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Synchronous primary endometrial and ovarian cancers: how to diagnose, differentiate and treat in the light of recent available literature data

Synchroniczny rak endometrium i jajnika – jak diagnozować, różnicować i leczyć na podstawie dostępnych danych literaturowych

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Summary: SEO – synchronous endometrial ovarian cancer is a well-known phenomenon, which has for years been managed as two primary independent cancers. The results of recent molecular studies, especially next-generation sequencing, suggest that the condition should be regarded as a continuum, with its origin probably lying in the endometrium or endometrial foci. It has been found that 0.7% to 1.0% of endometriosis patients may develop malignant lesions. Although SEO is being increasingly studied, diagnostics and treatment still leave many questions. The most important thing is to improve the diagnosis with rapid and simple detection. A few molecular methods are already known, but genetic diagnostic, still remains unclear. Old criteria implemented by Scully in 1998 should be nowadays complemented by immunohistochemical staining of estrogen and progestin receptors, bcl2 antibodies and molecular analyses of genes: *B-catenin*, *PTEN*, *KRAS*, *TP53*, *PIK3CA* and microsatellite instability. Will genetic diagnostics preserve fertility in young patients with SEO? This paper reviews relevant literature to determine a strategy for distinguishing between SEO and metastatic cancers, and presents management options for patients with SEO.

Keywords: **endometriosis, synchronous primary cancers, endometrial cancer, ovarian cancer, prognosis**

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GENERAL DEFINITIONS

Although there is no universally-accepted definition of synchronous cancer, it is mostly assumed to refer to two or more neoplasms identified simultaneously in the same patient or a second tumor identified up to six months after the initial diagnosis. Another term worth describing is metachronous cancer. These types of cancers may develop consecutively (metachronously) from six months to years after the resection of the first primary tumor [49]. Metachronous cancers originally were described as a phenomenon of colon cancer [11]. Any effective diagnosis of two independent primary carcinomas or metastases will impact treatment and prognosis and hence should involve cooperation between the pathologist and the surgeon.

WHAT IS SEO?

The most frequently-occurring synchronous simultaneous cancer is known as a SEO (Synchronous Endometrial-Ovarian cancer) [33]; however, despite its frequency the diagnosis presents a challenge. SEO should be differentiated from primary tumor with metastasis. Most cases of SEO consist of low-grade adenocarcinoma of the uteri FIGO 1 or 2 and endometroid low-grade ovarian cancer. Difficulties in the diagnosis arise in those cases which show discordant features, some favoring primary independent neoplasms and others being more characteristic of metastasis (e.g. a low-grade endometrial adenocarcinoma with only superficial myometrial invasion associated with bilateral ovarian endometrioid adenocarcinomas in the absence of endometriosis or high-grade endometrial carcinomas, which may present with metastases even when there is minimal myometrial invasion) [44, 48]. One general principle used in determining tumor origin in pathology is the identification of a recognized tumor precursor, such as in situ or intraepithelial carcinoma, because the presence of such a lesion is considered strong evidence of tumor development at a particular anatomic site [44]. Synchronous endometrial and ovarian cancers are diagnosed in about 2% to 5% of all women with endometrial cancer. They are also identified in 10% to 40% of women with ovarian cancers especially those with origin in endometriosis foci [26, 30, 33, 47]. Al Hilli et al. used data from the Rochester Epidemiology Project and reported the incidence of synchronous EC/OC (age-adjusted to the 2000 US female total) during the study period (1945–2008) on 0.61 (95% CI, 0.30–0.92) per 100.000 person-years. In their study, SEO was more frequent in women under 50 years (9.4% vs 3.1%) than in the general population [1]. Recent results of retrospective observational study conducted in the USA (Surveillance, Epidemiology, and End Results Program between 1973 and 2013) published by Matsuo et al. suggest that the incidence of synchronous ovarian cancer has decreased among endometrial cancer whereas synchronous endometrial cancer has increased among epithelial ovarian cancer during the 30-year timeframe [33].

RISK FACTORS FOR SEO

As SEOs are diagnosed mostly in the early stage, typically as adenocarcinoma, it is very important to distinguish them from metastatic cancer. In addition, as they also mostly affect younger, nulliparous women, it is important not to overtreat them [37]. Women diagnosed with endometrial cancer in their early 40s should also be tested for synchronous ovarian cancer [13]. This group of women tends to present hereditary non-polyposis colon cancer syndrome (HNPCC). Almost one third of patients with endometrial cancer and SEO present no known risk factors [5] and the majority of SEO cases are sporadic cancers [27].

One of the risk factors for SEO described in literature is endometriosis. Endometriosis shares certain characteristics with malignancy, such as tissue invasion, angiogenesis and the development of local and distant foci [2, 50]. Other risk factors are collected in Table 1. Recent studies on atypical foci of endometriosis and deep infiltrating endometriosis shed the light on SEO phenomenon.

Genetic mutations in endometriosis and SEO

It has recently been proposed that endometriosis may act as a precursor of gynecology tract cancers. Some molecular features, such as mutations in *ARID1A*, *PTEN*, *KRAS* and *PIK3CA*, microsatellite instability and p53 loss are common in endometriosis, ovarian and endometrial cancer [26]. In an NGS (next generation sequencing) study of 22 cases of SEO, Hajkova et al. report a clonal origin by at least one shared mutation in *PTEN*, *AKT1*, *PIK3CA*, *KRAS*, *TP53* and *ARID1A* [21]. In addition, it is possible that endometriosis and endometrioid ovarian carcinoma might represent two distinct biological entities characterized by the same pathogenetic mechanism, i.e. transtubal reflux [16]. In recent years, the molecular basis for carcinogenesis has been extensively studied in endometriosis foci. A literature review suggests that a number of pathologies, including endometrial changes such as hyperplasia and cancer, endometriosis, EAOC (Endometriosis Associated Ovarian Cancer) and adenomyosis, may derive from the disruption of normal endometrial processes [53].

The precise nature of the relationship, however, depends on the type of the tumor. For example, the presence of endometriosis increases the risk of clear cell and endometroid ovarian cancer (EOC) [46, 55], with the risk of EOC estimated as being 0.9% to 4.5% higher. The risk of endometrial cancer is not necessarily increased [19].

The mutations that occur in some endometriosis foci, such as already mentioned overexpression of p53, mutations in *PTEN*, *K-RAS*, *PIK3CA* and the *B-catenin* gene, as well as loss of *ARID1A* expression, may promote tumorigenesis [19]. *PIK3CA* has been found to be commonly mutated in the endometrial glands, often without

Table 1. Risk factors for SEO

Risk factors	Evaluated in:	Methods of evaluation	Results
Endometriosis	Kelemen et al. 2017 [26]	Alberta Cancer Registry; 52 cases of SEO	Endometriosis of the ovary decreased risk of SEO (OR = 0.45, 95% CI = 0.23–0.87, p = 0.02) in comparison to EC or OC
	Wu et al. 2017 [54]	Case report; whole genome sequencing and pathological reports	SEO accompanied by peritoneal lesions typical for endometriosis, endometrial ovarian cyst
	AlHilli et al. 2012 [1]	Database Rochester Epidemiology Project; histopathologic assessment	No concurrent endometriosis with non-endometroid OC; endometroid type of OC accompanied by endometriosis
BMI> 26 kg/m2	Soliman et al. 2004 [41]	Single care center; 84 patients	Median BMI – 28
Nulliparity	Soliman et al. 2004 [41]	Single care center; 84 patients	33% nulliparous woman
	Rodolakis et al. 2012 [37]	Series of 30 cases; pathological reports, clinical characteristics	37% nulliparous woman
HNPCC syndrome	Dogan et al. 2017 [13]	Case report and literature review	HNPCC analysis by immunohistochemistry after detection of SEO
	Soliman et al. 2005 [40]	Single care center; 102 patients; anamnesis (Amsterdam criteria) and protein expression testing for MSH2, MSH6, and MLH1	7% of women met either clinical or molecular criteria for Lynch syndrome
Age < 45 years	Soliman et al. 2004 [41]	Single care center; 84 patients	Median age < 50 year
	Song et al. 2013 [43]	Korean Gynecologic Oncology Group Study	4.5% SEO < 40 year
	AlHilli et al. 2012 [1]	Database Rochester Epidemiology Project	Patients age 42–52 years
Oral Contraception	AlHilli et al. 2012 [1]	Database Rochester Epidemiology Project	More frequent usage by EC patients than SEO patients; use was associated with a lower likelihood of synchronous EC/OC (OR, 0.10; 95% CI, < 0.01–0.87)

transformation, suggesting that this mutation may be the first step of carcinogenesis in endometriosis foci. The progression of endometriosis is associated with mutation in *ARID1A* [45], and both endometriosis and cancer are associated with overexpression of COX 2 and angiogenesis [14, 29]. COX 2 is a rate-limiting enzyme in the biosynthesis of prostaglandin E2: prostaglandin E2 is known to promote carcinogenesis and reduce immune performance by increasing proliferation and neovascularization. In addition, iron has been observed in the fluid of endometriotic cysts, which may cause genetic mutations by enhancing oxidative stress, and chronic inflammation and estrogen stimulation have also been recorded in both endometriosis and endometrial cancer.

In contrast, Kelemen et al. in a study comparing SEO patients with endometrioid and clear cell ovarian cancer patients found no association between endometriosis in the ovary and SEO, suggesting that endometriosis may not be the mechanism by which SEO cancers arise; even so, mutations in *MLH1*, *PTEN* and *MSH2* were found in both entities [26]. When interpreting these findings, however, it is important to note that the endometriosis rate is typically underestimated in patients with SEO or ovarian cancers, as not every patient with SEO is diagnosed laparoscopically for endometriosis before surgery for cancer.

DIAGNOSIS

Clinical evaluation

SEO patients most commonly present abnormal uterine bleeding (AUB) as a sign of endometrial cancer and ovarian cyst during ultrasound examination. In patients with SEO, one tumor is typically symptomatic, while the

Table 2. Scully's criteria of SEO (1998)

Feature	SEO
Histology type of tumors	Dissimilarity of tumors
Myometrial invasion	No or superficial
Vascular invasion	No
Presentation of ovarian endometriosis	Yes
Genetic abnormalities in the tumor	Yes

Table 3. Features used to classify synchronous endometrial and ovarian carcinomas as independent primary tumors or as metastasis from endometrium to ovary

METASTASIS	bilateral ovarian tumors; small ovarian tumors; ovarian surface involvement; multinodular growth in the ovary; tumor in lymphovascular spaces; negative PAX-8, membranous form of B catenin, CTNNB1 absent; TP53 overexpressed
SEO	tumor confined to uterus and ovary; no direct extension between tumors; identical histotype/grade; minimal or no myometrial invasion; low grade; no lymph-vascular tumor emboli; any distant metastasis

other one is an incidental finding [17]. Patients with AUB should undergo an endometrium biopsy or D&C (diagnostic &curettage) procedure. Diagnostic ultrasound should be performed. If endometrial cancer is diagnosed, staging should be done in MRI/CT/ultrasound according to ESGO/ESMO/ESTRO guidelines [www.esmo.org]. If ovarian tumor is the first diagnosis, endometrium should be carefully assessed in with an ultrasound and tested if suspected of malignancy. These steps should be finished before implementing surgical treatment. Moro et al. reported some sonography differences between SEO and primary cancer with metastases. The ovarian masses were more often multilocular-solid in the SEO group than those in the metastasis group, and were less likely bilateral [34].

Histopathological diagnosis

For the physician and the pathologist, the most important step in formulating the prognosis and further therapy is to confirm the presence of synchronous primary neoplasms. In 1998 Scully proposed criteria to distinguish between SEO and a disseminated cancer. He described three different possibilities: endometrial cancer with metastasis to an ovary, ovarian cancer with metastasis to the endometrium and SEO [39]. In the first two possibilities, the involvement of fallopian tube could be highly important for the differential diagnosis, while the criteria for SEO are presented in Table 2. Soliman at al., based on Scully's criteria, listed a number of features that can predict SEO, which are as follows: histologic dissimilarity of tumors, endometrial cancer stage I (non-invasive or with superficial invasion), absence of nodal metastases, ovarian tumor not exceeding ovarian capsule, presence of ovarian endometriosis and the absence of any spread of these tumors [42]. Other pathological features that can be used to differentiate between SEO and metastatic tumors are given in Table 3.

However, pure histopathological criteria have been criticized as being too difficult to apply in practice, because some cases are indeterminate, with features supportive of both independent primary tumors and a single tumor with metastasis [17]. In addition, after implementation of a new TCGA classification of endometrial cancer [6], synchronous ovarian carcinoma has been seen in hypermutated endometrial carcinomas with mismatch repair deficiency (MMR), in ultra-mutated endometrial carcinomas with mutations in the exonuclease domain of polymerase-epsilon (POLE), and in endometrial carcinomas with low mutation burden/few somatic copy number abnormalities (characterized by wildtype p53 expression) [17].

Molecular testing

In questionable cases, immunohistochemical and DNA profile can be determined in cytometric studies to distinguish between primary tumors and metastases. ER, PR and bcl2 antibodies appear to play a valuable role as they demonstrate different immunostaining patterns [21]. In addition, further molecular analyses of genes: *B-catenin*, *PTEN*, *KRAS*, *TP53*, *PIK3CA* and microsatellite instability should be tested in doubtful cases. Mutations of the *CTNNB1* gene, which encodes β-catenin, occur in a wide spectrum of cancers [16], particularly primary endometrial and ovarian cancer, and the membranous form of B catenin, CTNNB1, may be absent in metastasis. Furthermore, data show that molecular genetic classification of synchronous independent versus metastatic tumors based on beta-catenin expression/mutation correlates with clinical outcome [24]. In addition, because PAX-8 (member of the paired box (PAX) family of transcription factors, targeting, i.a, BRCA1) is expressed in primary ovarian cancer but not EC metastases, it can serve as a useful marker to differentiate between the two [16]. However, some studies suggest that molecular analysis and immunochemistry can have limited value in diagnosis [21]. In such a case, a comparison of mtDNA could also be

Table 4. The most frequent genetic mutations typical for SEO

Genetic change	Authors	Conclusions
PTEN mutation (human putative protein tyrosine phosphatase)	Lin et al., 1998 [31]	high incidence of PTEN/MMAC1 mutations and 10q23 loss of heterozygosity (LOH) in SEO
Microsatelliteinstability (MSI)	Kaneki et al., 2004 [25]	most patients (82%) properly diagnosed as having single or double clonal tumors
A panel of 73 genes (219 kbp)	Hájková et al., 2019 [21]	Clonal origin confirmed in all cases by at least one shared mutation in PTEN, AKT1, PIK3CA, KRAS, TP53 and ARID1A
LOH, PTEN and MSI	Fujii et al., 2002 [15]	35% of synchronous tumors – monoclonal, 47% – polyclonal, 18% – undetermined using genetic assessment that correlated with histopathological findings
Combined genetic and statistical method based on LOH and MSI	Brinkmann et al., 2004 [4]	53% concordance between genetic and histopathology diagnoses; genetic analysis with implication for clinical management; performed rapidly as a diagnostic test with paraffin-embedded tissues.

effective in differentiating between SEO and metastases when both tumors demonstrate the same mutation. The method of analysis of mt DNA is well described by Perrone et al. [36]. Guerra et al. present the evaluation of B-catenin and CTNNB1 expression and mt DNA genotyping as an effective approach to identify between SEO and primary cancer with metastasis [20].

SEO patients should also be interviewed and tested for Lynch syndrome. Between 7% and 9% of women with SEO have Lynch Syndrome and some relatives with HNPCC associated cancer [43]. Women with HNPCC have 40% to 60% lifetime risk of developing endometrial cancer and 10% to 12% risk of developing ovarian cancer [42]. The genes *MLH*1, *MSH2*, *MSH6* and *PMS2* are known for mismatch repair and should be tested, as they display defects in about 5% of endometrial cancer cases; in addition, microsatellite instability (MSI), loss of heterozygosity (LOH) and the pattern of X chromosome inactivation can also be useful indicators. Typically, synchronous ovarian cancer is of clear cell origin in the cases with Lynch syndrome [13, 41]. In conclusion, some genetic defects in SEO are the same in Lynch Syndrome (MSI, MLH1, MSH2, MSH6 mutations, loss of the patterns expression), but there is no evidence that SEO is a part of Lynch Syndrome. However, women with SEO having relatives with SEO history or HNPCC associated cancer should undergo genetic testing including MSI and IHC toward Lynch Syndrome [41].

It has been proposed that all SEO are clonally related, and therefore that naming SEO as "two independent primary tumors" may be inappropriate [2, 17, 38]. SEOs have been found to present histological dissimilarity, and that correct molecular diagnosis requires nonsynonymous mutation in at least one gene (*PTEN*, *PIK3CA*, *KRAS*, *AKT1*, *TP53*, *ARID1*A): although diagnosis should primarily be based on morphological analysis, molecular profiling can nevertheless be helpful in formulating a prognosis and predicting treatment [21]. A detailed description of molecular testing used for genetic mutations typical for SEO is listed in Table 4.

An interesting direction of studies is the use of a miRNA signature to differentiate SEO from metastases. One study by Hui et al. indicates that primary ovarian and endometrial cancers demonstrate different miRNA signatures [23].

Although no universal diagnostic gold standard currently exists for SEO, new light is being increasingly shed by many studies in different fields. The diagnostic process should be varied: it should incorporate validated methods such as preoperative ultrasound and/or MRI, postoperative pathomorphological analysis (Scully's criteria) or various molecular methods and analyses of gene alternations. Molecular diagnosis should start with finding typical mutation for nonsynonymous genes in SEO (like NextGene) [54]. Moreover, MSI analysis is helpful to distinguish primary cancers from metastases. If it is not enough, DNA profiling should be helpful. This range of tools should be supplemented in the future.

TREATMENT

Surgery

Traditionally, when a patient was recognized with SEO, the cancer with a diagnosed higher stage was treated first [42]; in 50% to 70% of cases, it was a low-grade endometroid ovarian tumor. Surgery such as hysterectomy, bilateral salpingo-oophorectomy or pelvic and or /pelvic + paraaortic lymphadenectomy should be first-line treatment. The average age of patients is 50 years, which is why radical surgery is the best solution. For young women there is no definitive opinion which medical strategy should be taken. According to oncological guidelines, standard surgical treatment should be performed. Younger patient with SEO who wish to maintain fertility should be counseled before surgical treatment [7]. They should have genetic testing for Lynch syndrome and BRCA mutation as positive test affects their survival rate and should be a contraindication for conservative management [35]. There were some ideas to perform diagnostic laparoscopy in a young patient

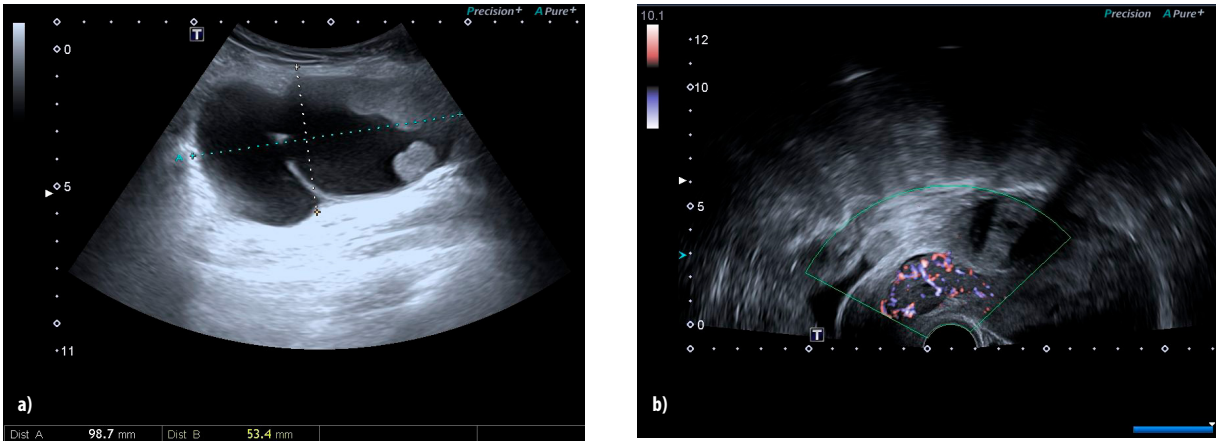

Fig. 1. a) Ultrasound photo of ovarian tumor (pT1a for ovarian cancer) with a postoperative diagnosis of SEO; b) Ultrasound photo of cervical involvement of cancer; figures courtesy of Maja Kufelnicka-Babout

desiring to maintain fertility with early stage of endometrial cancer to find ovarian malignancy, but according to Song et al. this is not mandatory and therapy may by started with conservative treatment like hormonotherapy (for early stage of endometrial cancer) [43]. These procedures should be modified in the case of G3 ovarian tumor, lesions in the upper abdomen, mucinous subtype of the ovarian or endometrial cancer being present. In these cases, cytoreductive surgery is the first line treatment and fertility sparing surgery should not be recommended [9].

Adjuvant treatment

Possible further treatment is based on radiotherapy, chemotherapy or re-operation. It has been suggested that in most cases the choice of adjuvant therapy depended on the stage and grade of ovarian cancer, as these neoplasms demonstrated greater risk of unfavorable prognosis and recurrence [12]. Adjuvant therapy should be planned individually for the patient after analyzing histological and molecular dates or risk factors.

Bese et al. noted that not only was the stage of ovarian cancer found to be a significant risk factor for recurrence when SEO was diagnosed, but the patient age, menopausal status, the presence of lymphadenectomy, grade of endometrial tumor, omental metastasis and residual tumor also played a role [3]. Solmaz et al. reported that optimal cytoreduction, early-stage disease and LVSI are the most significant factors affecting survival in women with SEO [40].

Gilk et al. proposed that no adjuvant therapy is needed in low-risk synchronous endometrial and ovarian carcinomas when they are grade 1 or 2 'endometrioid' carcinoma at both sites. In this case, the risk of recurrence was found to be equivalent to a combination of stage IA endometrial and stage IA ovarian carcinomas [16]. Any other combination of ovarian and endometrial tumor is to be treated in compliance with guidelines – mainly with paclitaxel and carboplatin as for epithelial ovarian cancer [28]. Concomitant radiation is sometimes considered for intermediate or high-risk endometrial cancer in SEO patients according to ESMO/ESTRO guidelines [10].

The use of radiotherapy in patients with synchronous cancers, who are being treated with adjuvant chemotherapy, is not yet well established [12]. One study found combined radiotherapy and chemotherapy to offer no significant advantage over a regimen based on doxorubicin, cisplatin and cyclophosphamide inpatients with endometrial cancer and ahigh risk of relapse; however, an insignificant trend was observed that radiotherapy delayed local relapses and chemotherapy delayed metastases [32]. Despite the large body of evidence regarding the use of radiotherapy in endometrial cancer, such as brachytherapy alone or combined with external beam therapy, no consensus exists on the optimal method for treating SEO. Wang et al. achieved best PFS and OS in patients with locally-advanced endometrioid adenocarcinoma using combined chemotherapy and radiation therapy [51]. Multi-center studies and international collaboration should be undertaken to establish appropriate adjuvant therapy for SEO patients. Wang et al. propose that more aggressive adjuvant therapy may be considered for older patients, postmenopausal patients and/or patients with advanced endometrial tumors, omental metastases, and residual tumor tissue [52].

PROGNOSIS

After treatment, the SEO patient should undergo gynecological and oncological surveillance every three to four months for the first two years, then every six months until the end of five years after treatment [10]. Patients who had received conservative treatment to maintain fertility should undergo radical treatment just after delivery.

A patient with SEO appears to have a better prognosis than those with single cancer with metastasis [8]: SEO patients typically demonstrate a 5-year survival rate of 60%, which is twice that of patients with single organ

cancer with metastasis [52]. Kelemen et al. studied 293 endometrioid and clear cell ovarian cancers with 52 cases of SEO in this group and confirmed that there were no significant differences in survival between patients with single ovarian cancer and with SEO [26]. Zhan et al. assessed survival rates in patients with stage IA endometrial carcinoma with synchronous stage IA ovarian carcinoma and found that synchronous carcinoma had no significant effects on survival outcomes [56].

CONCLUSIONS

SEO are more likely to occur in younger, nulliparous, obese premenopausal women than in those with either ovarian or endometrial cancer. Differentiation can be performed by histopathological methods or by molecular approaches, depending on the cost and ease of access to molecular methods. Among the malignancies of the female reproductive tract, simultaneous low-grade tumors offer better prognosis than advanced stage tumor with metastases. Risk factors for recurrence should be carefully evaluated to propose the best adjuvant treatment for the patient. Appropriate anamnesis should be obtained and genetic consultation should be offered to determine the family history of the patient with regard to other related cancers. Further studies should examine the potential value of miRNA signature and next generation sequencing. The discovery of a new diagnostic solution may finally allow the formulation of new diagnostic and treatment management strategies for SEOs, especially if a patient wants to maintain fertility.

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