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Uterine carcinosarcoma: the TAG systematic review

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Summary

Uterine carcinosarcoma (UCS: uterine malignant mixed Müllerian tumor, uterine MMMT, uterine MMT) is an uncommon but aggressive malignancy. Given that UCS is metaplastic carcinoma, the stage system is according to the 2009 FIGO (Federation of International Gynecology and Obstetrics) staging system for endometrial cancer. In addition, UCS is included into the classification of mixed epithelial and mesenchymal tumors of the uterus, based on the current 2014 World Health Organization (WHO) classification. The diagnosis of UCS is made in the presence of high-grade malignant epithelial and mesenchymal components typically showing a sharp demarcation. The principal treatment in early and locally advanced UCS is a complete and comprehensive staging surgery, including total hysterectomy, bilateral salpingo-oophorectomy, and systematic lymphadenectomy. For advanced-stage UCS, *en-bloc* debulking surgery is also beneficial for the patients. Multi-agent chemotherapy with and without radiotherapy is often prescribed for patients with UCS, because it might be associated with a better progression-free survival and overall survival. This review summarizes and analyzed the updated information of this highly aggressive disease.

Key words: Endometrial cancer; Uterine carcinosarcoma; Uterine malignant mixed Müllerian tumor.

Introduction

Mixed epithelial and mesenchymal tumors of the uterus are a heterogenous group of neoplasms, including uterine carcinosarcoma (UCS), adenosarcoma, adenofibroma, adenomyoma, and atypical polypoid adenomyoma, based on the current 2014 World Healthy Organization (WHO) classification [1]. Adenosarcoma has been extensively reviewed before [2]. In brief, adenosarcoma is a mixed benign or atypical epithelial and low-grade malignant mesenchymal tumor l [2]. The clinical features of adenosarcomas are generally considered as a neoplasm of low malignant potential, although adenosarcoma might have local recurrence or even have a distal metastasis. The typical pathological feature is a phylloides-like (leaf-like or club-like) architecture, and consists of dilated or slit-like or club-like glands, which is lined by cuboidal or low columnar cells in the epithelial part and contains low-grade spindled and/or round cells with scant cytoplasm, which concentrate around or beneath the glandular elements (periglandular cuffing) in the stromal component [1, 2]. Some adenosarcoma is associated with sarcomatous overgrowth, which is unlike the conventional types of adenosarcomas, confined to the endometrium or cervical mucosa [1]. These adenosarcoma with sarcomatous overgrowth may involve deep myometrial and vascular invasion, which is the most important prognostic factor [2].

Adenofibroma is also a biphasic tumor mixing with benign epithelial and mesenchymal components, which typically occurs in the endometrium without stromal or myometrial invasion [3]. The tumor mainly occurs in the perimenopausal or postmenopausal women, with the most common symptom, including abnormal vaginal bleeding followed by less frequent abdominal pain or uterine enlargement or a polypoid tumor projecting from the cervix. Grossly, adenofibromas are polypoids tumors, which vary from soft to firm, to rubbery, and appear tan-brown with foci of hemorrhage [3]. Microscopically, adenofibromas consist of a mixture of bland glandular epithelium (columnar, flattened or cuboidal epithelium, not significantly proliferative, and most often of endometrioid type, line cysts, and cleft-like space) and hypocellular stroma (fibrous containing fibroblasts and collagen with small uniform and

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bland nuclei). The broad papillary or polypoid stromal fronds, covered by epithelium appear relatively acellular and project from the surface of the tumor or extend into cystic spaces [3]. Total hysterectomy is a best choice of the treatment, but curative local excision can be accepted in young women who require preservation of the uterus [3].

The other subtype of mixed epithelial and mesenchymal tumors of the uterus is adenomyoma (endometrioid-type adenomyomata) or its variance—atypical polypoid adenomyoma [4-6]. Atypical polypoid adenomyoma consists of endometrioid-type glands embedded in a myomatous or fibromyomatous stroma, which is most commonly located in the lower segment of the uterus [1]. Patients with atypical polypoid adenomyoma is relatively younger (mean age 40 years), often presents menorrhagia, and abnormal uterine bleeding [7]. Grossly, the tumor is a broad-based polypoid lesion. Microscopically, the tumor showed the crowded, or widely separated and haphazardly arranged with a vague lobular architecture endometrioid-type glands, which exhibit mild or, at most, moderate cytological atypia [1]. Immunohistochemically, the mesenchymal cells react for smooth-muscle marker, and endometrioid-type glands are reactive for cytokeratin, estrogen receptor, and progesterone receptor [1]. Total hysterectomy is the treatment of choice, although complete resection is acceptable for cure, especially applicable in young women who would like to maintain their fertility. However, recurrence may occur if there is incomplete excision or there is complex architecture of atypical polypoid adenomyoma [1].

Traditionally, UCS is included in the sarcoma category, and as such is the most common of the uterine sarcomas [8]; therefore, this review is a series review of uterine sarcomas followed by the previous two articles, including part I: uterine leiomyosarcoma (uLMS) and part II: uterine endometrial stromal sarcoma (uESS) [2,9]. This topic is limited to review the category of the biphasic malignant neoplasm- UCS (uterine malignant mixed Müllerian tumor, uterine MMMT, uterine MMT).

Overview

UCS is no longer considered as sarcoma, due to its different spreading pattern as a dedifferentiated or metaplastic form of endometrial cancer [10, 11] and in which the mesenchymal part retains epithelial features (i.e., "conversion theory", which is supported by various molecular studies reporting similar chromosomal aberrations, cytogenetic aspects, concordant loss of heterozygosity, identical *p*53, and *K-ras* mutations, and matching X inactivation patterns in both histological components of the majority of UCS cases), supporting the conclusion that most of these UCS lesions are monoclonal, and indirectly the possibility of the stem cell origin theory (a single cell progenitor for UCS) [12,13]. Kalluri and Weinberg suggested that the UCS cells have the phenotypic plasticity to experience not only an epithelial-mesenchymal transition (EMT) but also a mesenchymal-epithelial transition (MET), which could partly explain the aggressive clinical nature of UCS, if cells might have the ability to be independent of basement membrane signals and to convert between cell types [14]. UCS shares the similar risk factors, a similar disease pattern, a similar sensitivity to chemotherapy, and similar immunohistochemical and molecular studies compared with endometrial cancer. Like endometrial cancer [8, 15-21], UCS risk is increased in the setting of increased estrogen levels, including tamoxifen use, nulliparity, as well as obesity and decreased by the use of oral contraceptives. Patients treated with tamoxifen have a two-fold increase in the incidence of endometrial cancer and eight-fold increase in the incidence of UCS [13]. Surprisingly, black race had a higher risk for UCS than whites or oriental race did; in addition, the recurrence rates were higher and mortality was higher in the black race [13].

UCS behaves more aggressively than usual type of endometrial cancers, even for grade 3 endometrioid-type endometrial cancer or other subtypes of the type II endometrial cancers, such as uterine serous carcinoma, and uterine clear cell carcinoma. Furthermore, spread to pelvic lymph nodes (PLN) and para-aortic lymph nodes (PALN) is common in patients with UCS and distant metastases are relatively frequently noted in the UCS. The revised FIGO (International Federation of Gynecology and Obstetrics) 2009 classification distinguishes UCS from other uterine sarcomas, and classifying it together with endometrial cancer [22, 23], and the American Joint Committee on Cancer (AJCC) tumor-node-metastases (TNM), and FIGO surgical staging system for UCS is shown in the Table 1. However, the audience should be informed that many previous studies still included UCS as one of the uterine sarcomas.

Pathological features

Grossly, UCS is a bulky, necrotic and hemorrhagic polypoid tumor, filling the endometrial cavity and protruding through the cervical orifice [1]. Microscopically, the diagnosis of UCS should identify high-grade malignant epithelial and mesenchymal components typically showing a sharp demarcation between both [1]. The tumor is typically composed of cells displaying anaplasia with notable variation in nuclear size and shape, anomalous mitotic figures, and giant cells [12]. The most common epithelial components are shown in order, including serous, grade 3 endometrioid, clear cell and undifferentiated carcinoma, and the mesenchymal component can be homologous (uterine type tissue) or heterologous (non-gynecologic tissue, most commonly bone or cartilage). Similarly to the epithelial component, the typical homologous component is high-grade stromal sarcoma. The heterologous components are found in association with areas of undifferentiated sarcoma or stroma sarcoma, and rhabdomyosarcoma is the most

Table 1. — *2009 FIGO (Federation International Gynecology and Obstetrics) and 2010 American Joint Committee on Cancer (AJCC-tumor, lymph node and metastases) system-TNM staging for uterine carcinosarcoma.*

FIGO	*TNM*	*Definition*
I	T1N0M0	Tumor confined to the corpus uteri
IA	T1aN0M0	Tumor limited to endometrium or invades < 1/2 of the myometrium
IB	T1bN0M0	Tumor invades ≥ 1/2 of the myometrium
II	T2N0M0	Tumor invades stroma of the cervix without extending beyond uterus
III		Tumor invades serosa, or adnexa or vagina or parametrium or pelvic or para-aortic lymph nodes
IIIA	T3aN0M0	Tumor invades serosa and/or direct extension or metastases to the adnexa
IIIB	T3bN0M0	Tumor invades vagina (direct extension or metastases) or parametrium
IIIC	T1-T3N1M0	Pelvic and/or para-aortic lymph node metastases
IIIC1	T1-T3N1M0	Pelvic lymph node metastases
IIIC2	T1-T3N2M0	Para-aortic lymph node metastases with and without pelvic lymph node metastases
IV		Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	T4N0M0	Tumor invades bladder mucosa and/or bowel (bullous edema is not sufficient to classify a tumor as T4)
IVB	T1-T4N0-N1M1	Distant metastasis, including inguinal lymph nodes, intraperitoneal diseases, or lung, liver or bone.

Tx: primary tumor cannot be assessed; T0: no evidence of primary tumor; TIS: carcinoma in situ (preinvasive carcinoma); Nx: regional lymph node cannot be assessed; N0: no regional lymph node metastases; N1: regional lymph node metastatic to pelvic lymph nodes; N2: regional lymph node metastatic to para-aortic lymph node, with or without pelvic lymph node metastases; M0: no distant metastases; M1: distant metastases. Positive cytology has to be reported separately without changing the stage.

common heterologous component, followed by chondrosarcoma, osteosarcoma, and liposarcoma [12]. Generally, immunohistochemical staining, thought to be useful in the differential diagnosis between dedifferentiated carcinomas and UCS, is of little value in the confirmed UCS. The immunohistochemical profiles of UCS are characterized by consistent positive staining of the malignant epithelial elements with anti-cytokeratin antibodies and epithelial membrane antigen (EMA), and the mesenchymal components are generally positive immunoreactivity for vimentin [7, 12]. Other approach is included to identify the heterologous component. For example, nuclear staining with myogenin and myoD1 helps to identify the rhabdomyosarcoma [1].

The molecular characteristics of UCS are relatively complicated, and UCS often shows extreme chromosome instability with complex karyotypes [8]. The following alternation has been reported before, including an activated AKT pathway, PI3K3CA/AKT mutations, *K-ras* mutations, amplification of ErbB-2 (Her2/Neu), overexpression of cyclooxygenase-2 (COX-2), and over expression of vascular epithelial growth factor (VEGF) [8]. Tumors that may raise problems in the diagnosis of UCS include other types of "high-grade" endometrial cancer, an unusual variant of endometrioid adenocarcinoma (corded and hyalinized endometrioid adenocarcinoma, which is characterized by cords of epithelioid cells, spindle cells, and a hyalinized stroma with presence of areas of a diffuse growth of fusiform cells sometimes), and the combination of an undifferentiated endometrial carcinoma and a low-grade endometrioid adenocarcinoma (mixed endometrioid and undifferentiated carcinoma or dedifferentiated carcinoma containing non-cohesive cells typically positive with cytokeratins and epithelial membrane antigen and associated with mismatch repair abnormalities) [1].

For the clinical purpose, percentages and types of the epithelial and mesenchymal elements should be mentioned which is suggested by the International Collaboration on Cancer Reporting (ICCR) [23], since the nature of the mesenchymal component is a powerful prognostic indicator; those tumors with heterologous elements having a significantly worse prognosis than those with only homologous mesenchymal component (three-year survival rate of 45% and 93%, respectively) in the patients with surgico-pathological Stage I UCS [24]. A recent multi-center retrospective study in Japan evaluated 906 patients with UCS and found that high-grade/homologous was the most common type (40.8%) followed by high-grade/heterologous (30.9%), low-grade/homologous (18%), and low-grade/heterologous (10.3%) [25]. The worst prognosis of patients with UCS was high-grade/heterologous group with five-year survival rate of 34% ($p = 0.024$), followed by high-grade/homologous (45.8%, $p = 0.017$), but not low-grade/heterologous (50.6%, $p = 0.089$) were independently associated with decreased progression-free survival (PFS) compared to low-grade/homologous (60.3%) [25]. Finally, the Matsuo *et al.* study also showed that carcinoma components tended to spread by lymphatic system while sarcoma components tended to spread at the local and certain region sites ($p < 0.001$) [25].

Clinical features

Patients with UCS, elder age (mean age of 70 years) often present with abnormal vaginal bleeding, bloody discharge, watery discharge, abdominal pain or uterine enlargement, but it is very difficult to make an accurate diagnosis by means of cervicovaginal cytology, dilatation and curettage, or endometrial biopsy, and are often misdiagnosed as endometrial cancer. USC appears as a large

mass accompanied by dilatation of the uterine cavity and myometrial invasion mostly in the fundal area. On ultrasound, tumor often appears a hyperechoic mass lesion. On CT, tumor was a heterogeneously hypodense and ill-defined contrast-enhanced mass. On MRI, tumor was a large exophytic, heterogeneous high signal intensity mass on T2-weighted MRI, and contained strongly enhanced areas with the mass [8].

Preoperative serum level of CA 125 is increased in UCS with extrauterine spread and deep myometrial invasion [8, 12, 13]. Elevated levels of CA 125 were also reported to be associated with the presence of serous epithelial component [8]. However, the implication of this in clinical practice is not yet confirmed [8, 13].

Treatment

UCS is a far more aggressive tumor, and 60% of patients are diagnosed with extrauterine spread and recurrence occurs in more than half of patients after aggressive multimodality treatment, contributing to the worst prognosis of UCS [8]. In the absence of standard guidelines specific for UCS, most gynecological oncologists perform the same survival treatment for aggressive endometrial cancer.

Surgery

Similar to the management of endometrial cancer [26-28], staging surgery, including total hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymphadenectomy (pelvic lymph node dissection and para-aortic lymph node dissection: PLND and PALND), or consideration of cytoreduction (debulking surgery if appropriate) is the most important procedure in the management of patients with UCS. The role and extent of LND in the management of women with endometrial cancer remains debated, partly because of low-grade (grade 1 and 2) and early stage (stage I) is most commonly found in patients with endometrial cancer, especially endometrioid subtype and premenopausal women and partly because of low incidence of PLN and/or PALN metastases in women with FIGO IA grade 1 or grade 2 pure endometrioid endometrial cancer. By contrast, it is believed that retroperitoneal lymphadenectomy is important as part of staging surgery for disease not only for treatment planning but also for prognosis in patients with UCS [29]. In addition, patients with UCS who underwent retroperitoneal lymphadenectomy had a better overall survival (OS) than those who did not, even though these patients had the corpus-confined diseases, in which tumors apparently limited to the uterus [30]. Furthermore, our recent publication also supported the importance of PLND and PALND as a part for staging surgery, even for type I pure endometrioid-type endometrial cancer [31]. A retrospective analysis of data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI) between January 1, 1988 and November, 2003 enrolled a total of 1,855 women with UCS undergoing primary surgical treatment, and the results showed that five-year OS, DFS, and median survival were significantly improved for patients (n = 965, 57%) receiving lymph node dissection (LND) as compared to patients (n = 732, 43%) who did not receive LND (49% *vs*. 34% on five-year OS rate; 42% *vs*. 27% on eight-year OS rate; 54 months [95% confidence interval (CI) 44-72 months] *vs*. 25 months [95% CI 22-29 months] on median survival), contributing to a better chance to survive (hazard ratio [HR] 0.69, 95% CI 0.60−0.79) [29]. The data of the SEER also emphasized the important role of complete LND, because there was no statistically significant difference of five-year OS and median survival of these UCS patients with and without radiotherapy (35.8% *vs*. 33.4% on five-year OS rate, and 29 months *vs*. 23 months on median survival, $p = 0.2632$), if these patients did not undergo LND [29]. Furthermore, among patients who did undergo LND, radiotherapy was not associated with an OS (HR 0.92, 95% CI 0.76−1.11) [29]. Alagkiozidis *et al.* evaluated 158 patients with UCS as well as other subtypes of endometrial cancer (115 patients with uterine papillary serous carcinoma and 561 patients with endometrioid carcinoma) and 73% of the patients with UCS were treated with LND [30]. The authors found that the performance of LND is associated with improved OS, and of most importance, a continuum of improved OS was noted in correlation with increased lymph node count, contributing to 28% and 14% risk of death reduction for the first and second year, respectively; therefore, the authors concluded that the extent of the LND is inversely correlated with the risk of death for the first two years [30]. The data on patients with surgically and pathologically staged IIIA-IVB pure endometrioid-type endometrial cancer in the Taiwanese Gynecology Oncology Group (TGOG-2005) showed that complete PLND and PALND could provide a better chance of DFS (HR 0.269, 95% CI 0.163−0.445, $p < 0.001$) and OS (HR 0.142, 95% CI 0.077−0.261, $p < 0.001$) [31].

Surgery for early-stage UCS

For all early-stage cases of UCS, complete staging surgery is of paramount importance, since nearly one-fifth of patients with a supposed early-stage UCS were upstaged after PLND and PALND. In addition, pelvic washings should be obtained, although the pelvic washings do not impact FIGO stage. The result of a Gynecologic Oncology Group (GOG) pathologic study enrolling 203 women with early-stage (Stage I, II) UCS showed that 40 of these supposed early-stage UCS women had metastases [32]. This study also showed the interesting findings that the features of the stromal component of the primary tumors, such as grade, mitotic index, and the presence and types of heterologous elements was not associated with the presence

of metastases at operation; by contrast, high-grade, serous, and clear cell carcinomatous components as well as deep myometrial invasion, lympho-vascular space invasion (LVSI), and involvement of the isthmus or cervix were associated with a higher frequency of metastases [32].

Because minimally invasive surgery (MIS) can be applicable in the management of patients with endometrial cancer, it may be reasonable to consider the use of MIS in the selected patients. The results from American College of Surgeons-National Surgical Quality Improvement Project's database comparing 1269 exploratory laparotomies and 807 minimally invasive surgeries showed the feasibility and safety of using MIS in the treatment for endometrial cancer [33]. The data from Taiwan also supported the safety of MIS in the patients with endometrial cancer [34-37]. While to explore the outcome of GOG LAP2 study [38,39], there were 41 patients with UCS in a total of 2489 patients. Although LAP2 supported the use of MIS for staging uterine malignancies, and concluded that this study did not reveal any evidence of a particular subgroup that could not be treated with MIS, it is hard to convince us the safety and feasibility of the use of MIS for UCS. In addition, one case of port site metastases occurs in the UCS patients undergoing MIS [39], suggesting the potential widespread during the MIS procedure. Although port site metastases also occurred in the use of MIS for endometrial cancer [40], however, the pattern of disease might show some differences, because our previous reports showed the port site metastases might be secondary to the far-advanced gynecologic malignancies [40-42]. In addition, a clinically supposed early-stage UCS seemed to be highly risky for upstaged diseases (for example, 20% of early-stage UCS showed the positive lymph node metastases) and lymph node metastases might be one of precipitating factors to port site metastases [40]. Therefore, the feasibility and safety of MIS for UCS needs the answers after a large-scale population study.

Surgery for advanced-stage UCS

Similar to type II or high-grade endometrioid type endometrial cancer, UCS often belongs to the advanced stage when the diagnosis is made. The initial surgical treatment should attempt to finish the *en bloc* total excision of the tumors or complete debulking surgery (cytoreductive surgery, similar to the treatment for epithelial ovarian cancer, primary peritoneal serous carcinoma, and primary fallopian tube cancer) to minimize the residual tumors [43-48]. As shown before, the data from TGOG-2005 showed that patients who were treated with extensively complete PLND and PALND not only had a better DFS (hazard ratio [HR] 0.269, 95% confidence interval [CI] 0.163−0.445, $p < 0.001$) but also had a better OS (HR 0.142, 95% CI 0.077−0.261, $p < 0.001$) compared with those who were not treated with PLND and PALND [31]. This concept of the successful management of far-advanced endometrial cancers might also fit that of advanced-stage UCS. A retrospective study from the Memorial Sloan-Kettering Cancer Center evaluated 44 patients with far-advanced (III and IV) UCS and the data showed that complete gross resection was associated with a median OS of 52.3 months compared to 8.6 months in patients with gross residual disease ($p < 0.0001$), suggesting that cytoreductive surgery, with a goal of achieving a complete gross resection, is associated with an improvement in OS in the far-advanced UCS patients [49]. A multi-center, retrospective study from Japan enrolling 225 patients Stage III-IV UCS between 2007 and 2012 to explore the benefits of cytoreductive surgery for UCS [50]. The results showed that more than three-fourths of patients who received optimal cytoreductive surgery (defined by a maximum residual tumor of ≤ one cm) had a significantly better PFS than those patients who received suboptimal cytoreductive surgery did (11.5 months [95% CI 10.6−13.4 months] *vs*. 8.1 months [95% CI 5.1−9.5 months], $p < 0.0001$), contributing to significantly prolonged OS in patients with optimal debulking surgery compared to those without (37.9 months [95% CI 28.3-not reached] *vs*. 18 months [95% CI 9.6−21 months], $p < 0.0001$) [50]. In addition, this study in Japan also supported the benefits of PLND since PLND was associated with improved OS. Therefore, the authors concluded that optimal debulking surgery and PLND are associated with improved OS in advanced UCS patients [50].

In summary, complete staging surgery and cytoreductive surgery might be one of the most important essential parts in the management of women with various stages of UCS. Because of the frequency of both distant (a high rate of micro-metastatic disease) and local recurrence (local aggressiveness) after definitive surgery, postoperative adjuvant therapy is always considered in an attempt to control disease spread. However, systemic chemotherapy, radiotherapy either through vaginal brachytherapy, or through pelvic external beam radiation, and observation are all acceptable adjuvant management opinions, based on the individual patient's condition and physician's preference, even though it is believed that successful disease control for UCS might involve both the local and systematic diseases. The following sections are discussed for the role of postoperative adjuvant therapy in the management of patients with UCS.

Adjuvant therapy in the early stage UCS

As shown above, an early SEER analysis showed that LND led to a significant improvement in OS in the UCS patients compared to those who did not have LND and this survival advantage remained, regardless of whether these UCS patients without LND received adjuvant radiotherapy or not [29], hinting that postoperative adjuvant radiotherapy for incomplete staging surgery (LND was not included)

may not be adequate for the control of the diseases. Therefore, a widely accepted paradigm of treatment includes definite surgery and adjuvant chemotherapy, while postoperative radiation therapy is a subject to controversy [51].

However, the data of the SEER enrolling 2,342 patients with all-staged UCS (more than 70% of patients were Stage I and II) showed that longer survival was found in the group of patients who received adjuvant radiation therapy compared to that in the group of those who did not [51]. The OS was 42 months (95% CI 37−52 months) in the postoperative radiation group compared to that of 22 months (95% CI 19-25 months) in the surgery alone group, $p < 0.0001$ [51]. In addition, the patients with postoperative radiation therapy also had a significantly better cause-specific survival than those without radiation therapy did (57 months [95% CI 42−87 months] *vs*. 28 months [95% CI 24−32 months], $p < 0.0001$) [51], suggesting that the patients undergoing surgery followed by postoperative adjuvant radiation therapy took advantages for better survival than the patients undergoing surgery alone did. In fact, there was a significant association between the AJCC stage at presentation and treatment by postoperative radiation therapy: specifically, 41.6% of patients with AJCC Stage I received postoperative radiation therapy, 81.1% with AJCC Stage II, 29.0% with AJCC Stage III, and 16.3% with AJCC Stage IV [51]. In fact, the results of the early SEER enrolling 2,677 women between 1989 and 1999 also reported increased survival in the surgery plus postoperative radiation therapy group compared with that in the surgery alone, albeit in a population of mixed uterine sarcoma [52]. Similarly, Wright *et al.* evaluated the outcomes of 667 patients with early-stage UCS (Stage I and II) and 235 patients treated with subsequently radiation therapy after surgery [53]. The authors found that postoperative radiation therapy reduced the risk of death by 21% (HR 0.79, 95% CI 0.7−0.9) [53]. Radiation reduced mortality rates in patients with UCS who had not undergone LND but had only a marginal effect on survival in LND patients without LN metastases [53].

The findings of the SEER were also supported by another multi-institutional study, which enrolled 118 women with early-stage UCS [54]. This study included 80% of patients who underwent lymphadenectomy (n = 94), 37 patients received postoperative observation (31%), 19 patients received postoperative chemotherapy alone (16%), 24 patients received postoperative radiation alone (20%), and 38 patients received postoperative combination of chemotherapy and radiation (32%) [54]. In agreement of benefits of the using PLND and/or PALND in the management of patients with UCS to improve OS in the SEER report [51], LND provided a better chance for OS (HR 0.24, 95% CI 0.09−0.61, $p = 0.003$) [54]. However, in terms of considering freedom from vaginal failure in these patients with UCS, adjuvant therapy after definite surgery, regardless whether chemotherapy, radiation therapy or combination of chemotherapy and radiation therapy were used provided the less frequency of vaginal recurrence (HR 0.58, 95% CI 0.38−0.88, $p = 0.01$) [52]. Furthermore, adjuvant therapy was also associated with PFS (HR 0.74, 95% CI 0.56−0.99, $p = 0.04$) [54]. Therefore, the authors concluded that the combined approach of surgery, chemotherapy, and external beam radiation with or without brachytherapy could produce favorable survival and recurrence outcomes in patients with UCS [54].

A GOG (GOG20) phase III trials was conducted to evaluate the effect of adjuvant doxorubicin in 156 women with Stage I or II uterine sarcoma, including UCS, and the results showed that adjuvant doxorubicin contributed to a lower recurred rate (41% *vs*. 53%, respectively), but it did not reach statistical significance [55]. In addition, there was no difference of PFS and OS between the two arms [55].

A phase III prospective randomized trial conduced by the GOG (GOG 150) analyzing 206 patients aimed to compare the impact of adjuvant external beam radiation alone (n = 105) and chemotherapy alone (n = 101) [56]. The results showed a trend towards reduction in local recurrence in the external beam radiation group (17% *vs*. 24% in chemotherapy alone group) [56]. The European Organization for Research and Treatment of Cancer- Gynecological Cancer Group (EORTC-GCG 55874) enrolled 94 patients with UCS [57]. The results showed that external beam radiation therapy significantly improved locoregional control (24% in the external beam radiation therapy *vs*. 47% in the observation) [57]. However, both studies (GOG 150 and EORTI-GCG 55874) failed to provide any benefit in terms of survival [53, 54], but the GOG 150 study favored the use of combination chemotherapy in future trials based on observed differences (the estimated death rate was 29% lower among the combination chemotherapy groups (HR 0.712, 95% CI 0.484−1.048, $p = 0.085$) [56]. The chemotherapy regimen of the GOG 150 comprised intravenous (IV) cisplatin (20 mg/m^2/day for four days) that was to be followed by a one-hour IV administration of ifosfamide (1.5 g/m^2/day IV for four days) with mesna (120 mg/m^2 IV bolus over 15 minutes on day one, followed by 1.5 g/m^2/day IV continuous infusion for four days beginning with day one) every three weeks for three cycles [56]. An early report of the SEER showed that propensity score-adjusted HR for patients receiving postoperative radiation therapy alone versus neither LND nor radiation therapy (HR 0.92, 95% CI 0.76−1.12) and both LND and radiation therapy versus radiation therapy alone (HR 0.92, 95% CI 0.76−1.11) were non-significant; therefore, the authors concluded that the use of adjuvant radiotherapy conferred no OS benefits in 1855 patients with AJCC Stages I-III UCS [29].

In summary, after the maximum surgical effort, chemotherapy and radiation therapy and combination of both therapies are recommended for all early-stage UCS. A multi-institutional study of outcomes in Stage I-III UCS (n = 303) concluded that observation after surgery was as-

sociated with poor outcomes in UCS compared to chemotherapy and radiation therapy alone [58]. Therefore, only patients with 2009 FIGO Stage IA without myomatrial invasion could be treated with definite comprehensive staging surgery alone, because there exist no randomized trials that have evaluated the value of adjuvant chemotherapy in these patients group. For patients with stage over 2009 FIGO Stage IA without myometrial invasion, multimodality therapy might be associated with improved PFS compared to chemotherapy alone [58], although chemotherapy with and without external beam whole abdominal radiation with or without brachytherapy is still highly recommended in the early-stage UCS patients after definite comprehensive staging surgery.

Adjuvant therapy in the advanced stage UCS

As shown above, an early SEER analysis showed that LND led to a significant improvement in OS in the UCS patients compared to those who did not have LND, and this survival advantage has remained, regardless of whether these UCS patients without LND received adjuvant radiotherapy or not [29], hinting that definite comprehensive staging surgery is a key component in the management of patients with UCS at any stage successfully. Of course, this concept is also the best choice in the treatment for advanced stage UCS. Based on the far-advanced stage diseases of UCS, postoperative adjuvant chemotherapy is strongly recommended. However, the value of postoperative adjuvant radiation therapy in the treatment of UCS was found in the findings from the SEER, because within the postoperative radiation therapy group, an increased survival in the postoperative radiation therapy patients diagnosed both between 1999 and 2004 and 2005-2010, and the magnitude of increase in survival in the recipients of postoperative adjuvant radiation therapy, suggesting the possibility of international cooperative trials [51].

In terms of chemotherapy, what is the appropriate chemotherapy treatment for UCS? The main agents included ifosfamide (32%-36% response rate), cisplatin (19% response rate), and paclitaxel (18% response rate) [8, 59]. Doxorubicin and its variant form-pegylated liposomal doxorubicin, unlikely to treat for uterine sarcoma, are only minimally active (10% response rate), but data are limited [59]. Etoposide and topotecan are also only minimally active [8]. Finally, the combination of weekly gemcitabine and docetaxel for second-line treatment of recurrent UCS also failed to show additional benefits [60]. Many clinical trials have been finished or ongoing.

Two prospective randomized trials had compared single-agent chemotherapy and combined chemotherapy with ifosfamide [58, 59, 61]. A GOG (GOG108) phase III trial compared single-agent ifosfamide (1.5 g/m^2/day for five days, every three weeks) without mesna protection to combination chemotherapy with cisplatin (20 mg/m^2/day for five days, every three weeks) in 194 women with advanced or recurrent UCS, and the results showed that the combination of cisplatin and ifosfamide resulted in a higher response rate (57% *vs*. 39%, respectively) and a slightly prolonged median PFS (six months *vs*. four months, respectively), but there was still absence of statistically significant difference of OS between the two arms [61]. A GOG (GOG160) trial enrolled 179 women with advanced or recurrent UCS to test the effect of combination of paclitaxel and ifosfamide compared to ifosfamide alone, and the results showed that women who received the combination of ifosfamide (1.6 gm/m^2/day for three days, every three weeks) and paclitaxel (135 mg/m^2 on day 1, every three weeks) had a significant improvement of the objective response rate (45% *vs*. 29%), PFS (5.8 months *vs*. 3.6 months), and OS (13.5 months *vs*. 8.4 months) compared to those who were treated with single-agent ifosfamide (two g/m^2/day for three days, every three weeks) [62]. Both trials were included into the 2013 Cochrane database review system, and the results showed that 373 women with Stage III to IV persistent or recurrent disease who received combination therapy had a significantly lower risk of disease progression and death and than women who received single agent ifosfamide, after adjusting performance status (HR 0.72, 95% CI 0.58−0.90 for PFS; HR 0.75, 95% CI 0.60−0.94 for OS, respectively) [63], which contributed to the most popular regimen (ifosfamide and paclitaxel) in the current practice.

Similar to the regimen selected in the advanced-stage epithelial ovarian cancer, the combination of paclitaxel and carboplatin is another better choice in patients with UCS based on the findings of retrospective studies (a median PFS of 18 months, and a median OS of 25 months in six patients and a median PFS of 12 in 12 recurrent UCS patients and 16 months in 20 persistent UCS patients, respectively) [64, 65]. In addition, several phase II studies have tested its effectiveness [8, 59]. The response rate ranged from 54% to 62% [66, 67]. Pectasides *et al.* further added pegylated liposomal doxorubicin (25 mg/m^2/day one hour) into the combination of paclitaxel (175 mg/m^2/day three hours) and carboplatin (area under the curve 5) in the management of 29 women with advanced or recurrent UCS, and the results showed the median PFS of 8.2 months (95% CI 4.1−12.2 months) and a median OS of 16.4 months (95% CI 14.7−18.0 months) [68]; however, this study did not seem to provide a further benefit of survival compared with the regimen of paclitaxel and carboplatin as previous studies shown [66, 67]. Therefore, the ongoing phase III trial (GOG261) is testing the effectiveness of paclitaxel and carboplatin compared to the combination of ifosfamide and paclitaxel [8, 59]. In Table 2, we summarized the most popular and active chemotherapy regimens for women with advanced or recurrent UCS.

Table 2. — *The current acceptable regimen in the management of women with advanced or recurrent uterine carcinosarcoma.*

Authors (months)	Chemotherapy	Dose (Interval)	Patients (n)	RR; PFS-OS
Sutton 2000 [61] (Phase III trial to compare ifosfamide alone)	Ifosfamide+cisplatin	1.5 g/m^2/day for 5 days+20 mg/m^2/day for 5 days (21 days)	92	54%; 6-9.4
Homesley 2007 [62] (Phase III trial to compare ifosfamide alone)	Ifosfamide+paclitaxel	1.6 g/m^2/day for 3 days+135 mg/m^2/day (21 days)	88	45%, 5.8-13.5
Powell 2010 [66] (Phase II)	Paclitaxel+carboplatin	175 mg/m2+ AUC 6 (21 days)	46	54%, 7.6-14.7
Lancour 2011 [67] (Phase II)	Paclitaxel+carboplatin	175 mg/m2+ AUC 6 (21 days)	23	62%, 9.5-21.1

Ifosfamide dose is adjusted by previous radiotherapy (1.2 g/m^2/day). Mesna is used two grams intravenously during 12 hours beginning 15 minutes before the ifosfamide infusion or 1.33 gm orally one hour before and eight hours after the ifosfamide infusion for three to five days, based on the use of ifosfamide.

RR: response rate; PFS: progression-free survival; OS: overall survival.

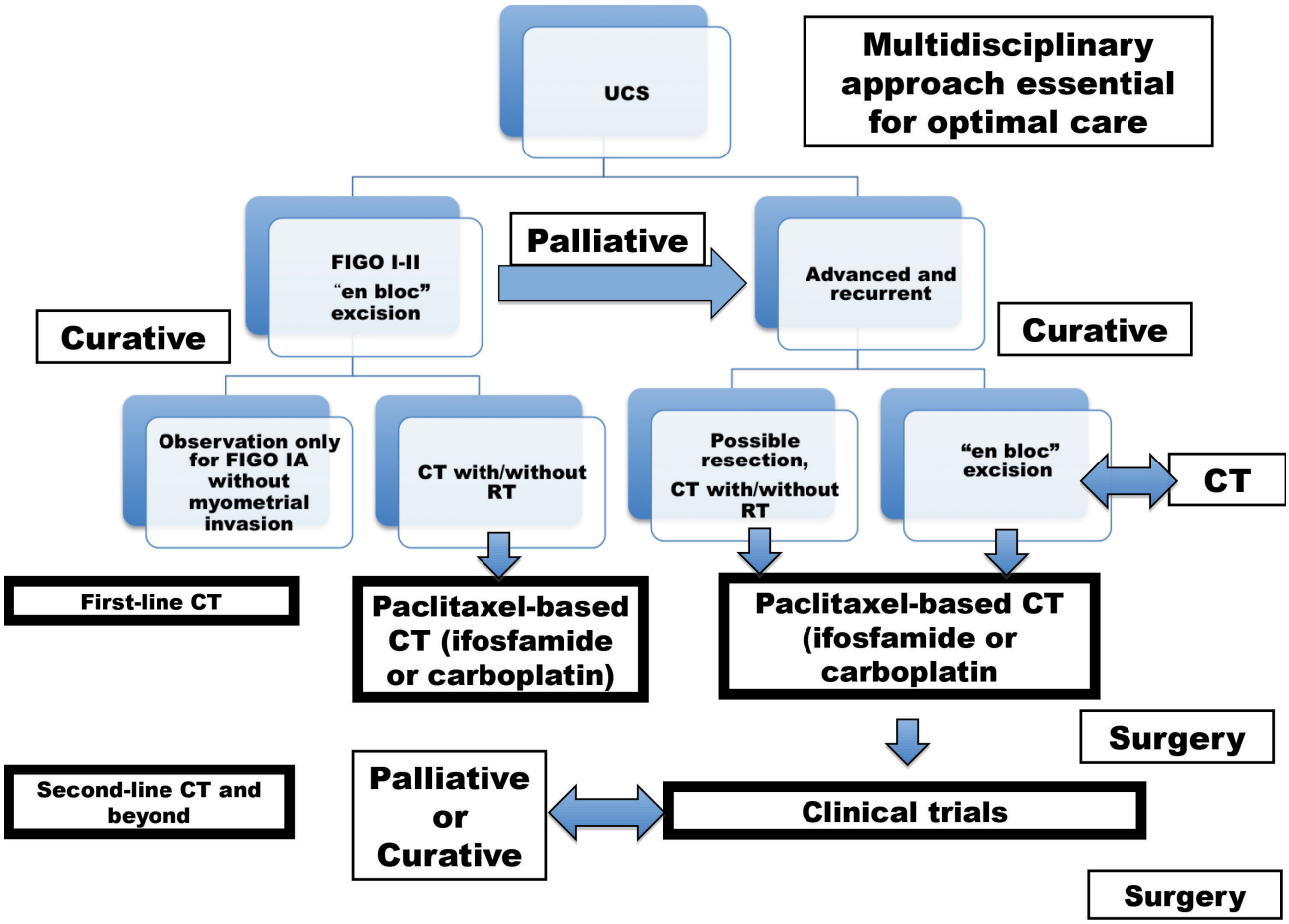

Figure 1. — The therapeutic strategy for women with uterine carcinosarcoma. UCS: uterine carcinosarcoma; FIGO: International Federation of Gynecology and Obstetrics: CT: chemotherapy; RT: radiation therapy.

Future perspectives

Besides conventional chemotherapy, new target therapy might be another choice in the management of these highly lethal diseases. To explore this relatively promising topic, we conducted an extensive literature review up to April 22, 2016 to investigate the target therapy and uterine carcinosarcoma using the following strategies to identify the publications addressing the potential target therapy in the management of women with UCS. The term "uterine car-

cinosarcoma and target" was used to search PubMed (http://www.ncbi.nlm.nih.gov/pubmed/?term=uterine+carcinosarcoma%2C+target). This search criteria identified 15 published articles, suggesting that the information of target and UCS is much limited. Combination of weekly 25 mg temsirolimus (one of mammalian target of rapamycin (mTOR) inhibitors)/2,000 mg metformin daily has been used in the management of 21 patients with advanced/refractory cancers, including two UCS, and the results showed good toleration and modest effectiveness among this heavily pretreated patient cohort [69]. Numerous correlative scientific investigations have demonstrated that the HER2 (ERBB2) gene is amplified in 17−33% of UCS, suggesting the potential opportunities (trastuzumab and other anti-HER2 therapy) for further clinical study [70]. To target angiogenesis, a phase II study enrolled 45 patients with UCS, and only two patients (4%, 90% CI 1−13%) experienced a partial response and 8 (18%, 90%CI 9−30%) had PFS more than six months and median PFS was 1.9 months and median OS was 5.9 months [71]. Although this trial failed, association between pre-treatment vascular epidermal growth factor A and prognosis of patients with UCS might support further evaluation of anti-angiogenic therapies in UCS [71].

Conclusion

In summary, the management of women with UCS should be initiated with comprehensive staging surgery, including total hysterectomy, bilateral salpingo-oophorectomy, PLND, and PALND for the earl-stage UCS, and cytoreduction effort for advanced stage UCS, because *en-bloc* resection with total free of residual tumor or only presence of minimal residual tumor is a key factor to obtain the better disease control and subsequent OS. The postoperative adjuvant therapy is needed for all stage patients, except for those patients with FIGO IA without myometrial invasion. Multi-modality treatment, including paclitaxel-based combination chemotherapy such as paclitaxel-carboplatin or paclitaxel-ifosfamide is the well-accepted regimen so far. Of course, the use of radiation therapy should be based individually. The recently acceptable therapeutic strategy in the management of UCS is shown in Figure 1.

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References

[1] McCluggage W.G.: "A practical approach to the diagnosis of mixed epithelial and mesenchymal tumors of the uterus". *Mod. Pathol.*, 2016, *29*, S78.

[2] Horng H.C., Wen K.C., Wang P.H., Chen Y.J., Yen M.S., Ng H.T., *et al.*: "Uterine sarcoma part II-uterine endometrial stromal sarcoma: the TAG systematic review". *Taiwan J. Obstet. Gynecol.*, 2016, *55*, 472.

[3] D'Angelo E., Prat J.: "Pathology of mixed Mullerian tumors". *Best. Pract. Res. Clin. Obstet. Gynecol.*, 2011, *25*, 705.

[4] Tsui K.H., Lee F.K., Seow K.M., Chang W.C., Wang J.W., Chen S.U., *et al.*: "Conservative surgical treatment of adenomyosis to improve fertility: Controversial values, indications, complications, and pregnancy outcomes". *Taiwan. J. Obstet. Gynecol.*, 2015, *54*, 635.

[5] Horng H.C., Chen C.H., Chen C.Y., Tsui K.H., Liu W.M., Wang P.H., et al.: "Uterine-sparing surgery for adenomyosis and/or adenomyoma". *Taiwan. J. Obstet. Gynecol.*, 2014, *53*, 3.

[6] Tsui K.H., Lee W.L., Chen C.Y., Sheu B.C., Yen M.S., Chang T.C., et al.: "Medical treatment for adenomyosis and/or adenomyoma". *Taiwan. J. Obstet. Gynecol.*, 2014, *53*, 459.

[7] Chen Y.J., Li Y.T., Huang B.S., Yen M.S., Sheu B.C., Chow S.N., et al.: "Medical treatment for heavy menstrual bleeding". *Taiwan. J. Obstet. Gynecol.*, 2015, *54*, 483.

[8] Cantrell L.A., Blank S.V., Duska L.R.: "Uterine carcinosarcoma: A review of the literature". *Gynecol. Oncol.*, 2015, *137*, 581.

[9] Wen K.C., Horng C.C., Wang P.H., Chen Y.J., Yen M.S., Ng H.T., *et al.*: "Uterine sarcoma part I-uterine leiomyosarcoma: the Topic Advisory Group (TAG) systematic review". *Taiwan J. Obstet. Gynecol.* 2016, *55*, 463.

[10] Prat J., Mbatani N.: "Uterine sarcomas". *Int. J. Gynecol. Obstet.*, 2015, *131*, S105.

[11] Chao K.C., Wang P.H., Chang C.C., Lai C.R., Ng H.T.: "Establishment and characterization of a cell line, MT-213-VGH, isolated from a mixed müllerian tumor of the uterus". *Acta Cytol.*, 2001, *45*, 683.

[12] Artioli G., Wabersich J., Ludwig K., Gardiman M.P., Borgata L., Garbin F.: "Rare uterine cancer: carcinosarcomas. Review from histology to treatment". *Critical. Rev. Oncol. Hematol.*, 2015, *94*, 98.

[13] El-Nashar S.A., Mariani A.: "Uterine carcinosarcoma". *Clin. Obstet. Gynecol.*, 2011, *54*, 292.

[14] Kalluri R., Weinberg R.A.: "The basics of epithelial–mesenchymal transition". *J. Clin. Invest.*, 2009, *119*, 1420.

[15] Chen P., Yang C.C., Chen Y.J., Wang P.H.: "Tamoxifen-induced endometrial cancer". *Eur. J. Gynaecol. Oncol.*, 2003, *24*, 135.

[16] Wang P.H., Chao H.T.: "A reconsideration of tamoxifen use for breast cancer". *Taiwan. J. Obstet. Gynecol.*, 2007, *46*, 93.

[17] Lee W.L., Chao H.T., Cheng M.H., Wang P.H.: "Rationale for using raloxifene to prevent both osteoporosis and breast cancer in postmenopausal women". *Maturitas*, 2008, *60*, 92.

[18] Lee W.L., Cheng M.H., Chao H.T., Wang P.H.: "The role of selective estrogen receptor modulators on breast cancer: from tamoxifen to raloxifene". *Taiwan. J. Obstet. Gynecol.*, 2008, *47*, 24.

[19] Lee W.L., Cheng M.H., Tarng D.C., Yang W.C., Lee F.K., Wang P.H.: "The benefits of estrogen or selective estrogen receptor modulator on kidney and its related disease-chronic kidney disease-mineral and bone disorders: osteoporosis". *J. Chin. Med. Assoc.*, 2013, *76*, 365.

[20] Lee W.L., Lee F.K., Su W.H., Tsui K.H., Kuo C.D., Hsieh S.L., *et al.*: "Hormone therapy for younger patients with endometrial cancer". *Taiwan. J. Obstet. Gynecol.*, 2012, *51*, 495.

[21] Lee W.L., Yen M.S., Chao K.C., Yuan C.C., Ng H.T., Chao H.T., *et al.*: "Hormone therapy for patients with advanced or recurrent endometrial cancer". *J. Chin. Med. Assoc.*, 2014, *77*, 221.

[22] Wen K.C., Sung .PL., Wang P.H.: "Re: the revised 2009 FIGO stag-

ing system for endometrial cancer: should the 1988 FIGO stages IA and IB be altered?" *Int. J. Gynecol. Cancer*, 2012, *22*, 178.

[23] McCluggage W.G., Colgan T., Duggan M., Hacker N.F., Mulvany N., Otis C., et al.: "Data set for reporting of endometrial carcinomas: recommendations from the International Collaboration on Cancer Reporting (ICCR) between United Kingdom, United States, Canada, and Australasia:". *Int. J. Gynecol. Pathol.*, 2013, *32*, 45.

[24] Ferguson S.E., Tornos C., Hummer A., Barakat R.R., Soslow R.A.: "Prognostic features of surgical stage I uterine carcinosarcoma". *Am. J. Surg. Pathol.*, 2007, *31*, 1653.

[25] Matsuo K., Takazawa Y., Ross M.S., Elishaev E., Podzielinski I., Yunokawa M., *et al.*: "Significance of histologic pattern of carcinoma and sarcoma components on survival outcomes of uterine carcinosarcoma". *Ann. Oncol.*, 2016, *27*, 1257.

[26] Lee F.K., Yen M.S., Wang P.H.: "Is it safe to preserve the ovary of premenopausal women with supposed early-stage endometrial cancer"? *Taiwan. J. Obstet. Gynecol.*, 2016, *55*, 1.

[27] Li Y.T., Teng S.W.: "Surgery for endometrial cancer". *Taiwan. J. Obstet. Gynecol.*, 2016, *55*, 152.

[28] Wang P.H., Horng H.C., Chen C.P.: "Is it safe to use minimally invasive surgery in the management of endometrial cancer". *Taiwan. J. Obstet. Gynecol.*, 2016, *55*, 155.

[29] Nemani D., Mitra N., Guo M., Lin L.: "Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: A SEER analysis". *Gynecol. Oncol.*, 2008, *111*, 82.

[30] Alagkiozidis I., Weedon J., Grossman A., Wang P., Mize B., Wilson K., *et al.*: "Extent of lymph node dissection and overall survival in patients with uterine carcinosarcoma, papillary serous and endometrioid adenocarcinoma: a retrospective cohort study". *Int. J. Surgery*, 2015, *24*, 9.

[31] Chen J.R., Chang T.C., Fu H.C., Lau H.Y., Chen I.H., Ke Y.M., *et al.*: "Outcomes of patients with surgically and pathologically stage IIIA-IV pure endometrioid-type endometrial cancer". *Medicine (Baltimore)*, 2016, *95*, e3330.

[32] Silverberg S.G., Major F.J., Blessing J.A., Fetter B., Askin F.B., Liao S.Y., *et al.*: "Carcinosarcoma (malignant mixed mesodermal tumor) of the uterus. A Gynecologic Oncology Group pathologic study of 203 cases". *Int. J. Gynecol. Pathol.*, 1990, *9*, 1.

[33] Scalici J., Laughlin B.B., Finan M.A., Wang B., Rocconi R.P.: "The trend towards minimally invasive surgery (MIS) for endometrial cancer: an ACS-NSQIP evaluation of surgical outcomes". *Gynecol. Oncol.*, 2015, *136*, 512.

[34] Wang P.H., Yuan C.C., Lee W.L., Chin T.W.: "Laparoscopic surgery for early-stage endometrial cancers". *Gynecol. Oncol.*, 2008, *108*, 456.

[35] Lee C.L., Huang K.G., Wu P.J., Lee P.S., Yen C.F.: "Long-term survival outcome of laparoscopic staging surgery for endometrial cancer in Taiwanese experience". *Taiwan. J. Obstet. Gynecol.*, 2014, *53*, 57.

[36] Chiou H.Y., Chiu L.H., Chen C.H., Yen Y.K., Chang C.W., Liu W.M.: "Comparing robotic surgery with laparoscopy and laparotomy for endometrial cancer management: a cohort study". *Int. J. Surg.*, 2015, *13*, 17.

[37] Chu L.H., Chang W.C., Sheu B.C.: "Comparison of the laparoscopic versus conventional open method for surgical staging of endometrial carcinoma". *Taiwan. J. Obstet. Gynecol.*, 2016, *55*, 188.

[38] Walker J.L., Piedmonte M.R., Spirtos N.M., Eisenkop S.M., Schlaerth J.B., Mannel R.S., *et al.*: "Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group Study LAP2". *J. Clin. Oncol.*, 2009, *27*, 5331.

[39] Walker J.L., Piedmonte M.R., Spirtos N.M., Eisenkop S.M., Schlaerth J.B., Mannel R.S., *et al.*: "Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 Study". *J. Clin. Oncol.*, 2012, *30*, 695.

[40] Wang P.H., Yen M.S., Yuan C.C., Chao K.C., Ng H.T., Lee W.L., *et al.*: "Port site metastasis after laparoscopic-assisted vaginal hysterectomy for endometrial cancer: possible mechanisms and prevention". *Gynecol. Oncol.*, 1997, *66*, 151.

[41] Wang P.H., Yuan C.C., Lin G., Ng H.T., Chao H.T.: "Risk factors contributing to early occurrence of port site metastases of laparoscopic surgery for malignancy". *Gynecol. Oncol.*, 1999, *72*, 38.

[42] Lai C.R., Yen M.S., Wang P.H.: "Neoplasms in the trocar site and peritoneal papillary serous cystadenocarcinoma". *Taiwan. J. Obstet. Gynecol.*, 2014, *53*, 139.

[43] Lee W.L., Chang W.H., Wang K.C., Guo C.Y., Chou Y.J., Huang N., *et al.*: "The risk of epithelial ovarian cancer of women with endometriosis may be varied greatly if diagnostic criteria are different: a nationwide population-based cohort study". *Medicine (Baltimore)*, 2015, *94*, e1633.

[44] Horng H.C., Teng S.W., Huang B.S., Sun H.D., Yen M.S., Wang P.H., *et al.*: "Primary fallopian tube cancer: domestic data and up-to-date review". *Taiwan. J. Obstet. Gynecol.*, 2014, *53*, 287.

[45] Chang W.H., Wang K.C., Lee W.L., Huang N., Chou Y.J., Feng R.C., et al.: "Endometriosis and the subsequent risk of epithelial ovarian cancer". *Taiwan. J. Obstet. Gynecol.*, 2014, *53*, 530.

[46] Wang K.C., Chang W.H., Lee W.L., Huang N., Huang H.Y., Yen M.S., *et al.*: "An increased risk of epithelial ovarian cancer in Taiwanese women with a new surgico-pathological diagnosis of endometriosis". *BMC Cancer*, 2014, *14*, 831.

[47] Wu H.H., Wang P.H., Yeh Y.J., Chen Y.J., Yen M.S., Huang R.L., *et al.*: "Serum cytokeratin-19 fragment (Cyfra 21-1) is a prognostic indicator for epithelial ovarian cancer". *Taiwan. J. Obstet. Gynecol.,* 2014, *53*, 30.

[48] Wen K.C., Sung P.L., Yen M.S., Chuang C.M., Liou W.S., Wang P.H.: "MicroRNAs regulate several functions of normal tissue and malignancies". *Taiwan. J. Obstet. Gynecol.*, 2013, *52*, 465.

[49] Tanner E.J., Leitao M.M. Jr., Garg K., Chi D.S., Sonoda Y., Gardner G.J., et al.: "The role of cytoreductive surgery for newly diagnosed advanced-stage uterine carcinosarcoma". *Gynecol. Oncol.*, 2011, *123*, 548.

[50] Harano K., Hirakawa A., Yunokawa M., Nakamura T., Satoh T., Nishikawa T., et al.: "Optimal cytoreductive surgery in patients with advanced uterine carcinosarcoma: A multi-institutional retrospective study from the Japanese gynecologic oncology group". *Gynecol. Oncol.*, 2016, *141*, 447.

[51] Manzerova J., Sison C.P., Gupta D., Holcomb K., Caputo T.A., Parashar B., *et al.*: "Adjuvant radiation therapy in uterine carcinosarcoma: A population-based analysis of patient demographic and clinical characteristics, patterns of care and outcomes". *Gynecol. Oncol.*, 2016, *141*, 225.

[52] Brooks S.E., Zhan M., Cote T., Baquet C.R.: "Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989-1999". *Gynecol. Oncol.*, 2004, *93*, 204.

[53] Wright J.D., Seshan V.E., Shah M., Schiff P.B., Burke W.M., Cohen C.J., *et al.*: "The role of radiation in improving survival for early-stage carcinosarcoma and leiomyosarcoma". *Am. J. Obstet. Gynecol.*, 2008, *199*, 536.e1.

[54] Guttmann D.M., Li H., Sevak P., Grover S., Jacobson G., Feldman A., *et al.*: "The impact of adjuvant therapy on survival and recurrence patterns in women with early-stage uterine carcinosarcoma: a multi-institutional study". *Int. J. Gynecol. Cancer*, 2016, *26*, 141.

[55] Omura G.A., Blessing J.A., Major F., Lifshitz S., Ehrlich C.E., Mangan C., *et al.*: "A randomized clinical trial of adjuvant adriamycin in uterine sarcomas: A Gynecologic Oncology Group Study". *J. Clin. Oncol.*, 1985, *3*, 1240.

[56] Wolfson A.H., Brady M.F., Rocereto T., Mannel R.S., Lee Y.C., Futoran R.J., *et al.*: "A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I-IV carcinosarcoma (CS) of the uterus". *Gynecol. Oncol.*, 2007, *107*, 177.

[57] Reed N.S., Mangioni C., Malmström H., Scarfone G., Poveda A., Pecorelli S., et al.: "Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: an European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group study (protocol

55874)". *Eur. J. Cancer*, 2008, *44*, 808.
[58] Dickson E.L., Vogel R.I., Gehrig P.A., Pierce S., Havrilesky L., Secord A.A., *et al.*: "A multi-institutional study of outcomes in stage I-III uterine carcinosarcoma". *Gynecol. Oncol.*, 2015, *139*, 275.
[59] Berton-Rigaud D., Devouassoux-Shisheboran M., Ledermann J.A., Leitao M.M., Powell M.A., Poveda A., *et al.*: "Gynecologic Cancer InterGroup (GCIG) consensus review for uterine and ovarian carcinosarcoma". *Int. J. Gynecol. Cancer*, 2014, *24*, S55.
[60] Miller B.E., Blessing J.A., Stehman F.B., Shahin M.S., Yamada S.D., Secord A.A., *et al.*: A phase II evaluation of weekly gemcitabine and docetaxel for second-line treatment of recurrent carcinosarcoma of the uterus: a gynecologic oncology group study. *Gynecol. Oncol.*, 2010, *118*, 139.
[61] Sutton G., Brunetto V.L., Kilgore L., Soper J.T., McGehee R., Olt G., *et al.*: "A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus: A Gynecologic Oncology Group Study". *Gynecol. Oncol.*, 2000, *79*, 147.
[62] Homesley H.D., Filiaci V., Markman M., Bitterman P., Eaton L., Kilgore L.C., *et al.*: Gynecologic Oncology Group: Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study". *J. Clin. Oncol.*, 2007, *25*, 526.
[63] Galaal K., van der Heijden E., Godfrey K., Naik R., Kucukmetin A., Bryant A., et al.: "Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma". *Cochrane Database Syst. Rev.*, 2013, *2*, CD006812.
[64] Toyoshima M., Akahira J., Matsunaga G., Niikura H., Ito K., Yaegashi N., et al.: "Clinical experience with combination paclitaxel and carboplatin therapy for advanced or recurrent carcinosarcoma of the uterus". *Gynecol. Oncol.*, 2004, *94*, 774.
[65] Hoskins P.J., Le N., Ellard S., Lee U., Martin L.A., Swenerton K.D., *et al.*: "Carboplatin plus paclitaxel for advanced or recurrent uterine malignant mixed mullerian tumors. The British Columbia Cancer Agency experience". *Gynecol. Oncol.*, 2008, *108*, 58.
[66] Powell M.A., Filiaci V.L., Rose P.G., Mannel R.S., Hanjani P., Degeest K., *et al.*: "Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study". *J. Clin. Oncol.*, 2010, *28*, 2727.
[67] Lacour R.A., Euscher E., Atkinson E.N., Sun C.C., Ramirez P.T., Coleman R.L., *et al.*: "A phase II trial of paclitaxel and carboplatin in women with advanced or recurrent uterine carcinosarcoma". *Int. J. Gynecol. Cancer*, 2011, *21*, 517.
[68] Pectasides D., Pectasides E., Papaxoinis G., Xiros N., Sykiotis C., Papachristodoulou A., *et al.*: "Combination chemotherapy with carboplatin, paclitaxel and pegylated liposomal doxorubicin for advanced or recurrent carcinosarcoma of the uterus: clinical experience of a single institution". *Gynecol. Oncol.*, 2008, *110*, 299.
[69] Khawaja M.R., Nick A.M., Madhusudanannair V., Fu S., Hong D., *et al.*: "Phase I dose escalation study of temsirolimus in combination with metformin in patients with advanced/refractory cancers". *Cancer Chemother. Pharmacol.*, 2016, *77*, 973.
[70] Diver E.J., Foster R., Rueda B.R., Growdon W.B.: "The therapeutic challenge of targeting HER2 in endometrial cancer". *Oncologist*, 2015, *20*, 1058.
[71] McMeekin D.S., Sill M.W., Darcy K.M., Abulafia O., Hanjani P., Pearl M.L., *et al.*: "A phase II trial of thalidomide in patients with refractory uterine carcinosarcoma and correlation with biomarkers of angiogenesis: a Gynecologic Oncology Group study". *Gynecol. Oncol.*, 2012, *127*, 356.

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