, 24 guidelines were excluded as they did not contain any recommendations. After our search, a new version of the ESGO-ESMO-ESP consensus conference was released and therefore updated (Figure 1). The eleven included guidelines are summarised in Table 3. As shown, most guidelines recommend the use of the SEE-FIM protocol in RRSO specimens. Three guidelines[24–26] provide recommendations on immunohistochemistry (IHC). One of these recommends IHC in all RRSO specimens, one only for suspicious lesions and one states that there is no consensus about the usefulness and necessity of IHC staining. There was variation in the recommendations for additional diagnostics and staging. Some guidelines do not recommend staging, others advise discussing the possibility of staging with the patient.[27] The most recent ESMO-ESGO-ESP guideline, released by the most renowned European oncological societies, recommends peritoneal staging and for *BRCA1* PV carriers to perform endometrial sampling or consider hysterectomy. Chemotherapy is not recommended within the guidelines. One guideline[28] states that participation in prospective clinical trials should be strongly encouraged,

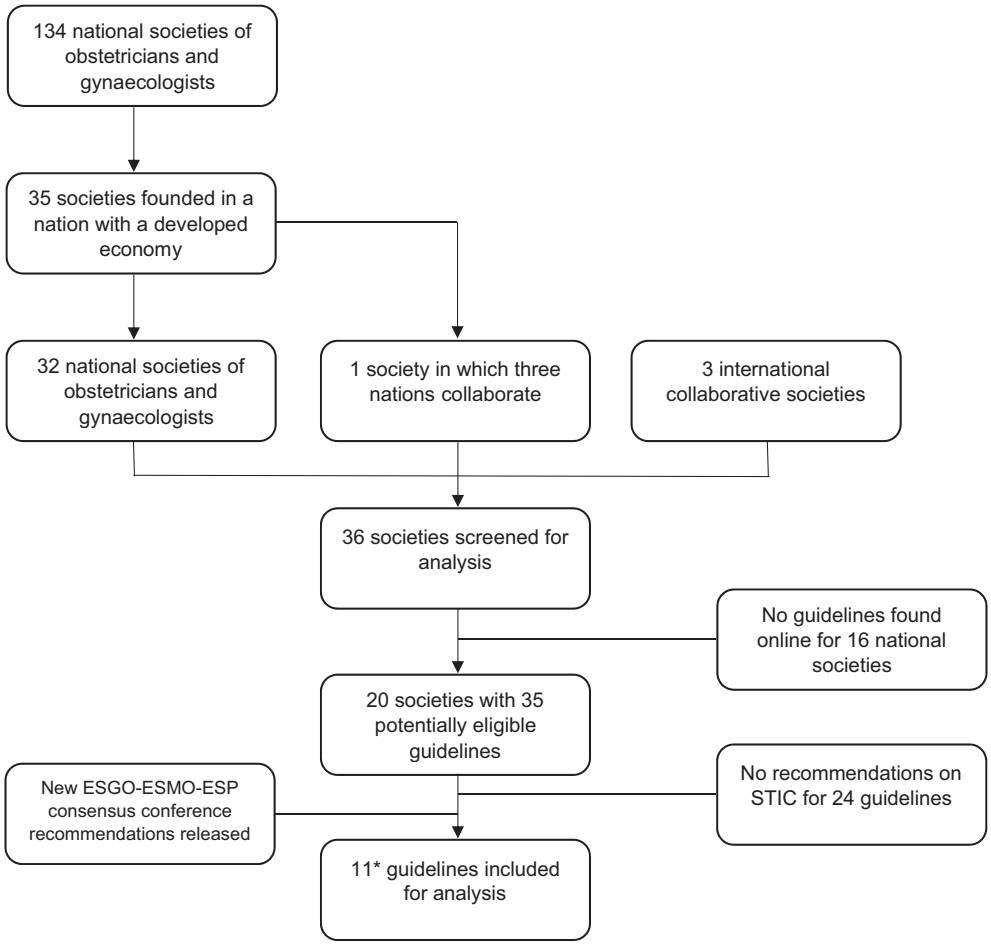

FIGURE 1 Flowchart of the search of guidelines. *ESGO-ESMO-ESP consensus conference recommendations were updated.

due to insufficient scientific evidence regarding staging and adjuvant treatment.

4 | DISCUSSION

4.1 | Main findings

This is the first international focus group study to identify professionals' opinions and clinical practices regarding diagnosis and management of isolated STIC. Most professionals consider the SEE-FIM protocol as a standard of care in high-risk patients whereas variation exists for the general population. Professionals recommended confirmation of STIC diagnosis by a specialised gynaecologic pathologist due to low interobserver reproducibility. Most professionals expect there will be morphological criteria that stratify STIC in relation to their future risk of PC. There is no consensus regarding the necessity of additional diagnostics, staging surgery and follow-up leading to a wide variation in clinical practice even within countries mainly due to lack of evidence. Professionals indicated that international collaboration in a prospective registration study is needed to generate evidence regarding diagnosis, treatment and long-term outcomes.

We found a general lack of (inter)national guidelines. Many recommendations address the importance of using the SEE-FIM protocol for high-risk patients, and three guidelines recommend genetic testing for STIC cases within the general population. The lack of guidelines mirrors the current paucity of data available in the literature and underlines the strong need for further studies.

4.2 | Interpretation

The use of the SEE-FIM protocol is universally accepted in high-risk patients undergoing RRSO, whereas the histopathological assessment of fallopian tubes for the general population is variable. Implementation of the SEE-FIM protocol across the entire population would likely increase STIC detection, but the cost-effectiveness is questionable as its incidence is expected to be very low (<0.01%).[8] Concerns about the suboptimal reproducibility of STIC diagnosis was another important finding. Carlson et al.[17] reported that reproducibility among experienced gynaecologic pathologists was moderate ($\kappa = 0.453$) (no 95% IC interval given) using H&E staining and improved by adding immunohistochemistry for p53 and Ki67. Visvanathan et al.[15] observed a good reproducibility of $\kappa = 0.73$ (95% CI

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TABLE 3 Overview of current guidelines regarding isolated STIC.

Country/region	Year	Recommendations
The Netherlands[26]	2015	During histopathological examination after RRSO, both fallopian tubes should be completely enclosed according to the SEE-FIM protocol, to detect STIC There is no consensus about the usefulness and necessity of analysing the sections immunohistochemically The clinical consequences and advice after a STIC diagnoses vary widely, from surgical staging, a diagnostic laparoscopy to 'doing nothing' Insufficient research has been conducted into the long-term follow-up of women with an occult intraepithelial carcinoma (STIC), to provide treatment advice Little series currently show a good prognosis without additional diagnostics or therapy
France[36]	2017	Bilateral adnexectomy surgical specimens must be subject to an exhaustive histological study protocol (complete inclusion of the surgical specimens according to the SEE-FIM protocol) to avoid missing an occult invasive tubal or ovarian cancer The finding of STIC does not currently lead to any specific treatment after adnexectomy
United States[37]	2017	Complete, serial sectioning of the ovaries and fallopian tubes is necessary, with microscopic examination for occult cancer. Rather than taking only one or two representative sections from each ovary, the complete ovaries and fallopian tubes should be serially sectioned and evaluated Because occult cancer may be found only through serial sectioning and thorough evaluation of the ovaries and tubes, it is possible that some subsequent primary peritoneal carcinoma actually represents the recurrence of a previously unrecognised occult cancer
United States[40]	2023	Peritoneal washings should be performed at surgery and pathologic assessment should include fine sectioning of the ovaries and fallopian tubes.
Canada[24]	2018	All RRSO specimens must be processed following published guidelines for what is commonly known as SEE-FIM protocol Processing of histologic sections should include sections for immunohistochemistry in addition to routine haematoxylin and eosin sections Diagnosis and reporting of occult cancers and significant precursor lesions (STIC) should follow published criteria to improve diagnostic reproducibility
Europe[32]	2024	SEE-FIM is recommended in RRBSO [IV, A; consensus: 85.4%]. It is suggested that the pathologist examines microscopically the whole fimbriae in benign conditions [V, B; consensus: 87%] In STIC, staging of the peritoneum is recommended [II, A; consensus: 97%]. In STIC, it is recommended that (re)-staging is carried out, preferably by a minimally invasive procedure [III, B; consensus: 92%] In STIC, hysterectomy should be considered, particularly in patients with a gBRCA1-mut [IV, A; consensus: 82%]. In STIC, if the uterus is preserved, endometrial sampling in patients with a gBRCA1- mut is recommended [IV, B; consensus: 100%]. In STIC, lymphadenectomy is not recommended [V, E; consensus: 95%] Adjuvant ChT is not recommended in surgically staged STIC [IV, D; consensus: 100%] In cases of STIC, testing for gBRCA1/2-muts and other high-penetrance hereditary genes is mandatory [II, A; consensus: 100%]
Romania[38]	2019	Tubes must be handled as little as possible during surgery to prevent traumatic exfoliation of the cells Both ovaries and fallopian tubes must be placed in endobags when extracted from the pelvis. Both ovaries and fallopian tubes must be process according to protocol (*protocol not specified*)
Austria, Germany and Switzerland[25]	2021	If there is a known BRCA germline mutation or a suspicion of a BRCA germline mutation, the material after prophylactic salpingo-oophorectomy must be examined with the SEE-FIM protocol In case of opportunistic salpingectomy, at least the fimbriated end should be complete to be examined. The tube can be made in several representative cuts For lesions suspicious for serous tubal intraepithelial carcinoma (STIC) an immunohistochemical examination for p53 (aberrant expression in STIC) and Ki67 (>10% in STIC) can be used to confirm the diagnosis If a serous tubal intraepithelial carcinoma (STIC) is detected, the patient should be informed about the risk of an already existing invasive process If a serous tubal intraepithelial carcinoma (STIC) is detected, the possibility of staging surgery to exclude a higher-grade lesion needs to be discussed with the patient
Norway[27]	2022	In case of STIC it is recommended to perform a surgical procedure with a midline incision. During the surgical procedure ascites or peritoneal rinsing fluid should be collected for cytology, systematic description of the entire abdominal cavity (and if applicable a PCI score), suspicious lesions should be excised and frozen sections are applicable. Besides a hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy should be performed. Premenopausal patients are assessed individually It has not been shown that lymphadenectomy and/or chemotherapy give a better prognosis if only STIC has been detected and is therefore not recommended Histology with SEE-FIM procedure (3 mm close sections) of tubes/ovaries is recommended The patient should be recommended BRCA1–2 testing Follow-up as in carcinoma

(Continues)

TABLE 3 (Continued)

Country/region	Year	Recommendations
Spain[39]	2022	Due to the possibility of occult cancer (2–17%), including STIC, the pathological examination must be performed following the SEE-FIM protocol
Sweden[28]	2023	A through histological examination of the tubes must be done In case of isolated STIC after opportunistic salpingectomy, referral to a gynaecological tumour surgery centre is recommended for information, hereditary cancer history collection and referral to the genetics clinic Due to insufficient scientific evidence, supplementary staging surgery and/or adjuvant cytostatic treatment is not recommended in case of STIC found in risk reduction salpingo-oophorectomy (RRSO) or opportunistic salpingectomy Within the framework of a clinical study, follow-up is recommended for isolated STIC found at RRSO or opportunistic salpingectomy. Participation in prospective clinical studies is strongly encouraged.

0.58, 0.86) among gyanecologic pathologists combining morphology with IHC. Consistency in STIC diagnosis is key, because of the increased risk of PC that is reported after an isolated STIC.[7,29,30] Secondly, it is pivotal to expand research regarding STIC and the role of salpingectomy, to improve the understanding of pathophysiological pathways of HGSC. The presence of pathology protocols, central pathology review and internal consultation were considered important to improve reproducibility. For the future, artificial intelligence may enhance reproducibility, and the first study demonstrated its ability to identify abnormal epithelium.[31]

Another topic of discussion was the possibility that STIC may not be one single entity, but a heterogeneous group of lesions with different morphological features conferring different prognoses. Understanding which morphologic and/or molecular profiles are associated with a higher risk of subsequent PC could stratify patients with isolated STIC, although there is no current literature available.

There is wide variation in management following STIC diagnosis, ranging from no further actions to staging surgery, CT-scans and/or follow-up.

Staging surgery is inconsistently performed and its impact on prognosis is not clear. Whether staging should be performed for all patients or dependent on abdominal washings and the presence/type of PV was discussed. Considerations were also made regarding the necessity of oophorectomy, hysterectomy, omentectomy and lymphadenectomy. In a recent meta-analysis,[30] 7.3% (7/99) received chemotherapy and 26% (25/99) underwent staging surgery after a diagnosis of isolated STIC. Staging surgery varied from hysterectomy with salpingo-oophorectomy to salpingo-oophorectomy with omentectomy. At staging surgery, 3 of 25 patients (12%) were diagnosed with HGSC. During a mean follow-up of 55.5 months, nine (9.1%) HGSC occurred, of which none had undergone previous staging surgery. It is possible that these patients were understaged, but numbers are too small to draw conclusions. The mean time of 58.5 months between STIC and PC makes it less likely that these patients were all understaged at time of diagnosis.

The new ESGO-ESMO-ESP consensus conference recommendations advise to stage the peritoneum in cases of isolated STIC[32]; in *BRCA1* PV-carriers endometrial sampling should be performed or hysterectomy considered. The consensus rates of these recommendations were high (82%–100%) however no efficacy data is available.

Peritoneal washings are inconsistently performed during risk-reducing surgery, ranging from routinely to not at all depending on centre and professional. Some suggested that additional diagnostics should only be conducted when malignant cells are detected at cytology. Positive washings have been reported in association with STIC at RRSO (32%, 10/31).[33] Conversely, malignant washings and normal histology of tubes and ovaries at RRSO are reported rarely, leading some authors to question the additional clinical value of this procedure.[34] Whether patients with positive washings at STIC diagnosis constitute a sub-category at higher risk of subsequent PC is unknown. Further studies and longer follow-up are needed.

Professionals agreed that when an isolated STIC is diagnosed in the general population, referral for genetic testing is recommended. Whether the presence of a PV should impact further management is not clear. In our previous study, age at RRSO and type of BRCA-PV were associated with the risk of having an isolated STIC. However, when STIC was found, age and type of BRCA-PV no longer appeared to influence the risk of PC.[7] Thus, presumably the management of isolated STIC should not be influenced by age or by the presence/type of BRCA-PV.

Nearly all professionals advised against systemic treatment for isolated STIC, with either chemotherapy or PARP-inhibitors, mainly because efficacy data is lacking and treatments are toxic. Most professionals would only consider systemic treatment within a clinical trial which is not easily arranged for such a rare disease. Moreover, the administration of chemotherapy for what is considered a precancerous condition is an ethical debate and is viewed by most as overtreatment.

Recommendations for follow-up vary among professionals and currently, there are no data on its impact on long-term prognosis. The recently identified increased risk of PC[7] may lead clinicians to be more inclined to follow-up, although screening for HGSC with ultrasound and/or CA125 appeared ineffective in previvors.[35] Additionally, as the risk for PC increases over time (10.5%

(95% CI, 6.2–17.2) at five and 27.5% (95% CI 15.6–43.9) at 10 years),[7] it is not clear how long follow-up should last and what it should entail.

The pathophysiological mechanism of STIC leading to PC is not yet clear, and this was considered a barrier in counselling patients. It could be a 'recurrence' due to exfoliated cells from STIC or a 'new' independent primary cancer. A better understanding of the pathophysiology beneath this event is therefore crucial.

Concerning future research, professionals mentioned the need to start a prospective international collaboration and registration of cases which can be used to relate pathology to long-term outcomes, including the development of PC. A more in-depth analysis of the origin of PC after STIC is important to understand the pathophysiological pathways. Awaiting more data, to improve patients' management and clinical practice, quantitative studies like a Delphi study should be undertaken to generate consensus among professionals.

4.3 | Strength and limitations

A large international panel of professionals participated, with high response (50.4%) and participation rates (81.6%). The multidisciplinary background of professionals gave depth to the discussion. Geographical provenience was diverse; however, as the majority came from Europe and North America, there is the potential for demographic bias. Due to the design, data are qualitative in nature and thus more in-depth assessment was possible, although quantitative data could be valuable to quantify the extent and level of agreement on certain domains.

5 | CONCLUSIONS

Many uncertainties exist about diagnosis, counselling, treatment and follow-up of isolated STIC, due to lack of data and consensus. Clinical guidelines are limited in providing recommendations. Our study highlights the clinical gaps that need investigation to standardise clinical practice among professionals and it provides useful recommendations in cases of isolated STIC.

International collaboration is necessary given the rarity of STIC, and prospective registration is desirable.

AUTHOR CONTRIBUTIONS

S.N., C.F., M.H.D.B., J.B., M.S., M.P.S., J.A.H. and R.H. were involved in the focus groups and critical appraisal. S.N. and C.F. performed the data collection, were involved in analysing the data and wrote the original draft of the manuscript. M.P.S., J.A.H. and R.H. supervised the study. All authors contributed to acquisition of data by participating in the focus group sessions, critically revised the manuscript and provided final approval of the version to be published.

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CONFLICT OF INTEREST STATEMENT

The authors declare the following conflicts of interest: Janine L. Bakker: advisory boards for Novartis, Gilead and a webinar for AstraZeneca. Marcus Q. Bernardini: advisory boards for GSK, AstraZeneca and Integra. Ranjit Manchanda: research funding into surgical prevention of ovarian cancer from Barts Charity, Rosetrees Trust; Topic Advisor for the NICE Guideline—'Ovarian cancer: identifying and managing familial and genetic risk'; research funding outside this area from Yorkshire Cancer Research, Eve Appeal, GSK and NHS England; advisory board membership from GSK, Astrazeneca and Everything Genetics Limited. W. Glenn McCluggage: member of the National Institute for Health and Care Excellence Committee in the United Kingdom; providing guideline 'Ovarian Cancer: identifying and managing familiar and genetic risk'; member of the Central Pathology Review Committee and Trial Management group of 'Protector' (preventing ovarian cancer through early excision of tubes and late ovarian removal) in the United Kingdom. Shibani Nicum: No COI for this manuscript. Disclosures: advisory boards/speaker honoraria: GSK, AstraZeneca, Roche, Clovis; institutional research funding: AstraZeneca. Joseph T. Rabban: reports that his spouse receives salary and stock options from Merck & Co. Rebecca L. Stone: consulting for Astrazeneca (ongoing); advisory board for GlaxoSmithKline (6/26/21 only); research grant from Pacira Pharmaceuticals (ongoing).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL

This study was not subject to the Dutch 'Medical Research Involving Human Subjects Act', as assessed by the institutional review board of the Radboud University Medical Center (reference nr. 2023/16234).

CONSENT TO PUBLISH

All the authors give consent to publish.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

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