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Serous endometrial intraepithelial carcinoma (SEIC): Current clinical practice in The Netherlands

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ABSTRACT

Introduction: Serous endometrial intraepithelial carcinoma (SEIC) is a rare diagnosis, defined as an intraepithelial lesion with cells identical to serous type endometrial carcinoma. SEIC is considered to be potentially metastatic, however clear and robust data on prognosis are lacking, potentially leading to variability in clinical management. **Objective:** The aim is to establish the opinion of gynecologists on the optimal management of patients with SEIC. **Methods:** An online questionnaire with 15 multiple choice questions was sent to all gynecologists with expertise in gynecological oncology in 19 expert centers in The Netherlands. **Results:** A total of 24 gynecologists participated. The majority of respondents (n = 18/24, 75%) do not consult a guideline regarding the treatment of SEIC. In current practice, 14 of the 24 respondents perform surgical staging in women with SEIC (58.3%) while seven choose hysterectomy with bilateral salpingo-oophorectomy (29.2%), and three (12.5%) have no firm preference. Eleven of the 14 respondents who perform a surgical staging procedure believe that this is certainly the optimal treatment. The majority of respondents have no firm opinion on whether lymph node sampling or lymph node dissection is preferable during surgical staging (n = 15/23, 65.2%). Most respondents do not give adjuvant therapy (n = 15/24, 62.5%), 25.0% recommend brachytherapy (n = 6/24). Follow-up is for 5 years in almost all cases (n = 23/24). **Conclusion:** There is no consensus on the optimal surgical treatment and the use of adjuvant therapy for patients with SEIC. Our research team is therefore conducting a nationwide cohort study in which treatment modality, morbidity and survival will be evaluated.

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Introduction

Serous endometrial intraepithelial carcinoma (SEIC)(ICD-O code 8441/2) is defined as a non-invasive lesion of the endometrial epithelium, replacing the native surface of the endometrium.[1,2] This intraepithelial lesion would appear to have a malignant potential, as cases with extrauterine spread of disease – even at time of presentation – have been described.[3–6] The World Health Organization (WHO) defined SEIC as a specific diagnosis in 2012[7] and since then only a few studies have focused on women with isolated SEIC. In the fifth edition of the WHO classification of tumours, SEIC is considered to be potentially metastatic: “In the absence of

demonstrable invasion, the intraepithelial lesions can shed malignant cells and metastasize to extrauterine sites.”[2] There have been several hypotheses as to the mechanism of dissemination of malignancy in SEIC. Current evidence supports the idea that the extrauterine tumor cells are not independent but are metastatic from the (superficial) uterine tumor.[6,8]

SEIC is a histopathological diagnosis; the cells of SEIC are identical to the malignant tumor cells in invasive uterine serous carcinoma.[8–11] Uterine serous carcinoma represents 10% of all endometrial carcinomas, but has highly aggressive behavior, and contributes disproportionately to relapse and deaths when compared to the endometrioid type of endometrial cancer.[12–14] In 2018, a total of 382,069 women were diagnosed with endometrial cancer worldwide (all histological types) and this number represents 4.4% of all malignancies in females.[15] To our knowledge, there are no reliable prevalence rates for SEIC in the general population. Currently, several names are used in the medical literature: ‘endometrial carcinoma in situ’, ‘non-invasive endometrial serous

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carcinoma', 'superficial serous carcinoma', 'minimal uterine serous carcinoma' and 'serous endometrial intraepithelial neoplasia'. It has been suggested that the term SEIC should be used, to standardize international nomenclature.[8]

Although it is generally accepted that SEIC is a non-invasive lesion which can present with disseminated disease, there are in fact few data on the prognosis of patients with SEIC. The WHO recommends surgical staging of disease (hysterectomy, bilateral salpingo-oophorectomy, omentectomy, lymph node sampling, peritoneal biopsies and peritoneal washings).[2,7] However, in patients with SEIC there is no international guideline, nor is there evidence – besides the statement of the World Health Organization – on the optimal surgical approach. In daily practice, clinicians may be uncertain whether to perform a complete staging procedure or not. In the absence of guidelines, clinical practice may vary from hysteroscopic resection to complete surgical staging. According to a cohort study by Pathiraja, optimum surgical staging with appropriate adjuvant treatment should at least be considered when treating these patients.[1]

This study describes current clinical practice in The Netherlands and the attitude of Dutch gynecologists towards the treatment of SEIC.

Methods

Population

An open, online questionnaire was sent to all 19 Dutch centers for gynecological oncology. A mailing list of gynecologists trained in gynecological oncology was created by contacting the 19 medical centers (of which seven are academic medical centers) who organize and perform the treatment of uterine carcinoma. All gynecologists from these hospitals who are trained in gynecological oncology and have expertise in endometrial malignancy were contacted by e-mail or by telephone. All gynecologists gave their consent for participation prior to the link for the online survey being sent.

Questionnaire

The questionnaire was developed and then checked using the 'Checklist for Reporting Results of Internet E-Surveys (CHERRIES)[16]. The questionnaire was conducted using Google Forms (Google, Menlo Park, USA, 1998. <https://www.google.com/forms/about/>). The questions were composed and formulated by the main researcher (CS) who is a gynecology resident and further reviewed and adjusted by one gynecologist with expertise in gynecological oncology (WH) and one gynecological oncologist (HB). The link to the questionnaire was first sent in March 2020. Two reminders were sent after 4 and 6 weeks. The link was closed after 10 weeks. The participating gynecologists could only respond once. Since this study population consists exclusively of physicians, ethical approval was not necessary.

The questionnaire consisted of 15 questions, all multiple choice. After each question, there was the possibility to add additional information or elaborate more on the topic. Additionally, three fictitious cases were presented, each with a question attached. All 18 items were designed to evaluate current clinical practice and current attitudes towards the management of patients with SEIC. The questions covered the number of patients that were treated in the hospitals, which diagnostic tests were used, whether there were local guidelines used for the initial and/or adjuvant treatment, whether the gynecologist always performed surgical staging and whether there were local guidelines regarding the duration of follow-up. Regarding the therapeutic options, several options were provided: no treatment ('watchful waiting'), hysteroscopic

polypectomy, hysterectomy with bilateral salpingo-oophorectomy or a surgical staging procedure. Surgical staging includes – according to international guidelines – aspiration of peritoneal washings, inspection of all visceral organs, hysterectomy and bilateral oophorectomy, infracolic omentectomy, biopsy of suspect lesions and suspect adhesions, biopsy of the peritoneum (recto-uterine pouch; urinary bladder; pelvic peritoneum; paracolic gutters; diaphragm) and lymph node sampling (minimum of 10 lymph nodes from the *para*-aortic, paracaval and pelvic regions).

Analysis

The outcomes of the questionnaire were collected and analyzed with SPSS v.25, using descriptive statistical methods.

Results

A total of 24 gynecologists participated, from 16 different medical centers (appendix 1)(16 out of 19 medical centers were included, with a response rate of 84.2%). Of all participants 18 (75.0%) were gynecological oncologists, four (16.7%) were gynecologists with expertise in gynecological oncology and two (8.3%) were fellows. With respect to the number of patients with SEIC treated in the previous five years: 13 out of the 24 respondents (54.2%) estimated that they had treated 5–10 patients. Of all respondents (n = 24) 95,8% (n = 23/24) claimed to have treated at least one patient in the previous five years (table 1). The majority of respondents do not use – or do not have – a clinical guideline in their medical center (n = 18/24, 75.0%). Six (25.0%) do consult a clinical guideline when treating patients with SEIC.

Regarding the diagnostic tests used for SEIC: twenty two respondents (91.7%, n = 22/24) use CA-125 as a biomarker. A computed tomography (CT) scan is often used for imaging of the thoracic and abdominal organs: twenty respondents (83.3%, n = 20/24) perform a CT scan of both the abdomen and thorax, two (2/24, 8.3%) use CT imaging only for the abdomen and two do not use computed tomography at all (2/24, 8.3%).

Current clinical treatment varies from therapeutic hysteroscopy to complete surgical staging (table 2a). The majority of respondents perform complete surgical staging (n = 14/24, 58.3%) whereas seven choose for hysterectomy with bilateral salpingo-oophorectomy (n = 7/24, 29.2%). When the diagnosis SEIC is an incidental finding after polypectomy or hysterectomy performed for another indication, 62.5% of respondents (n = 15/24) go on to perform surgical staging, while 33.3% (n = 8/24) prefer to opt for follow-up alone. One respondent would perform a computed tomography scan and then discuss with the patient whether surgical staging or chemotherapy with radiotherapy is preferred (n = 1/24, 4.2%)(table 2b).

When surgical staging is performed, this always includes hysterectomy with bilateral salpingo-oophorectomy and biopsy of the omentum. Biopsies of the peritoneum and diaphragm are carried out by 73.9% of respondents (n = 17/23). Sampling of pelvic and *para*-aortic lymph nodes is included in the staging procedure by 21/23 respondents (87.5%), while two opt for lymph node dissection (n = 2/23, 8.7%). Cytological examination of peritoneal washings is included by 78.3% (n = 18/23)(table 3).

Three respondents provided extra details regarding their clinical practice: (1) "the treatment depends on whether the pathological result was extracted from a polyp or if it was obtained through aspiration of the endometrial lining: in the first scenario resection of the polyp is performed, in the second scenario a hysterectomy with oophorectomy is performed"; (2) "when the pathological result is obtained from aspiration of the endometrium a hysterectomy is performed, since it is then often described as a serous

Table 1
Number of estimated patients treated with SEIC per participant in the last five years.

Number of patients	n	%
0	0	0
1–5	7	29.2
6–10	13	54.2
11–15	1	4.2
16–20	0	0
>20	2	8.3
'I don't know'	1	4.2

Table 2a
Current treatment – SEIC suspected after biopsy or polypectomy.

Type of treatment	N	%
Hysterectomy + bilateral salpingo-oophorectomy	7	29.2
Surgical staging	14	58.3
Other: polypectomy if SEIC is limited to an uterine polyp	2	8.3
'I don't know'	1	4.2

Table 2b
Current treatment – when SEIC was a coincidental finding after hysterectomy.

Type of treatment	N	%
Surgical staging	15	62.5
Follow-up ('watchful waiting')	8	33.3
Other: depending on imaging (computed tomography)	1	4.2

Table 3
Current practice during surgical staging.

Components of the surgical procedure during surgical staging	Number of participants (n)*	%
Hysterectomy	23	100
Bilateral salpingo-oophorectomy	23	100
Lymph node sampling	18	78.3
Lymphadenectomy	2	8.7
Biopsy of the omentum	23	100
Biopsy of the peritoneum	17	73.9
Biopsy of the diaphragm	17	73.9
Cytological examination from peritoneal washings	18	78.3

*23 out of the 24 participants answered this question

endometrial carcinoma rather than SEIC"; (3)"surgical staging is the first choice of treatment, however without examination of peritoneal washings". When gynecologists were asked for their opinion on the optimal treatment for patients with SEIC, complete staging was considered to be the optimal treatment by 50.0% (12/24), whereas 37.5% (n = 9/24) consider hysterectomy with salpingo-oophorectomy to be the optimal treatment. Three respondents (n = 3/24, 12.5%) are unsure when asked for their opinion on optimal treatment for patients with SEIC (table 4a). Of those 14 gynecologists who choose surgical staging as their current practice, 11 consider this to be the optimal treatment (n = 11/14, 78.6%), two answered that hysterectomy and bilateral salpingo-

Table 4
Opinion on the optimal treatment of SEIC.

Type of treatment	Current treatment		Preferred treatment		Difference	
	n	%	n	%	n	%
Hysterectomy + BSO	7	29.2	9	37.5	+2	+8.3
Surgical staging	14	58.3	12	50	-2	-8.3
Other	2	8.3	0	-	-2	-8.3
'I don't know'	1	4.2	3	12.5	+2	+8.3

*BSO: bilateral salpingo-oophorectomy

oophorectomy might be the optimal treatment rather than surgical staging (n = 2/14, 14.3%) and one does not have an opinion on the optimal treatment (n = 1/14, 7.1%). All seven gynecologists who choose hysterectomy with bilateral salpingo-oophorectomy (100%, n = 7/7) believe that this is indeed the optimal treatment for SEIC (Fig. 1). Regarding the optimal surgical treatment, the majority of respondents are unsure whether lymph node sampling or lymph node dissection should be performed during surgical staging (n = 15/23, 65.2%). Five respondents (21.7%, n = 5/23) assert that lymph node sampling should be carried out, while three (13.0% n = 3/23) feel that neither sampling nor dissection is necessary.

With regard to adjuvant treatment, 62.5% of respondents (n = 15/24) do not give any adjuvant therapy after complete surgical staging. Of the respondents who do give adjuvant therapy, six recommend brachytherapy (table 5).

The majority of respondents have a follow-up protocol lasting 5 years (n = 23/24, 95.8%). When asked for the optimal follow-up management, 50.0% (n = 12/24) prefer a follow-up duration of five years, one respondent (n = 1/24, 4.2%) prefers a follow-up duration of two years, one (n = 1/24, 4.2%) prefers no follow-up at all and the other 10 respondents do not have an opinion on the optimal follow-up management (n = 10/24, 41.7%).

Discussion

This study illustrates that SEIC is a rare diagnosis in the clinical practice of most gynecologists with expertise in gynecological oncology in The Netherlands. Therefore, there is no overall certainty about the management of patients with SEIC. Within this study, there was no consensus on the optimal surgical and adjuvant treatment. Most respondents do not consult or do not have a clinical guideline for the management of patients with SEIC. Current clinical management varies among medical centers. However, surgical staging is the most frequent primary treatment, in keeping with the recommendations of published case series.[1,4,11,17,18]

The biological behavior of SEIC is unpredictable. There are cases described with extrauterine disease at time of first presentation. However, the pathophysiology of metastasis in the context of SEIC is not well understood. The rarity of the diagnosis together with the variety of terminology used leads to insufficient prognostic data. The effect of surgical staging on the survival of patients with SEIC is unknown. Since there is little literature on the management of SEIC, international guidelines do not provide clear and specific recommendations. For example, the joint guideline for management of patients with endometrial carcinoma from the European Society of Gynaecological Oncology (ESGO) / European Society for Radiotherapy and Oncology (ESTRO) / European Society of Pathology (ESP) does not use the term SEIC, but considers non-invasive carcinoma of the uterus with abnormal P53 as an entity with intermediate risk (even when restricted to a polyp) which should be treated with surgical staging and adjuvant chemotherapy or radiotherapy. This joint guideline considers that there is no consensus on which type of adjuvant treatment is preferable, and this must be decided on a case by case basis. [19] The guideline of the

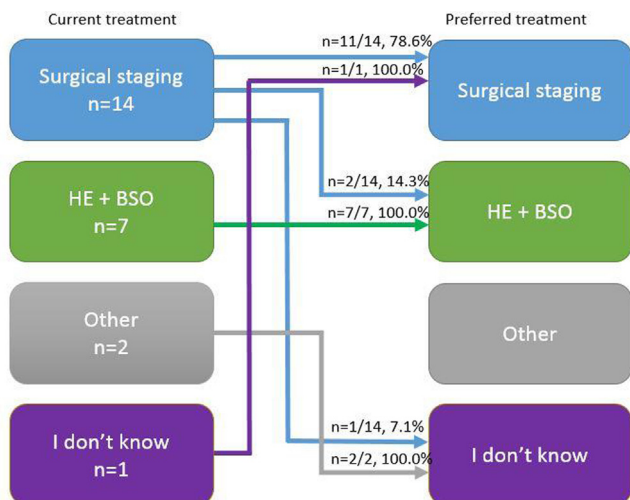


Fig. 1. Current surgical treatment and preferred surgical treatment.

Table 5
Current adjuvant therapy.

Type of adjuvant therapy	n	%
None	15/24	62.5
Brachytherapy	6/24	25.0
External-beam radiotherapy	1/24	4.2
Chemotherapy	1/24	4.2
'I don't know'	1/24	4.2

National Comprehensive Cancer Network in the USA recommends surgical staging and adjuvant therapy for serous carcinoma FIGO 1A and includes no separate section for the management of patients with SEIC.[20,21] The main issue is that the evidence for lymph node sampling, in particular lymph node dissection, is limited. It is uncertain whether SEIC metastasizes to pelvic or para-aortic/paracaval lymph nodes. Our hypothesis is that superficial intraepithelial carcinoma may spread through the tubes into the peritoneal cavity. Whether lymph node sampling or dissection is indicated in the treatment of SEIC remains unclear. In conclusion, it is of great importance to evaluate the influence of the choice of therapeutic management on the (disease free) survival. Staging is a comprehensive surgical procedure with a risk of complications, whether with laparotomy or with minimally invasive techniques. [22,23] Therefore, it is important to understand the influence of staging on (disease free) survival of patients with SEIC, and to assess whether the benefits of staging outweigh the potential risks. The authors of this article are therefore conducting a nationwide cohort study of 50 patients with SEIC where treatment modality, morbidity, progression free survival and overall survival will be evaluated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author contribution

This manuscript was drafted by Ciska Slaager, supervised and advised by the other members of the SEIC research team (Ward Hofhuis, Heleen van Beekhuizen, Patricia Ewing-Graham and Klaas Hoogduin).

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Appendix A

Table A1

Table A1
Participating medical centers with number of participants.

Medical center	City	n
Albert Schweizer ziekenhuis	Dordrecht	1
Amsterdam University Medical Center	Amsterdam	1
Amphia Ziekenhuis	Breda	1
Antoni van Leeuwenhoek Ziekenhuis	Amsterdam	2
Bravis Ziekenhuis	Bergen op Zoom	1
Erasmus Medisch Centrum	Rotterdam	2
Franciscus Gasthuis en Vlietland	Rotterdam	1
Groene Hart Ziekenhuis	Gouda	1
Isala Ziekenhuis	Zwolle	1
Leiden Universitair Medisch Centrum	Leiden	2
Medisch Spectrum Twente	Enschede	1
Radboud Universitair Medisch Centrum	Nijmegen	2
Reinier de Graaf Gasthuis	Delft	1
Universitair Medisch Centrum Groningen	Groningen	6
Universitair Medisch Centrum Utrecht	Utrecht	1
Total		24

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