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Squamous cell carcinoma arising from mature cystic teratoma of the ovary: A challenging question for gynecologic oncologists

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A B S T R A C T

Mature cystic teratomas of the ovary have an incidence of 1.2–14.2 cases per 100.000 people per year. Malignant transformation occurs in approximately 2% of the cases, and usually consists of squamous cell carcinoma. The preoperative detection is difficult and the diagnostic accuracy of ultrasound, magnetic resonance imaging, and computed tomography is debated. The diagnosis is frequently made in the operating room or on final histological examination. Standard treatment consists of bilateral salpingo-oophorectomy, total hysterectomy and comprehensive surgical staging in early disease and optimal cytoreductive surgery in advanced disease. Paclitaxel/carboplatin- based chemotherapy is the most used adjuvant treatment, whereas more aggressive regimens can be adopted in patients with high tumor burden or recurrent disease. The efficacy of radiotherapy is still unproven. The prognosis is poor when the tumor has spread beyond the ovary. There are few information to provide commonly accepted guidelines for this malignancy.

1. Introduction

Mature cystic teratoma [MCT] of the ovary arises from germ cells by failure of meiosis II or from a premeiotic cell in which meiosis I has failed, and it might consist of multiple cell types derived from one or more of the three germ layers (ectoderm, mesoderm and endoderm) (Surti et al., 1990; Caspi et al., 2003; Hackethal et al., 2008). It may occur at any age, with highest peak between 30 and 40 years (Nogales et al., 2003; Comerci et al., 1994; Morgante et al., 1998; Rim et al., 2006; Goudeli et al., 2016). The incidence of ovarian MCTs is approximately 1.2–14.2 cases per 100.000 people per year (Hackethal et al., 2008). They account for about 10–20% of all ovarian tumors and 60% of all benign ovarian tumors, represent the most common ovarian neoplasm in women younger than 20 years, and are bilateral in 10–17% of the cases (Hackethal et al., 2008; Comerci et al., 1994, 1994; Morgante et al., 1998; Rim et al., 2006; Goudeli et al., 2016). Ectodermal derivatives, which include keratinizing epidermis, sebaceous and sweat glands, hair follicles and neuroectodermal tissues, are often the most prominent (Black et al., 2015; Desouki et al., 2015). Mesodermal derivatives consist of muscle, bone, cartilage, fat, and occasionally teeth, whereas endodermal derivatives are represented by thyroid, salivary gland, respiratory and gastrointestinal tissues. The most common signs and symptoms include abdominal pain and distention, constipation, urinary frequency, and palpable abdominal or pelvic mass, but patients are usually asymptomatic or paucisymptomatic at diagnosis (Hackethal et al., 2008; Avcı et al., 2012). Few women present with an acute abdominal pain due to torsion or intraperitoneal rupture, that have been reported in 6.5–16% and 0.3–4% of the cases (Caruso et al., 1971; Park et al., 2008a), respectively. Invasion into adjacent viscera has been described in less than 1% of the cases (Park et al., 2008a).

Malignant transformation occurs in approximately 2% of the MTCs (range, 0.8%–5.5%) (Table 1) and usually consists of squamous cell carcinoma (Rim et al., 2006; Desouki et al., 2015; Dos Santos et al., 2007; Park et al., 2008b; Ulker et al., 2012; Oranratanaphan and Khemapech, 2013; Araujo et al., 2016; Koc et al., 2017; Trabzonlu et al., 2017) (Table 2).

Other less frequent malignancies include mucinous carcinoma (Black et al., 2015; Desouki et al., 2015; Araujo et al., 2016; Trabzonlu et al., 2017; Kim et al., 2003; Hershkovitz et al., 2013), adenocarcinoma arising from the respiratory ciliated epithelium (Yahata et al., 2008; Song et al., 2009), melanoma (Black et al., 2015), carcinoid (Desouki et al., 2015; Araujo et al., 2016; Kim et al., 2003; Devouassoux-Shisheboran et al., 2000), thyroid carcinoma (Desouki et al., 2015; Araujo et al., 2016; Trabzonlu et al., 2017; Devouassoux-Shisheboran et al., 2000), sebaceous carcinoma (Trabzonlu et al., 2017), oligodendroglioma (Trabzonlu et al., 2017) and sarcoma (Devouassoux-Shisheboran et al., 2000; Aygun et al., 2003; Contreras and Malpica, 2009; Kefeli et al., 2009; Yasunaga et al., 2011). The occurrence of different or mixed types of malignancies is exceptional (Hanada et al., 1981; Arora and Haldane, 1996; Cabibi et al., 2006; Allam-Nandyala et al., 2010a; Savitchi and Rao, 2012; Pongsuvareeyakul et al., 2017).

An expectant management is warranted only up to maximum

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Table 1
Incidence of malignant transformation in mature cystic teratoma of the ovary.

Author [ref]	Ovarian MCT	Malignant transformation
Rim et al., (2006)	637	11 (1.7%).
Trabzonlu et al. (2017)	218	8 (3.7%)
Araujo et al. (2016)	181	10 (5.5%)
Desouki et al. (2015)	956	26 (2.7%)
Ulker et al. (2012)	312	6 (1.9%)
Oranratanaphan and Khemapech (2013)	753	11 (1.5%)
Park et al. (2008b)	2019	16 (0.8%)

Legend: ref, reference; MCT, mature cystic teratoma.

diameter of 5–6 cm, and, since ovarian MTCs tend to grow over time, most patients undergo surgery (Alcázar et al., 2005; Sinha and Ewies, 2016). The laparoscopic approach is considered to be the gold standard (Sinha and Ewies, 2016). Salpingo-oophorectomy is recommended in postmenopausal women and in perimenopausal women with multiple cysts in the same ovary or with a large teratoma, whereas cystectomy is a rational option in younger women.

There are in literature case reports of intraperitoneal carcinomatosis after laparoscopic removal of a presumed benign MCT with evidence of malignant transformation at the histological examination of surgical sample (Wang et al., 2000, 2002; Mecke and Savvas, 2001; Wen et al., 2006; Bourdel et al., 2010). The spillage of cyst content should be always avoided, and the surgical removal must be performed with an endoscopic retrieval bag (Sinha and Ewies, 2016). If spillage does occur, the surgeon must carry out an accurate peritoneal washing with large amounts of warmed fluid.

2. Clinical presentation and diagnosis

The size of a malignant ovarian MCT ranges from 9.7 to 15.6 cm, and it is usually larger than that of a benign MCT (Hackethal et al., 2008; Rim et al., 2006; Desouki et al., 2015; Dos Santos et al., 2007; Park et al., 2008b; Ulker et al., 2012; Oranratanaphan and Khemapech, 2013; Araujo et al., 2016; Koc et al., 2017; Trabzonlu et al., 2017; Kikkawa et al., 1997; Allam-Nandyala et al., 2010b; Chen et al., 2008; Sakuma et al., 2010; Rekhi et al., 2015; Abhilasha et al., 2016) (Table 2). In the study of Desouki et al. (2015) the median diameter was 11.2 cm in the 12 cases with malignant trasformation *versus* 6.5 cm in benign tumors ($p < 0.001$). Bilaterality has been detected in less than 4% of the cases (Hackethal et al., 2008). Patients with this malignancy are 10–15 year older than those with benign MCT (Surti et al., 1990; Ulker et al., 2012). Chen et al. (2008) analyzed 220 cases of squamous cell carcinoma arising from MCT [SCC-MCT] of the ovary from 44 studies between 1976 and 2005 and they found that 66.8% of the patients were $\geq$ 50 year old. The widest series in the literature reports a mean age at presentation of 55 years, with a range from 19 to 87 years (Hackethal et al., 2008) (Table 2). This malignancy has been anecdotically reported in pregnant women (Budiman et al., 2010; Yun et al., 2013).

Patients with SCC-MCT of the ovary experience abdominal pain or have an abdominal palpable mass or swelling in 50–58.1% and 31–71.6 % of the cases, respectively, whereas other symptoms, such as urinary frequency or retention, vaginal bleeding, constipation or diarrhoea, weight less, cachexia and fever occur in 1–6% of cases (Hackethal et al., 2008; Park et al., 2008b; Kim et al., 2003; Chen et al., 2008; Abhilasha et al., 2016). The clinical manifestation as acute abdomen is extremely rare, especially in postmenopausal women (Okada et al., 2005; da Silva et al., 2009; Korkontzelos et al., 2010). Some cases of tumor associated hypercalcemia have been reported (Ribeiro et al., 1988; Takeuchi et al., 2000). Takeuchi et al. (2000) described a case complicated by hypercalcemia in a woman with high plasma levels of parathyroid hormone-related protein [PTH-rP] and immunohistochemical detection of PTH-rP in tumor tissues. Rojas et al. (2015) reported two unusual cases of squamous cell carcinoma in colon biopsies from postmenopausal women, that after surgical resection were proven to be the result of an ovarian SCC-MCT infiltrating the adjacent colon.

The preoperative detection of this malignancy is very difficult and the diagnostic accuracy of ultrasound, magnetic resonance imaging [MRI] and computed tomography [CT] is still debated (Avcı et al., 2012; Kido et al., 1999; Emoto et al., 2000; Outwater et al., 2001; Jung et al., 2002; Mori et al., 2003; Lai et al., 2005; Park et al., 2007; Patni, 2014; Kalampokas et al., 2014). Emoto et al. (Emoto et al., 2000), who performed a transvaginal color Doppler ultrasound in 88 patients with an ovarian tumor showing gray scale sonographic appearances of MCT, found a higher rate of intratumoral blood flow detection in SCC-MCTs (4 of 5, 80%) compared with benign teratomas (17 of 83, 20.5%, $p < 0.01$). Moreover, resistance index < 0.4 and pulsatility index < 0.6 were measured in all malignant teratomas with intratumoral blood flow compared with only one benign teratoma. Kido et al. (1999) described the MRI appearance of five women with six malignant MCTs of the ovary, consisting in squamous cell carcinoma in 4 cases, melanoma in one case, and transitional cell carcinoma in one case. The lesions appeared to be fat-containing tumors with a solid component in 4 cases, and showed a transmural extension in 4 cases and an extensive invasion into the uterus, vagina, and Douglas space in 3 cases. Peritoneal spreading was detected in one woman. Gadolium enhancement may be helpful in assessing whether a MCT has undergone malignant transformation.

The analysis of CT and MRI findings in 11 patients with this malignancy revealed that 9 (82%) tumors had soft tissue components and 8 (89%) of these had an obtuse angle between the soft tissue components and the inner wall of the cyst (Korkontzelos et al., 2010).

Preoperative serum levels of squamous cell carcinoma antigen [SCCA] are more frequently raised in patients with SCC-MCT than in those with benign MCT (Hackethal et al., 2008; Kikkawa et al., 1997; Emoto et al., 2000; Mori et al., 2003; Kikkawa et al., 1998; Suzuki et al., 2000) (Table 3). As far as other markers are concerned, serum CA125, CEA, CA19-9 and macrophage-colony stimulating factor [M-CSF] have been found to be eleveated in 59.1%, 65.0%, 64.7%, and 71.0%, respectively, of patients with SCC-MCT (Hackethal et al., 2008; Suzuki et al., 2000). Suzuki et al. (Suzuki et al., 2000) detected serum M-CSF above the upper limit of the normal (1056 U/ml) in 71.0% of 31 women with SCC-MTC compared with 13.5% of 133 women with benign MCT ($p < 0.0001$). In the same paper, raised levels of SCCA (> 2 ng/ml) and SCCA and/ or M-CFS were reported in 41.9% and 87.1%, respectively, of the cancer patients. Therefore, the combined assay of serum M-CSF and SCCA could be useful in the preoperative evaluation of a suspected MCT. Anyway, malignant transformation is usually diagnosed by definitive histopathologic examination of the surgical sample (Desouki et al., 2015; Ulker et al., 2012; Balık et al., 2013). A retrospective investigation on 316 intraoperative consultations for presumed MCT revealed that the sensitivity and positive predictive value of frozen section examination for the detection of malignancy were 80% and 100%, respectively (Desouki et al., 2015).

3. Pathological features and pathogenesis

On gross examination, a squamous cell carcinoma on a background of ovarian MTC may appear as a polypoidal lesion, an intramural nodule or a mural plaque, with areas of hemorrhage and necrosis, within a predominantly cystic mass, usually filled with pultaceous material and hair (Rekhi et al., 2015; Chiang et al., 2015). In the experience of an Indian tertiary referral center, microscopically all 12 tumors showed mature teratoma with squamous cell carcinoma as a discrete tumor or arising from the epithelium of the teratoma (Rekhi et al., 2015). It is noteworthy that in two cases the squamous cell carcinoma arise from the columnar epithelium undergoing squamous metaplasia.

Table 2
Characteristics of patients with malignant transformation arising from a mature cystic teratoma of the ovary.

Author [ref]	Patients (number)	Age[a] (years)	Tumor size (cm)	Squamous cell histology	Stage I[b]
[Koc et al., 2017]	18	48	12	66.7%(12)	72.2% (13)
Rim [Rim et al., 2006]	11	50.6	9.7	63.7% (7)	81.8% (9)
[Abhilasha et al., 2016]	10	53.5	NA	20% (2)	20.0% (2)
[Trabzonlu et al., 2017]	8	44.6	10.36	25% (2)	62.5% (8)
[Araujo et al., 2016]	10	37	15.6	40% (4)	60.0% (6)
Rekhi [Rekhi et al., 2015]	12	49	12.4	100% (12)[c]	58.3% (7)
[Desouki et al., 2015]	26	48.7	11.2	23%(6)	NA
[Ulker et al., 2012]	6	43	11.5	50%(3)	100%(6)
[Hackethal et al., 2008]	277	55	14.8	100%(277)[d]	49.7%(120/241)
[Oranratanaphan and Khemapech, 2013]	11	41.2	14.1	36.4%(4)	54.5% (6)
[Sakuma et al., 2010]	20	52.5	NA	75%(15)	55% (11)
[Park et al., 2008b]	16	50	14.5	75% (12)	43.7% (7)
[Chen et al., 2008]	220^	55	13.8	100%(220)[d]	44.5% (98)
[Dos Santos et al., 2007]	17	55	14.2	100%(17)[c]	47.1% (8)

Legend: ref, reference; NA, not available; SCC- MCT, squamous cell carcinoma arising in mature cystic teratoma.
[a] Mean or median.
[b] at presentation.
[c] study on SCC-MCTs in a cancer referral center.
[d] literature review on SCC-MCTs.

Table 3
Serum squamous cell carcinoma antigen levels in squamous cell carcinoma arising from mature cystic teratoma and in benign mature cystic teratoma of the ovary.

Author [ref.]	Cut off (ng/ml)	Elevated SCCA SCC-MCT	Elevated SCCA MCT
[Emoto et al., 2000]	1.5	4/5 (80%)	11/45 (24.4%)
[Mori et al., 2003]	2.5	32/39 (80%)	5 /81 (6%)
[Suzuki et al., 2000]	2	13/31 (41.9%)	20/133 (15.0%) $p < 0.01$

Legend: ref, reference; SCCA, quamous cell carcinoma antigen; SCC- MCT, squamous cell carcinoma arising in mature cystic teratoma; MCT, mature cystic teratoma.

Lymphovascular space involvement and perineural invasion were found in two patients and one patient, respectively. Data from literature showed that the grade of squamous cell carcinoma is well differentiated in 8.3–27.0%, moderately differentiated in 46.8–66.7%, and poorly differentiated in 25.0–26.1% of the cases, respectively (Chen et al., 2008; Rekhi et al., 2015). Anecdotal cases of *in situ* or microinvasive squamous cell carcinoma aring from MTC of the ovary have been reported (Chen et al., 2008; Dadhwal et al., 2002; Zakkouri et al., 2011; Togami et al., 2016).

If squamous cell lesions of the ovary are detected, the differential diagnosis should include SCC-MCT of the ovary and metastatic carcinomas especially from the cervix and vagina (Balık et al., 2013). The histogenesis of SCC-MCT of the ovary is still debated (Rekhi et al., 2015). This malignancy could arise from the epidermis, from the columnar epithelium (ciliated or nonciliated) or from a metaplastic squamous epithelium (Kikkawa et al., 1998; Hirakawa et al., 1989; Tseng et al., 1996; Iwasa et al., 2007). Iwasa et al. (2007) found positive immunostaining for CK10, usually expressed in the squamous epithelium, and for CK18, normally expressed in the columnar epithelium, in 33.3% and 66.7% of 21 SCC-MCTs of the ovary, respectively. These findings are similar to those observed for squamous cell carcinoma of cervix and lung, that arise from columnar epithelium through squamous metaplasia.

A few cases of squamous cell carcinomas of the ovaries have been associated with high-risk human papilloma virus [HPV] infection (Araujo et al., 2016; Chiang et al., 2015; Mai et al., 1996; Manolitsas et al., 1998; Verguts et al., 2007). Immunohistochemistry revealed HPV 16/18 in 4 (100%), HPV 31/33 in 2 (50%) and HPV 6/11 in none (0%) of 4 SCC-MCTs (Chiang et al., 2015). Strong and diffuse p16 expression was detected in 2 of 4 cases (50%), thus supporting the possibility that HPV is a risk factor for this malignancy (Araujo et al., 2016). However, other authors failed to demonstrate the presence of HPV (Yetman and Dudzinski, 1989; Liu et al., 2011), which could be partly due to the low sensitivity of the used techniques (Mai et al., 1996). Only a large cohort study with HPV sequence typing could elucidate the oncogenic role of these viruses.

Strong cyclooxygenase-2 [COX-2] expression has been detected in SCC-MCT, but not in benign MCT and in MTC with adenocarcinoma (Sumi et al., 2001). Therefore COX-2 would appear to be involved in the malignant transformation into squamous cell carcinoma.

4. Therapy

The standard primary treatment should consist of bilateral salpingo-oophorectomy, total hysterectomy and comprehensive surgical staging (peritoneal washing, omentectomy, appendectomy, peritoneal biopsies, and pelvic plus paraaortic lymphadenectomy) in early disease and optimal cytoreductive surgery in advanced disease (Hackethal et al., 2008; Ulker et al., 2012; Balık et al., 2013; Chiang et al., 2011). Unilateral salpingo-oophorectomy associated with comprehensive surgical staging can be taken into consideration in young women with early-stage disease wishing to preserve fertility, but few data are currently available in the literature about this conservative approach (Chen et al., 2008; Sakuma et al., 2010; Tseng et al., 1996). In the series of Tseng et al. (1996), four nulliparous women with stage Ia tumor underwent fertility-sparing surgery and two of them had successful pregnancies. In the review of Hackethal et al. (2008), 77% of patients had hysterectomy, 74% had bilateral salpingo-oophorectomy, 24% had unilateral salpingo-oophorectomy, 37% had omentectomy, 14% had lymphadenectomy, and 22% had other surgical procedures. In women with advanced disease lymphadenectomy was found to improve OS (mean, 59.2 months *versus* 40.4 months), whereas omentectomy failed to impact on the clinical outcome.

After comprehensive surgical staging patients with stage Ia tumor can undergo only observation, whereas chemotherapy is warranted for those with more advanced disease (Rim et al., 2006; Chen et al., 2008; Abhilasha et al., 2016; Tseng et al., 1996; Chiang et al., 2011). According to the analysis of Hackethal et al. (2008) on patients who received adjuvant chemotherapy with different drug combinations, only alkylating agent-based regimens significantly improved OS at univariate analysis. However, this finding was not confirmed at multivariate analysis.

Anyway, platinum- based chemotherapy has been frequently used in the first- line treatment. Some patients have received a combination of cisplatin, etoposide and bleomycin (PEB regimen), which is a standard treatment for germ cells tumors, but it is probably misadapted to squamous cell histology (Ribeiro et al., 1988; Tseng et al., 1996). Currently the combination of paclitaxel and carboplatin is the most commonly adopted regimen, although chemotherapy seems to be less effective in SCC-MCTs than in the common epithelial ovarian cancers (Avcı et al., 2012; Chen et al., 2008; Sakuma et al., 2010; Patni, 2014; Tseng et al., 1996; Chiang et al., 2011; Hurwitz et al., 2007). Goudeli et al. (2016) suggested to use the combination of paclitaxel, ifosfamide and cisplatin (TIP regimen), that obtained very good results as neoadjuvant chemotherapy in locally advanced squamous cell carcinoma of the uterine cervix (Zanetta et al., 1998; Buda et al., 2005; Lissoni et al., 2009; Gadducci et al., 2013), reserving a platinum- based doublet to women with less than optimal performance status. Ohtani et al.,(2000) reported the case of a patient with advanced disease who was resistant to a first- line treatment with cisplatin, vincristine, mitomycin C and bleomycin and who achieved an optimal response after dose-dense weekly paclitaxel /carboplatin-based chemotherapy.

The role of radiotherapy or chemoradiotherapy is controversial (Hackethal et al., 2008; Dos Santos et al., 2007; Ulker et al., 2012; Chen et al., 2008; Sakuma et al., 2010; Tseng et al., 1996; Rose et al., 1993; Beuzeboc et al., 1993; Kurtz et al., 1999; Chiang et al., 2011; Ito et al., 2012; Yoshida et al., 2016). A woman with bowel and peritoneal spread of disease received cisplatin/ 5- fluroracil-based chemotherapy and radiotherapy on the pelvis and aortic nodes and she was disease-free after 19 months (Beuzeboc et al., 1993). Yoshida et al. (2016) reported two cases in which radiotherapy or chemoradiotherapy had beneficial effects. One patient with pelvic recurrence after primary incomplete surgery, paclitaxel/ carboplatin- based chemotherapy and interval debulking surgery, received 50 Gy radiotherapy on the pelvis with optimal response and she was free of progression after more than 22 months. Another patient with residual tumor around left ureter after surgery received cisplatin/ 5-fluorouracil- based chemotherapy for 6 cycles. After the first cycles she underwent 54 Gy radiotherapy to the pelvis, the tumor reduced in size, and the patient was free of progression 27 months after surgery. Carbon ion radiotherapy obtained an optimal response in a woman with pelvic recurrence involving the rectum after primary surgery and paclitaxel/ carboplatin- based chemotherapy for FIGO stage IIc tumor (Ito et al., 2012). She has been clinically free of disease for 53 months. Similarly, Dos Santos et al., (2007) reported that the 4 women with stage Ia-IIb tumor who received adjuvant platinum-based chemotherapy with pelvic radiotherapy were still alive after a follow-up ranging from 12 to 56 months, and Tseng et al. (1996) suggested a multimodality treatment consisting of primary cytoreduction, cisplatin-based chemotherapy and radiotherapy for disease located into the pelvis. Conversely, radiotherapy to the pelvis (50.4 Gy) and para-aortic nodes (45 Gy) with concomitant cisplatin (1 mg/kg/weekly) and 3 cycles of adjuvant chemotherapy (cisplatin 75 mg/m^2 every 3 weeks) failed to control disease in a patient with para-aortic node involvement (Rose et al., 1993). In the study of Chen et al. (2008), adjuvant radiotherapy did not improve the clinical outcome of patients with both stage I - II and stage III -IV disease compared with surgery alone, and similarly, the review of Hachethal et at (Hackethal et al., 2008) showed that postoperative radiotherapy did not give any survival benefit.

Secondary cytoreductive surgery can be taken into consideration in accurately selected patients (Hurwitz et al., 2007; Glasspool et al., 2014). For instance, Hurwitz et al. (2007) reported the case of a woman who underwent complete debulking for abdominal recurrence and who subsequently developed a pelvic relapse 3 years later, as well as the case of another patient who underwent complete debulking for mesenteric recurrence and who was still alive with no evidence of disease 2.5 years later.

Table 4
Prognostic value of tumor stage, tumor size and debulking status.

Author [ref]	Variable	Clinical outcome
[Tseng et al., 1996]	Stage	2-year DFS
	I (n.13)	100%
	II (n. 2)	100%
	III (n.10)	30%
	IV (n. 1)	0% p = 0.0001
[Glasspool et al., 2014]	Stage I-I (n. 6)	4/6 survived over 5 years
	III (n .4)	4/4 deteriorated within 1 year
[Kikkawa et al., 1997]	Stage	5-year OS
	I (n.19) II (n. 5)	94.7%
	III (n.13)	80%
		12/13 DOD within 20 months; 1 living patient followed only for 2 months
		p < 0.0001
[Chen et al., 2008]	Stage I (n.98)	5-year OS
	II (n.33)	75.7%
	III (n.68)	33.8%
	IV (n. 7)	20.6%
		0% p < 0.0001
[Chen et al., 2008]	Tumor size	5-year OS
	≤ 13.8 cm (n.63)	50.5%
	> 13.8 cm (n.73)	42.2% p = 0.0349
[Kikkawa et al., 1997]	Residual disease (cm) 0 (n.26)	5 year OS
		79%
	> 0 (n.11)	10.1% p = 0.0002
[Tseng et al., 1996]	Residual disease (cm)	2-year DFS
	< 1 (n. 5)	60%
	≥ 1 (n.11)	0% p = 0.0210
[Sakuma et al., 2010]	Residual disease (cm)	mean survival (months)
	0 (n.13)	14 (range, 5-180)
	> 0 (n. 7)	7.8 (range = 1-16) p < 0.0001
[Chen et al., 2008]	debulking status	5-year OS
	optimal* (n.63)	76.0%
	Suboptimal (n.35)	24.5% p < 0.0001
[Abhilasha et al., 2016]	debulking status	5-year OS
	0 (n.6)	83% NED at a median follow-up of 10 months 100% progression within 3-4 months
	> 0 (n.4)	

Legend: DFS, disease-free survival; OS, overall survival; DOD, dead of disease ; NED, no evidence of disease.
* Non specified.

5. Prognosis

SCC-MCTs of the ovary have a significantly worse outcome compared with that of the common epithelial ovarian cancers, with a 5-year OS rate ranging from 28 to 66.7% (Avcı et al., 2012; Koc et al., 2017; Chen et al., 2008; Glasspool et al., 2014). Tumor stage and debulking status are the strongest prognostic variables (Table 4) (Hackethal et al., 2008; Rim et al., 2006; Kikkawa et al., 1997; Chen et al., 2008; Sakuma et al., 2010; Abhilasha et al., 2016; Tseng et al., 1996; Kashimura et al., 1989). Rim et al. (2006) administered adjuvant chemotherapy to 7 and chemotherapy and radiotherapy to 2 of the 11 patients with SCC-MTCs. All stage I patients were alive after a median follow-up of 31.8 months. Hackethal et al. (Hackethal et al., 2008) found that the 120 women with stage I disease had a significantly better OS compared with the 121 with more advanced disease and that OS differences among stages II, III, and IV were not significant. Chen et al. (Chen et al., 2008) reported that 5- year OS was significantly poorer for patients with tumor size > 13.8 cm compared with those with smaller tumor (p = 0.0349). However, only stage and debulking status were independent prognostic variables at multivariate analysis (p = 0.0371 and p = 0.0112, respectively).

The prognostic relevance of other variables is still debated (Table 5). Some authors (Chen et al., 2008; Sakuma et al., 2010) reported a better OS for women younger than 50 or 55 years, but others (Abhilasha et al., 2016; Tseng et al., 1996) did not confirm these observations. Some authors (Abhilasha et al., 2016; Tseng et al., 1996)

Table 5
Prognostic value of other variables.

Author [ref]	Variable	Clinical outcome
[Chen et al., 2008]	Age (years)	5-year OS
	≤ 55 (n.95)	58.1%
	> 55 (n.93)	39.8% p = 0.0310
[Tseng et al., 1996]	age (years)	2-year DFS
	< 50 (n. 9)	89%
	> 50 (n.17)	59% p = ns
[Sakuma et al., 2010]	age(years)	mean survival (months)
	< 50 (n. 9)	15.8
	> 50 (n.11)	9.8 p = 0.044
[Kikkawa et al., 1997]	vascular involvement	5-year OS
	negative (n.21)	70.3% 0% p = 0.0002
	positive (n.11)	
[Kikkawa et al., 1997]	mode of infiltration	100% NED after a median of 38 months (range, 6-80 months)
	α (n.11)	
	β (n.12)	33.3% DOD within 20 months
	γ (n. 9)	100% DOD within 19 months
		α vs β, p < 0.05;
		β vs γ, p < 0.005;
		α vs γ,p = 0.0001
[Tseng et al., 1996]	grade	2-year DFS
	1 (n. 2)	100%
	2 (n.12)	58%
	3 (n.12)	75% p = ns
[Kikkawa et al., 1997]	grade	5-year OS
	1 (n. 9)	28.1%
	2 (n.17)	53.1% 18.8% p = 0.0146
	3 (n. 6)	
[Kikkawa et al., 1997]	keratinization	5-year OS
	positive (n.14)	72.7%
	negative (n.18)	45.5%
		p = ns
[Chen et al., 2008]	Serum tumor marker	5-year OS
	SCC: negative (n. 6)	83.3%
	positive (n. 26)	39.1% p = 0.0415
	CA 125: negative (n.16)	92.9%
		18.0% p = 0.0004
	positive (n. 26)	100%
	SCC and CA 125:	78.8%
	all negative (n. 4)	13.9% p = 0.0114
	one positive (n.10)	55.6%
	both positive (n.17)	54.0% p = 0.8297
	CA 19.9 negative (n.10)	66.7%
		43.2% p = 0.3731
	positive (n.22)	
	CEA negative (n. 7)	
	positive (n.13)	

Legend; Legend: OS, overall survival; DFS, disease-free survival; α, carcinoma cells invaded the stroma expansively with a well-defined border between tumor and stroma; γ,carcinoma cells invade the stroma diffusely without a clear border; β,intermediate features between α and γ ; NED, no evidence of disease; DOD, dead of disease.

failed to detect a relationship between tumor grade and clinical outcome. Conversely, Kikkawa et al. (Kikkawa et al., 1997) reported that tumor grade as well as mode of infiltration had an independent prognostic relevance at multivariate analysis (p = 0.0154 and p = 0.0053, respectively).

As far as serum tumor markers are concerned, Hackethal et al. (Hackethal et al., 2008) reported a significantly better OS in patients with serum SCCA < 4.7 ng/ml compared with those with serum SCCA between 4.8 ng/ml and 16 ng/ml or serum SCCA > 16 ng/ml, as well as in women with serum CA 125 < 43 U/ml compared with those with serum CA 125 between 43 U/ml and 116 U/ml or serum CA125 > 116 U/ml. Similarly, in the review of Chen et al. (Chen et al., 2008) both serum CA125 and SCCA had a significant prognostic relevance, whereas serum CA19-9 and CEA did not correlate with the clinical outcome (Table 5).

6. Conclusions

Malignant transformation occurs in approximately 2% of the patients with MCTs of the ovary, and squamous cell carcinoma is the most common histotype. The clinical presentation is similar to that of other ovarian tumors, and in early-stage disease the diagnosis is frequently made unexpectedly in the operating room or on final histological examination. SCC-MCT is mainly found in women older 50 years, with elevated serum SCCA and CA125 levels, and with an ovarian tumor size > 10 cm. Therefore, patient age, serum marker assays, tumor diameter, and some sonographic or radiological findings could be useful to identify a subset of MCTs with the highest risk of malignant transformation. Patients with disease apparently confined to the gonad should undergo bilateral salpingo-oophorectomy, total hysterectomy and comprehensive surgical staging, whereas fertility- sparing surgery should be reserved to accurately selected cases. Primary debulking surgery is warranted in patients with advanced disease at presentation. Standard paclitaxel/carboplatin- based chemotherapy is the most used adjuvant treatment, whereas more aggressive regimens, such as dose-dose paclitaxel/ carboplatin-based chemotherapy or TIP regimen, can be taken into consideration in patients with high tumor burden or recurrent disease. The efficacy of radiotherapy or chemoradiotherapy is still unproven. The prognosis is good for properly staged Ia disease, whereas it is generally poor when the tumor has spread beyond the ovary. According to the 2014 Gynecologic Cancer InterGroup [GCIG] consensus, nowadays there are very few information to provide commonly accepted guidelines for the management of this malignancy (Glasspool et al., 2014). An international collaborative effort is strongly warranted to better elucidate the biology and to develop novel effective therapies of SCC-MCTs of the ovary.

Conflict of interest

The authors indicated no potential conflict of interest including any financial or personal relationships with other people or organizations that could inappropriately influence (bias) this work.

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