American Radium Society® Appropriate Use Criteria for Management of Uterine Carcinosarcoma

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Conflict of interest disclosure statement

All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society in perpetuity.

The ARS Appropriate Use Criteria Steering Committee reviewed these disclosures with the chair and co-chair of this document and approved participation of the panelists prior to starting development of this work. Disclosures potentially relevant to the content of this guideline are provided.

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Methodology

An extensive and updated analysis of current medical literature from peer-reviewed journals was conducted from January 1, 1990 to October 15, 2018 using and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[1] guidelines to search the Ovid MEDLINE(R) without Revisions database to retrieve a comprehensive set of relevant articles. We developed strategies using subject and combinations of keywords search terms. We reviewed the bibliographies of full articles for a comprehensive survey, and relevant studies were included. The literature was reviewed for quality of study design, cohort size, selection bias, variability of evaluation of participants in regard to time from exposure, and methods of assessments.

A well-established consensus methodology (modified Delphi)[2] was to rate the appropriate use of treatment procedures by the expert panel. The expert panel is composed of multidisciplinary panel of radiation, medical, and gynecologic oncologists as well as pathologists and radiologists with expertise in the management of uterine cancer.

Summary of Literature Review

Introduction

Endometrial cancer is the most common gynecological malignancy in the United States and second most common cause of gynecologic cancer mortality [3]. Uterine carcinosarcomas (UCS) (also known as malignant mixed Müllerian tumors) represent a rare but aggressive subset of invasive endometrial cancers, comprising less than 5% of uterine malignancies and are considered metaplastic carcinomas. They constitute a very heterogeneous group of patients and the majority of patients (up to 60%) will present with advanced extra uterine disease, with 10% presenting with metastatic disease [4]. They have worse survival outcomes when compared to uterine high-grade endometrioid adenocarcinomas [5]. Although UCS has traditionally been considered with other uterine soft tissue malignancies, its biology is more closely aligns with epithelial tumors such as uterine serous carcinoma. It is also a common clinical observation that while biphasic pathology exists in the primary lesion, only the epithelial component is identified in the metastatic and recurrent lesions.

The presentation and risk factors for UCS are similar to other endometrial carcinomas. The most common presentation is postmenopausal vaginal bleeding, followed by pelvic pain or pressure and vaginal discharge. Risk factors include obesity, nulliparity, older age, exogenous estrogen use, tamoxifen, and history of pelvic radiation treatment [4, 6].

The primary treatment for non-metastatic UCS is complete surgical staging with total hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, cytology of peritoneal washings, and omentectomy. The surgical approach, either minimally invasive or open, does not appear to affect outcomes in patients with these aggressive histological type [5]. Based on retrospective evidence, there is a role for maximal cytoreduction surgery for those with extra-uterine (stage III-IV) disease [7]. There is also evidence that sentinel

lymph node biopsies may be used on appropriate patients with requisite physician expertise [8]. Prior to surgery, imaging such as computed tomography, (CT), magnetic resonance imaging (MRI), or Positron emission tomography with 2-deoxy-2 fluoro- D glucose integrated with CT (^{18}F-FDG-PET/CT) in conjunction with serum CA-125 may be useful to help guide the surgical approach and discussion of management [9, 10].

There may be a role for a lymphadenectomy in patients with UCS, with some evidence that it is associated with longer survival (Variant 1). As shown in a large retrospective registry cohort from the Netherlands, lymphadenectomy that consisted of 10 nodes or more was associated improved survival over those with fewer or without lymphadenectomy in patients with UCS [11]. There were similar findings in a United States based registry study [12], as well as other retrospective evidence [13, 14]. A prospective clinical trial has not been conducted to test the hypothesis

Patients with UCS require adjuvant therapy to reduce the chance of tumor recurrence with the potential to improve overall survival. However, after surgery, no clear consensus has been established regarding adjuvant therapy for patients with UCS and options could be chemotherapy alone, radiation therapy (RT) alone or more frequently combined multi-modality therapy (CMT) (Variant 2).

The American Radium Society Appropriate Use Criteria (ARS AUC) presented in this manuscript are evidence-based guidelines for treatment of UCS that have been reviewed by a multidisciplinary expert panel. An extensive analysis of current medical literature from peer-reviewed journals was performed with application of consensus methodology to rate the appropriate use of imaging and treatment procedures for the treatment of UCS.

Rationale for Adjuvant Chemotherapy Alone

There have been several larger cooperative group trials that have been conducted to compare various approaches for adjuvant chemotherapy. In a prospectively randomized phase III study conducted by Gynecologic Oncology Group (GOG-108), Sutton et al reported the outcome of 224 women with advanced, persistent, or recurrent UCS randomized to receive ifosfamide with or without cisplatin. While there was a small progression-free survival benefit (PFS), there was no overall survival benefit (OS) with the addition of cisplatin [15].

A subsequent randomized phase III GOG-161 study (Homesley et al)[16] evaluated the addition of paclitaxel to ifosfamide in patients with stage III-IV UCS. This trial showed both a progression-free (PFS) and OS benefit with the addition of paclitaxel. The median PFS and OS for ifosfamide alone compared with the combination were 3.6 v 5.8 months and 8.4 v 13.5 months, respectively.

Recently, carboplatin and paclitaxel has been utilized more frequently for patients with advanced stage or high-grade endometrial carcinomas. Powell et al reported a prospective phase II study of carboplatin and paclitaxel in patients with stage III-IV UCS. Treatment was well tolerated with a 54% total overall response rate [17]. Consequently, GOG-261, a Phase III, non-inferiority, randomized clinical trial of ifosfamide and paclitaxel versus carboplatin and paclitaxel was

launched in 2011 and closed in 2014 enrolling patients with both endometrial and ovarian carcinosarcoma. While the results of this important study are not published yet in a full manuscript, the uterine cancer cohort has been recently presented. In this cohort of 536 patients, OS was 37 months in the carboplatin/paclitaxel arm and 29 months in the ifosfamide/paclitaxel arm, rejecting the null hypothesis of inferiority. These new data are confirming what had already been a common clinical practice [18]. Based on the totality of available evidence and a pooled Cochrane meta-analysis [19], adjuvant chemotherapy should strongly be considered for women with UCS.

Rationale for Radiation Treatment Alone

The European Organization for Research and Treatment of Cancer (EORTC 55874) conducted a phase III study of women with stage I-II uterine sarcomas (including carcinosarcomas, leiomyosarcomas and endometrial stromal sarcomas). Patients were randomized to receive adjuvant pelvic radiotherapy to 50.4 Gy in 28 fractions or observation. While, three or four field RT technique was mainly utilized, parallel opposed fields were permitted. None of the patients had adjuvant chemotherapy. As reported by Reed et al, 92 of 224 (41.1%) of the patients had UCS histology. There was an improvement in local control seen in women with UCS. This local control benefit, however, did not translate into an OS benefit [20]. Other multi-institutional retrospective studies have shown a similar local control benefit with the addition of pelvic radiation treatment when compared to surgery alone [21-25].

Wolfson et al reported on GOG-150, a randomized phase III trial comparing adjuvant chemotherapy alone (consisting of cisplatin-ifosfamide and mesna [CIM]) to whole abdominal radiotherapy (WART) in patients with stage I-IV UCS [26]. There was no difference in survival between the two treatment approaches. WART did not reduce abdominal recurrence compared to chemotherapy, although it is recognized that WART dose of 30 Gy is likely insufficient to control even microscopic disease. The estimated crude probability of surviving at least five years following diagnosis was approximately 35% for those randomized to WART versus 45% for chemotherapy and there were more abdominal recurrences in the WART arm (29 versus 19). Because of this and other cooperative trials that have failed to show a benefit using WART, its use has fallen out of favor for more tumor-directed and less toxic external beam radiation treatment techniques (see Radiation Treatment Volume and Planning).

Rationale for Combined Modality Therapy (CMT) (Chemotherapy and Radiation Treatment)

Sutton et al also conducted a phase II trial specifically for those with completely resected stage I-II disease and received adjuvant chemotherapy alone with cisplatin and ifosfamide. The authors concluded that this regimen is tolerable, however pelvic relapses were problematic with 12/23 relapses. This study suggests a benefit for CMT in early stage disease [27].

Adjuvant CMT for UCS has only been studied in single institutional prospective studies. Einstein el at reported a single institutional phase II prospective study evaluating CMT with a “sandwich approach” in patients with stage I-IV UCS. The chemotherapy consisted of 3 cycles of ifosfamide followed by external beam RT (EBRT) and vaginal brachytherapy (VBT), followed

by 3 more cycles of ifosfamide (sandwich). The EBRT consisted of a 4-field technique up to 45 Gy in 25 fractions, with extended field RT in two cases. The VBT was cylinder-based treating with a dose of 5 Gy to 5 mm depth of the upper 2/3 of the vaginal cuff. The majority (70%) completed prescribed therapy and the results showed reasonable oncologic outcomes with the main toxicities being hematologic. 2-year overall survival was 80.8% for women with stages I/II and 30.3% for women with stages III/IV [28].

In another prospective pilot study of 38 women with stage I-II UCS treated with adjuvant CMT, Manolitsas et al reported reasonable outcomes with multimodality therapy [29]. EBRT was offered after surgery to all patients, unless the patient underwent a complete lymph node dissection with negative nodes, in which case VBT was used. Chemotherapy consisted of cisplatin and epirubicin given in a sandwich approach. Those who did not received CMT had poorer outcomes when compared to those that completed therapy. With a mean follow-up of 55 months, the survival rate for those that completed CMT was 95% compared to 47% for those that did not. While there is a large selection bias with this type of analysis, it does support the use of CMT when tolerable.

Other evidence for the use of CMT in patients with UCS is extrapolated from study of high-risk or advanced stage endometrial carcinoma. A recently published randomized study has delved into the question of combining chemotherapy and radiation in this subset of patients with high-risk or locally advanced endometrial carcinoma. The PORTEC-3 trial randomized women with high-risk endometrial cancer (defined as stage I endometrioid grade 3 with deep myometrial invasion and/ or lymph-vascular space invasion, endometrioid stages II or III, or non-endometrioid stage I-III) after surgery to either adjuvant CMT or RT alone. Chemotherapy consisted of cisplatin concurrent with EBRT followed by 4 cycles of carboplatin and paclitaxel. This study did not include patients with UCS, however, a small subset did have high-risk histology such as clear cell or serous carcinoma. The authors of this study reported a statistically significant improvement in 5-year overall and failure-free survival with the addition of chemotherapy to radiation treatment. The greatest absolute benefits was found for women with stage III disease and those with serous carcinoma or both [30-31].

Salvage Management of Recurrence and Treatment of Metastatic disease

Salvage management is highly individualized, taking into account factors like site and size of recurrence, performance status, prior therapy, etc. (Variant 3). Metastatic disease also follows this paradigm and general best practices evaluating the risk/benefit ratio of any offered therapy. Enrollment on clinical trials should be also considered.

Personalization of radiation treatment volume and planning

There appears to be little or no role for WART in patients with UCS. When treating with EBRT, 3-dimentional technique or intensity modulated radiation therapy (IMRT) to encompass planning target volumes should be used. A recently published randomized phase III trial comparing IMRT to 4-field techniques in patients treated with post-operative radiation therapy for their cervical or endometrial cancer found a benefit in patient reported gastrointestinal and genitourinary symptoms when using IMRT [32].

When using IMRT, care should be taken to appropriately delineate the target volumes of the nodal areas at risk as well as the vaginal tissue. Contrast and vaginal markers could aid in this process, and a vaginal internal target volume (as known as an ITV) should be created by either performing a fusion between a full and empty bladder scan or adding a margin to the vagina to account for potential inter fraction motion due to different bladder or rectal filling. This along with lymph node contours with 7 mm margins (which should include the common iliac, internal and external iliac, obturator +/- para-aortic lymph nodes +/- presacral node with cervical stromal involvement) constitutes the clinical target volume (CTV). The CTV dose is 45-50 Gy at 1.8-2.0 Gy per fraction. An appropriate planning tumor volume (PTV) margin should be used depending on the immobilization and image guidance available [33-34]. Appropriate constraints on the bowel, bladder, and rectum should be applied during treatment planning.

When utilizing vaginal cuff brachytherapy, the vaginal treatment volume should include the proximal 3-4 cm of the vaginal length. Various dose prescriptions could be utilized when used alone or as a boost, as specified by the American Brachytherapy Society guidelines [33]. When vaginal cuff boost is utilized, common high-dose rate (HDR) prescription include 45 Gy external beam radiation treatment (EBRT) plus 6 Gy x 3 to the vaginal mucosa [35] (Variant 4).

Follow-up after Treatment

The panel supports a general examination, including a complete history and a pelvic-rectal examination, conducted every 3 months for the first two years and semiannually thereafter as suggested by the Society of Gynecologic Oncology [36]. It is recommended that all patients undergo a targeted investigation to rule out recurrence if symptomatic (Variant 5).

Summary of Recommendations

Due to the rarity of UCS, there is a paucity of prospective trials focusing on management of this this aggressive disease and hence there is no standard consensus for treatment strategy in women with UCS.

Given the aggressive nature of this malignancy, and until further research determines the most appropriate adjuvant therapy, it may be reasonable to counsel patients about combined modality treatment (CMT) with systemic chemotherapy with radiation therapy. Further prospective studies or multi-institutional retrospective studies are warranted to determine appropriate management of women with this rare histology.

● The panel recommends strongly that adjuvant CMT (chemotherapy and radiation treatment) is usually appropriate for the typical case of FIGO stage IB UCS. For women who had a hysterectomy without lymph node dissection, there was disagreement among the panel members on the necessity and extent of lymph node dissection.

● The panel recommends strongly that adjuvant chemotherapy with carboplatin and paclitaxel for women is usually appropriate.

● The panel recommends strongly that tumor volume-directed radiation treatment is usually appropriate in the adjuvant setting of women with early or advanced stage UCS. IMRT would be the recommended treatment technique after hysterectomy. For those receiving vaginal cuff brachytherapy, treating the entire vaginal length was not recommended by panel members.

● The panel does not recommend the routine use of adjuvant whole abdominal radiation treatment outside of a clinical trial setting.

● For women with recurrent disease after chemotherapy alone, the panel recommends, when feasible, surgical resection of the recurrent disease with CMD (chemotherapy and radiation treatment). Clinical trials should be strongly considered for these patients.

● The panel recommends strongly routine surveillance after treatment with routine imaging in the first 3 years.

Summary of Evidence

Of the 36 references cited in the ARS Appropriate Use Criteria for uterine carcinosarcoma document, 29 are categorized as therapeutic references including 12 well-designed prospective studies, 11 good quality studies, and 6 quality studies that may have design limitations.

There are 7 references that may not be useful as primary evidence.

The 36 references cited in the ARS Appropriate Use Criteria for uterine carcinosarcoma document were published from 1992 to 2019.

Although there are references that report on studies with design limitations, 29 well-designed or good quality studies provide good evidence.

Supporting Documents

For additional information on the ARS AUC methodology and other supporting documents go to http://www.americanradiumsociety.org/page/aucmethodology.

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The ARS Appropriate Use Criteria® and its expert panels have developed criteria for determining appropriate procedures for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide treating and referring physicians in making decisions regarding diagnosis and treatment of cancers and related or associated conditions. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate diagnostic procedures or treatments. Only those examinations or treatments generally used for evaluation of the patient's condition are ranked. Other procedures necessary to evaluate or treat other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate procedures or treatments. Procedures, techniques, or other interventions classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment, applications, and treatment protocols should be encouraged. The ultimate decision regarding the appropriate use of any specific examination or treatment must be made by the referring physician and oncologist in light of all the circumstances presented in an individual examination.

Clinical condition: **Incompletely staged uterine carcinosarcoma (UCS)**

Variant 1: **A 71-year-old woman with post-menopausal vaginal bleeding who underwent a hysteroscopy with dilation and curettage. Pathology showed uterine endometrioid carcinoma, grade 2. She underwent a minimally invasive simple hysterectomy with salpingo oophorectomy. No lymphadenectomy or peritoneal cytology was performed. A week later, final pathology showed UCS, invading 6 mm out of 14 mm myometrial thickness with cervical stromal involvement. There was no lymphovascular space involvement. Given the lack of complete surgical staging, and assuming negative radiologic studies, what procedures would be appropriate?**

Procedure	Rating category	Group Median Rating	SOE	SOR	Level of agreement
Observation	U	1	EC	↑	A
Radiation treatment alone	M	5	M	-	A
Chemotherapy alone	M	5	M	-	A
Radiation treatment with chemotherapy	A	7	M	↑	A
Surgical staging with pelvic lymphadenectomy	M	5	EC	-	A
Surgical staging with pelvic and paraaortic (PA) lymphadenectomy	M	5*	EC	-	D
Surgical staging with pelvic, PA lymphadenectomy and omentectomy	M	5*	EC	-	D
If no lymphadenectomy, multimodality treatment should be					
Combined Chemotherapy and vaginal cuff brachytherapy	M	5*	M	-	D
Combined Chemotherapy and pelvic external beam radiation treatment +/- vaginal cuff brachytherapy	A	8	EC	↑	A
Combined Chemotherapy with pelvic and para aortic external beam radiation treatment +/- vaginal cuff brachytherapy	M	5*	L	-	D

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Strength of Evidence (SOE): S Strong; M Moderate; L Limited; EC Expert Consensus; EO expert opinion

Strength of recommendation (SOR): ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Level of agreement: A Agreement, D Disagreement – * Disagreement is assigned a value of 5 as may be appropriate

Clinical condition: **Stage IB uterine carcinosarcoma (UCS)**

Variant 2: **A 64-year-old woman with post-menopausal vaginal bleeding undergoes total abdominal hysterectomy, salpingoophorectomy, pelvic/para-aortic lymphadenectomy, omentectomy and peritoneal cytology. Pathology review of the specimens reveals the following: UCS, invading 7 mm out of 10 mm myometrial thickness and negative peritoneal cytology. There was no lymphovascular space or cervical stromal involvement. All 12 examined pelvic and 3 paraaortic lymph nodes were negative for metastatic involvement.**

Procedure	Rating category	Group Median Rating	SOE	SOR	Level of agreement
Observation	U	1	S	↑	A
Radiation treatment alone	M	5*	S	-	D
Chemotherapy alone	M	5*	S	-	D
Radiation treatment with chemotherapy	A	8	M	↑	A
If chemotherapy alone, the recommended regimen is					
- Ifosfamide and paclitaxel	M	5*	S	-	D
- Carboplatin and paclitaxel	A	8	S	↑	A
- Cisplatin and ifosfamide	M	5*	M	-	D
If radiation treatment alone, the recommended treatment volume is					
- Pelvic external beam	A	8	M	↑	A
- Vaginal cuff brachytherapy	M	5*	L	-	D
- Pelvic external beam and vaginal cuff brachytherapy boost	A	5*	EC	-	D
- Whole abdominal RT	U	1	M	↑	A
Combined chemotherapy and vaginal cuff brachytherapy	M	5*	M	-	D
Combined chemotherapy and pelvic external beam radiation treatment +/- vaginal cuff brachytherapy	A	7	M	↑	A
If vaginal cuff brachytherapy is used, active vaginal length you would treat					
Upper one third-one half	A	8	EC	↑	A
Entire vaginal length	U	5*	L	↑	D

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Strength of Evidence (SOE): S Strong; M Moderate; L Limited; EC Expert Consensus; EO expert opinion

Strength of recommendation (SOR): ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Level of agreement: A Agreement, D Disagreement – * Disagreement is assigned a value of 5 as may be appropriate

Clinical condition: **Recurrent uterine carcinosarcoma (UCS)**

Variant 3: **A 69-year-old woman undergoes complete surgical staging. Pathology was consistent with stage IIIC1 UCS. Follow-up imaging 12 months after completion of 6 cycles of carboplatin and taxol chemotherapy alone showed interval disease progression with a biopsy-proven recurrent disease in a 3 cm right pelvic mass, potentially resectable. The patient is healthy otherwise.**

Procedure	Rating category	Group Median Rating	SOE	SOR	Level of agreement
Continue same chemotherapy alone regimen with 3 more cycles, no surgery	U	1	L	↑	A
Start different chemotherapy alone regimen, no surgery	M	5*	L	-	D
Surgical debulking alone	U	5*	L	↑	D
Surgical debulking followed by adjuvant chemo therapy	M	6	L	-	A
Surgical debulking followed by adjuvant radiation therapy	A	8	L	↑	A
Surgical debulking followed by adjuvant radiation and chemotherapy	A	5*	L	↑	D
Radiation treatment alone to the pelvis with curative intent	M	5*	L	-	D
Radiation treatment alone to the pelvic mass with palliative intent	U	5*	L	↑	D
Definitive radiation therapy with concurrent chemotherapy	U	3	L	↑	A
Consider palliative care/hospice approach	U	3	L	↑	A

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Strength of Evidence (SOE): S Strong; M Moderate; L Limited; EC Expert Consensus; EO expert opinion

Strength of recommendation (SOR): ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Level of agreement: A Agreement, D Disagreement – * Disagreement is assigned a value of 5 as may be appropriate

Clinical condition: **Stage IIIC1 uterine carcinosarcoma (UCS)**

Variant 4: **A 71-year-old woman who undergoes complete surgical staging including omentectomy after preoperative staging CT was negative for metastatic disease. Pathology is consistent with UCS, invading > 50% of myometrial thickness, with involvement of cervical stroma. Two out of 17 pelvic lymph nodes were involved (one left internal iliac and one common iliac node). Paraaortic lymphadenectomy was not performed. Peritoneal cytology and omental specimen were negative for malignant cells. There was no lymphovascular space involvement. She agreed to receive multimodality treatment (chemotherapy and radiation therapy).**

Procedure	Rating category	Group Median Rating	SOE	SOR	Level of agreement
Radiation Treatment Volume					
Pelvic external beam alone +/- vaginal cuff brachytherapy boost	M	5*	EC	-	D
Pelvic, and para-aortic external beam +/- vaginal cuff brachytherapy boost	A	7	L	↑	A
Vaginal cuff brachytherapy alone	U	3	L	↓	A
Radiation Therapy Technique					
2D	U	1	S	↑	A
3D conformal treatment	M	5	S	-	A
Intensity modulated radiation treatment (IMRT)	A	9	S	↑	A
Radiation treatment simulation					
Simulate the patient in prone position with a belly board device	M	5	L	-	**A**
Simulate with oral/IV contrast	A	8	M	↑	A
Simulate with vaginal cuff radio opaque marker	M	5*	L	-	D
Simulate with full and empty bladder	A	8	M	↑	A
Radiation Therapy dose to the pelvis and/or para-aortic Area					
45 Gy	A	8	S	↑	A
50.4 Gy	A	8	S	↑	A
45-50.4 Gy with vaginal cuff boost using brachytherapy	A	8	M	↑	A
If HDR brachytherapy vaginal cuff boost is used after 45 Gy to the pelvis, the recommended surface dose					
4 Gy x 3 fractions	A	5*	EC	↑	D
6 Gy x 3 fractions	A	8	EC	↑	A

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Strength of Evidence (SOE): S Strong; M Moderate; L Limited; EC Expert Consensus; EO expert opinion

Strength of recommendation (SOR): ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Level of agreement: A Agreement, D Disagreement – * Disagreement is assigned a value of 5 as may be appropriate

Clinical condition: **Follow-up after adjuvant treatment of uterine carcinosarcoma (UCS)**

Variant 5: **A 63-year-old woman undergoes complete surgical staging. Pathology showed UCS, >50% of myometrial thickness, with involvement of cervical stroma. Four pelvic lymph nodes out of 23 and 0 out 4 paraaortic lymph nodes were involved with carcinosarcoma. Assume adjuvant chemotherapy and radiation treatment (pelvic external beam RT including presacral nodes and vaginal cuff) has been completed.**

Procedure	Rating category	Group Median Rating	SOE	SOR	Level of agreement
Routine Follow-up Recommendations					
Follow-up visits every 3-6 months with pelvic examination with/without CA-125 levels for at least 5 years	A	9	M	↑	A
Discuss the use of vaginal dilator at least weekly for the first 12 months after treatment	A	9	M	↑	A
Consider routine imaging studies for follow-up after treatment	A	7	M	↑	A
If you follow-up with imaging studies in the first 3 years, how often you are routinely ordering it?					
Every 3 months	M	5*	L	-	D
Every 6 months	A	5*	M	↑	D
Every 12 months	M	5*	L	-	D

Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.

Rating Categories: U Usually not appropriate; M May be appropriate; A Usually appropriate

Strength of Evidence (SOE): S Strong; M Moderate; L Limited; EC Expert Consensus; EO expert opinion

Strength of recommendation (SOR): ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Level of agreement: A Agreement, D Disagreement – * Disagreement is assigned a value of 5 as may be appropriate