

Review

Clear Cell Carcinoma of the Endometrium: A Biological and Clinical Enigma

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Abstract. Clear cell carcinoma accounts for only 1 to 5.5% of all endometrial carcinomas, and it is often associated with an aggressive clinical behavior and a poor outcome. According to the FIGO Annual Report 2006, 5-year overall survival was 62.5% for patients with this histological type compared with 83.2% for those with endometrioid carcinoma of the endometrium. In contrast to endometrioid carcinoma and uterine papillary serous carcinoma (UPSC), the molecular pathways involved in the development of clear cell carcinoma are still unclear. Literature data on the pattern of failures and the optimal treatment modalities of the clear cell carcinoma are not well defined, largely because most papers have assessed clear cell carcinoma and UPSC together because of their rarity. Patients with clear cell carcinoma often experience relapse in the pelvis, in para-aortic nodes and at distant sites, whereas they do not seem to have a high propensity to fail in the abdomen. Total abdominal hysterectomy and bilateral salpingo-oophorectomy with comprehensive surgical staging is the standard surgical treatment of patients with clear cell carcinoma of the endometrium, whereas pelvic irradiation, with or without brachytherapy and/or para-aortic irradiation, whole-abdomen irradiation, and chemotherapy have been widely employed as postoperative therapy. However, no commonly accepted guidelines are currently available for the management of these patients. An adequate molecular characterization of clear cell carcinoma of the endometrium is strongly warranted in order to identify new biological prognostic variables of the disease and to develop novel molecular targeted therapies

The dualistic model for endometrial cancer, established on a morphological basis over 20 years ago, distinguishes this malignancy into two categories: type I estrogen-dependent endometrioid carcinoma (approximately 80-85%) and type II estrogen-independent non-endometrioid carcinoma (10-21%) (1-6). A decade later, different molecular profiles have been determined for these categories. Major alterations of type I carcinoma include *PTEN* gene silencing, defects in DNA mismatch repair genes, microsatellite instability and mutations in *KRAS* and/or β -catenin and/or phosphatidylinositol 3-kinase (*PIK3CA*) genes. Conversely, type II carcinomas often show *p53* gene mutations, *p16* gene inactivation, low *E-cadherin* expression, *Her-2/neu* overexpression, *STK15* amplification, and loss of heterozygosity on several chromosomes (2-14). A possible involvement of other oncogenes in endometrial carcinogenesis is currently under investigation (6). For instance, *CDC25* is a dual-specificity phosphatase that activate the cyclin/cyclin-dependent kinase complex thus resulting in cell cycle progression (15, 16). Wu *et al.* (17) found a high level expression of phosphorylated estrogen receptor- α (ER- α) and *CDC25B* in 65% of low-grade versus 17% of high-grade endometrioid endometrial carcinomas ($p < 0.01$). The same authors reported that high expression of *CDC25B* was much more common than high expression of phosphorylated ER- α (83% versus 22%; $p < 0.01$) in non-endometrioid endometrial carcinomas. Therefore, *CDC25B* may be involved by different mechanisms in the onset and progression of type I and type II tumors. Whereas *CDC25B* may function as a co-activator of ER- α in the development of endometrioid cancer, its oncogenic action in non-endometrioid cancer may be unrelated to ER- α .

The most common type II tumors are uterine papillary serous carcinoma (UPSC) and undifferentiated carcinoma, where clear cell carcinoma is much less frequent. Moreover other tumors and tumor-like lesions of the female genital tract may also contain clear cells and may occasionally be misinterpreted as clear cell adenocarcinomas. These conditions include microglandular hyperplasia, mesonephric

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hyperplasia, Arias-Stella change, smooth muscle tumors containing clear cells, dysgerminoma, yolk sac tumor, metastatic renal cell carcinoma, steroid cell tumors, hepatoid carcinomas, signet-ring-cell stromal tumors, and trophoblastic tumors (18).

Pathological Findings

Clear cell carcinoma of the endometrium, first described a century ago, received little attention until the publication of two pathological studies by Silverberg and De Giorgi (19) and Kurman and Scully (20) in the 1970s. Subsequently, other authors have investigated the surgical pathological findings and the clinical outcome of women with this malignancy, which currently accounts for 1 to 5.5% of all endometrial carcinomas (21-27).

Clear cell carcinoma is usually detected in postmenopausal women, with a mean age of 62 to 67 years, older than those with endometrioid carcinoma (22, 23, 26).

Grossly clear cell carcinomas often form fleshy and soft masses involving most of the endometrial surface (27, 28). Microscopically the neoplasm can exhibit different microscopic patterns, namely solid, papillary, tubular and cystic (28). The solid pattern consists of sheets of clear cells intermixed with eosinophilic cells, whereas papillary, tubular and cystic patterns are mainly composed of hobnail cells with interspersed clear and eosinophilic cells. The clear cytoplasm results from the presence of glycogen, and hobnail cells are cells with a naked nucleus that have discharged their glycogen and lost most of their cytoplasm. Nuclear atypia is usually marked and mitotic activity is high.

In contrast to endometrioid carcinoma and UPSC, limited information is currently available as to potential precursor lesions and the biological features of clear cell carcinoma of the endometrium. Fadare *et al.* (29) noted the presence of a spectrum of non-specific atypical glandular changes (isolated glands or surface epithelium with cytoplasmic clarity and/or eosinophilia and varying degrees of nuclear atypia) in the endometrium adjacent to clear cell carcinoma, and hypothesized that these lesions could represent the earliest morphologically recognizable precursor lesions of this malignancy. These precursor lesions were detected in 90% of 30 cases of endometrial clear carcinoma *versus* 0% of 68 controls represented by benign uteri or endometrioid carcinoma ($p < 0.001$). The immunohistochemical analysis showed that the mean p53 scores for the adjacent benign endometrium, precursor lesions and endometrial clear cell carcinoma were 0, 4.5 and 6.2, respectively, and that the corresponding values for *MIB-1* proliferation marker were 15%, 45% and 63%, respectively. Clear cell carcinoma also develops in the ovary, cervix and vagina, and displays very similar histological features (30). Cirisano *et al.* (24) assessed the surgical pathological findings of 574 surgically

treated patients with clinical stage I-II endometrial cancer, including 53 UPSCs and 18 with clear cell carcinoma. Rates for lymph node dissections were similar for grade (G) 3 endometrioid carcinoma (81%), UPSC (72%), and clear cell carcinoma (67%), although lymph node metastases were more frequent for type II tumors than for G3 endometrioid carcinoma. Lymph-vascular space involvement increased with the grade of endometrioid carcinoma and was highest for UPSC and clear cell carcinoma. Extra-uterine metastases occurred in 45% of clear cell carcinomas and 55% of UPSCs, confined to the inner one-half, *versus* 17% of G3 endometrioid carcinomas. These observations have been confirmed by other authors (31).

Immunophenotypic Profile

The immunophenotypic profile of clear cell carcinoma is not yet well defined. Vang *et al.* (32) analyzed the immunohistochemical expression of cytokeratin 7 (*CK7*), *CK20*, low and high molecular weight cytokeratin (*CAM5.2* and *34βE12*, respectively), carcinoembryonic antigen (*CEA*), Leu-M1, vimentin, ER, progesterone receptor (PR), BCL-2, p53, HER-2/neu, and CA-125 in 17 cases of primary clear cell carcinoma from different gynecological sites (11 ovary, 5 uterus, 1 vagina). The characteristic immunoprofile for all sites was positivity for CK7, CAM5.2, 34βE12, CEA, Leu-M1, vimentin, BCL-2, p53, and CA-125; variable positivity for ER and HER-2/neu; and negativity for CK20 and PR.

Arai *et al.* (33) found high expression of p53, cyclin A, and P-glycoprotein, and low or no expression of cyclin E, E-cadherin, and PR in 13 clear cell carcinomas compared with 144 endometrioid carcinomas of the endometrium.

P53 overexpression has been correlated with carcinogenesis more frequently in clear cell carcinoma than in endometrioid carcinoma but less frequently in clear cell carcinoma than in UPSC (32-35).

Cadherins are cell-surface glycoproteins that mediate cell-cell adhesion through a Ca²⁺-dependent mechanism. The significantly lower E-cadherin expression in clear cell carcinoma *versus* endometrioid carcinoma could suggest that the more aggressive biological behaviour of the former is partly due to a decrease in tumor cell cohesiveness (9, 13, 33).

The lack of PR positivity confirms that clear cell carcinoma is hormone independent and that progestin therapy has no role in the management of this histological type (32-34).

Poly (ADP-ribose) polymerase-1 (*PARP-1*) is a nuclear enzyme that catalyzes the poly (ADP-ribosylation) of target proteins and plays a major role in DNA repair (36, 37). Moreover, it regulates the transcriptional activities of steroid receptors (38, 39). PARP-1 expression gradually increases in non-atypical and atypical endometrial hyperplasia, reaching its highest level in G1 endometrioid carcinoma, and then decreases significantly towards G3 endometrioid carcinoma

(39). There is a positive correlation between PARP-1 and PR expression in endometrioid carcinoma, thus suggesting that PARP-1 is involved in progesterone action. Clear cell carcinoma, does not express PR and ER, shows moderate immunostaining for PARP-1. The role of PARP-1 in the development of this histological type is still unknown.

Transcription factor 2 gene (*TCF2*) encodes hepatocyte nuclear factor 1 β (HNF-1 β), which is involved in organogenesis, especially of the urogenital system, and carcinogenesis (40). Microarray analyses have disclosed that HNF-1 β is aberrantly up-regulated in clear cell carcinoma of the ovary as well as in ovarian endometriosis, which is often associated with clear cell carcinoma (41, 42). Yamamoto *et al.* (43) assessed HNF-1 β expression by immunohistochemistry in 186 ovarian carcinomas, including 40 clear cell carcinomas and 33 endometrial carcinomas, including 5 clear cell carcinomas. The incidence of HNF-1 β immunoreactivity was higher for clear cell carcinoma than for other histological types in both the ovary (100% versus 2%, $p < 0.0001$) and endometrium (100% versus 0%, $p < 0.0001$). HNF-1 β expression seems to be associated with physiopathological cytoplasmic glycogen accumulation in these organs.

Clear cell carcinoma often shows a higher Ki-67 proliferation index (34) and a greater number of cells expressing the proapoptotic gene *BAX* (44) compared with endometrioid carcinoma of the endometrium. A significantly higher apoptotic index has been detected in high-risk endometrial cancer, including G3 endometrioid carcinoma, clear cell carcinoma, UPSC and undifferentiated carcinoma than in G1-G2 endometrioid carcinoma (mean value=6.3% versus 2.7% $p < 0.0001$) (45). Conversely, there was no significant difference in the apoptotic index among the high-risk histological types.

Kangai (*KAI*)-1 or CD82, encoded by a metastasis suppressor gene, belonging to the family of tetraspanin proteins, is localized on the cell membrane and interacts with other tetraspanins, integrins and chemokines involved in cell migration, adhesion and signalling (46). Decreased *KAI*-1 expression has been related to cancer progression and aggressive biological behavior in different human malignancies. Briese *et al.* (47), reported that 93% of endometrioid tumors displayed a low or moderate immunostaining for *KAI*-1, whereas nearly all clear cell carcinomas and UPSCs were *KAI*-1 negative ($p < 0.001$). The reduction of *KAI*-1 expression could be an important step in endometrial carcinogenesis.

Treatment

The standard surgical treatment of clear cell carcinoma of the endometrium should consist of total abdominal hysterectomy and bilateral salpingo-oophorectomy, with comprehensive surgical staging including peritoneal washing,

omentectomy, and pelvic and para-aortic lymphadenectomy, although the extent of nodal resection is not well defined (random sampling versus resection of any enlarged lymph nodes versus systematic lymphadenectomy) (22-26, 48-56). The need for extended surgical staging is confirmed by the large retrospective study of Cirisano *et al.* (24) on patients with clinical stage I-II endometrial cancer, showing that an upstaging to surgical stage III-IV occurred in 39% of patients with clear cell carcinoma, 47% of those with UPSC and only 12% of those with endometrioid carcinoma.

As for adjuvant treatment, most authors have assessed clear cell carcinoma together with UPSC (31, 48, 54, 55, 57) and only a few studies have focused solely on clear cell histology (21, 26, 27, 58-60), mostly including a limited number of patients (59, 60) and lacking a detailed description of the adjuvant therapy administered (26, 27, 58) and the pattern of failure (27, 58). Therefore the optimal postoperative management of patients with clear cell carcinoma is far from being defined.

Abeler *et al.* (23) identified 181 patients with clear cell carcinoma of the endometrium in the tumor registry of the Norwegian Radium Hospital between 1970 and 1982. One hundred and forty-five patients underwent surgery plus radiotherapy, mainly represented by pelvic and/or vaginal irradiation. Tumor recurred in 44.5% of patients with stage I-II disease compared to 84.6% of those with stage III-IV disease. Two-thirds of relapses occurred outside the pelvis, and the most frequent extrapelvic sites of recurrence were the upper abdomen, lungs, and liver.

A phase I-II study of Gynecologic Oncology Group (GOG) assessed the clinical outcome of patients with clinical stages II UPSC and clear cell carcinoma treated with whole-abdomen irradiation plus a para-aortic boost in the case of para-aortic metastases (57). Of 13 patients with stage I-II clear cell carcinoma, 3 patients died of disease, 3 died of intercurrent or unknown disease, and 7 (54%) were alive and disease-free after an interval ranging from 59.9 months to 8 years and 9 months, with a 5-year progression-free survival of 53.9%. Sites of recurrence for disease-related deaths were lung (one case), vagina (one case), and unknown (one case), and time to recurrence ranged from 6.1 to 21.7 months. Smith *et al.* (54) assessed 26 patients with stage I-IV UPSC or clear cell carcinoma of the endometrium who received postoperative whole-abdomen irradiation. Three-year disease-free and overall survival were 47% and 68%, respectively, for the entire group, 87% and 87% for patients with stage I-II disease, and 32% and 61% for those with stage III-IV disease. According to these authors, whole-abdomen irradiation was an effective treatment for early-stage patients but not for those with advanced tumors for whom clinical trials of radiotherapy with concurrent or sequential chemotherapy were recommended.

Murphy *et al.* (25) analyzed 38 patients with clear cell carcinoma who underwent surgery with or without pelvic and para-aortic lymphadenectomy. Adjuvant treatment consisted of radiotherapy in 22 patients (pelvic irradiation in 13, vaginal brachytherapy in 2 and pelvic irradiation plus brachytherapy in 7), chemotherapy in 11 (8 alone and 3 after pelvic irradiation), hormone therapy in 3, and no further treatment in 5. The 5-year actuarial disease-free survival for the entire group was 38.5%. Sixteen (42%) patients relapsed after a median time of 18.4 months, and in detail 8 (21%) failed in the pelvis, 6 (16%) in the para-aortic lymph nodes and 2 (5%) in the abdomen, whereas 9 patients (24%) developed also recurrent disease in distant sites. It is noteworthy that pelvic failure did not occur in any of the 22 patients who received adjuvant radiotherapy *versus* 50% of the 16 women who did not ($p=0.0001$). Cumulative data from literature studies including solely clear cell carcinomas have reported an abdominal failure rate of approximately 11% (20, 23, 26, 48). These results appear to advise against the use of whole-abdomen irradiation in clear cell carcinoma, while supporting the combination of adjuvant locoregional irradiation and chemotherapy to better control both local and systemic disease (25). Most patients should receive pelvic irradiation, vaginal brachytherapy should be added for patients with cervical involvement or used alone in women with no myometrial invasion, whereas para-aortic irradiation should be taken into consideration to reduce the risk of para-aortic recurrence.

The GOG trial randomly allocated 422 stage III-IV endometrial cancer patients with residual disease less than 2 cm to receive whole-abdomen irradiation (30 Gy plus 15 Gy boost to the pelvis or to pelvic and para-aortic lymph nodes) *versus* chemotherapy consisting of doxorubicin (DOX; 60 mg/m²) + cisplatin (CDDP; 60 mg/m²) every 3 weeks for seven cycles followed by one cycle of single-agent CDDP (61). Of the enrolled patients, 17 had a clear cell carcinoma and 83 had a UPSC. The chemotherapy arm experienced a better 5-year progression-free survival [50% *versus* 38%, hazard ratio (HR)=0.71, 95% confidence interval (CI)=0.55-0.91, $p<0.007$] and a better 5-year overall survival (55% *versus* 42%, HR=0.68, 95% CI=0.52-0.89, $p<0.004$). No separate analysis was performed for patients with endometrioid *versus* non-endometrioid tumors. Adverse effects of treatment tended to be more frequent in the chemotherapy arm, but the majority of acute toxicities were expected and manageable.

Hogberg *et al.* (62) randomized 372 patients with high-risk endometrioid carcinoma or clear cell carcinoma, UPSC or undifferentiated carcinoma regardless of other risk factors, to undergo pelvic radiotherapy with or without brachytherapy *versus* radiotherapy plus 4 cycles of platinum-based chemotherapy [CDDP+DOX or epirubicin (EPIDOX), paclitaxel (TAX)+EPIDOX+carboplatin (CBDCA), or

TAX+CBDCA]. The HR for progression-free survival was 0.58 in favor of radiotherapy plus chemotherapy (95% CI, 0.34-0.99; $p=0.046$), which translated into an improvement of 5-year progression-free survival from 75% to 82%. In a randomized phase III GOG study on 273 patients with advanced or recurrent endometrial cancer of any histology (including 45 UPSCs and 8 clear cell carcinomas), the combination of DOX at 45 mg/m²+CDDP at 50 mg/m²+TAX at 160 mg/m² (3-hour infusion) with granulocyte-colony stimulating factor (G-CSF) support achieved an improvement in overall response rates (57% *versus* 34%, $p<0.001$), progression-free survival (median, 8.3 *versus* 5.3 months, $p=0.0001$), and overall survival (median, 15.3 *versus* 12.3 months, $p=0.037$) when compared with the combination of DOX at 60 mg/m²+CDDP at 50 mg/m² (63). Histological subtype was not related to the probability of response. Grade 2-3 peripheral neuropathy rates were higher for patients receiving the three-drug regimen. The GOG is currently comparing the combination of DOX+CDDP+TAX *versus* the less toxic regimen consisting of CBDCA+TAX in patients with advanced endometrial cancer. A case report recently showed that the combination of CBDCA plus weekly TAX is effective as neoadjuvant treatment in clear cell carcinoma of the endometrium (64). McKeekin *et al.* (65) assessed the relationship between histological type and clinical outcome in 1203 patients with advanced or recurrent endometrial cancer enrolled in four GOG first-line chemotherapy trials. Histological distribution was 18% UPSC, 3.7% clear cell carcinoma, 8.5% mixed carcinoma, 51.7% endometrioid carcinoma and 18.1% other histology. Chemotherapy was as follows: single-agent DOX or combination regimens including DOX in 12% of the patients; DOX+CDDP in 63%; DOX+TAX in 13%; and DOX+CDDP+TAX in 11%. There was a trend for a lower response rate for clear cell carcinoma (32%) compared with UPSC (44%) and endometrioid carcinoma (44%), but histological type was not an independent predictor of response, which did not support the exclusion of non-endometrioid tumors from future chemotherapy trials.

Prognosis

Clear cell carcinoma has a worse prognosis than endometrioid carcinoma of the endometrium (20, 21, 23, 25, 26, 48, 49, 54, 66) (Table I). According to the FIGO Annual Report of 2006, 5-year overall survival was 62.5% for 173 patients with clear cell carcinoma compared with 83.2% for 6735 patients with endometrioid carcinoma of the endometrium (HR=1.8, 95% CI=1.3-2.3) (66).

In the study of McMeekin *et al.* (65) including a large series of women with advanced disease treated with chemotherapy, the poorer clinical outcome was associated with clear cell carcinoma. Patients with this malignancy had a HR for

Table I. Five-Year survival of patients with clear cell carcinoma.

Authors	(ref.)	No. of pts	5-Year survival
Silverberg and De Giorgi	(19)	12	20.6%
Kurman and Scully	(20)	21	55.3%
Webb and Lagios	(21)	29	64%
Abeler <i>et al.</i>	(23)	181	43%*
Murphy <i>et al.</i>	(25)	38	38.5%
Creasman <i>et al.</i> **	(66)	173	62.5%

*Disease-free survival, **FIGO Annual Report.

progression and death of 1.52 (95% CI=1.11-2.09, $p=0.009$) and 1.51 (95% CI=1.1-2.07; $p=0.01$), respectively, compared with those with other histological types.

Some authors reported that early-stage clear cell carcinoma is associated with a better clinical outcome than early stage UPSC (26, 67). For instance, Carcangiu and Chambers (67), who reviewed 76 cases of pathological stage I-II clear cell carcinoma and UPSC, found that 5-year survival for stage I patients with clear cell carcinoma was 72% *versus* 44% for stage I patients with UPSC, and that the corresponding 5-year survival rates for stage II disease were 59% and 32%, respectively. Conversely, other authors failed to detect any significant survival difference between early-stage endometrial cancer patients with clear cell or serous papillary histology (51, 68). Several clinical-pathological variables have been correlated with the prognosis of patients with clear cell carcinoma, including tumor stage (21, 23, 48, 55, 58), myometrial invasion (23, 31, 48), lymph-vascular space involvement (31, 48, 55), and patient age (23, 47, 48). However, most papers have combined clear cell tumors and UPSCs in their analysis. In a Norwegian study including 181 patients with clear cell carcinoma, pathological stage, clinical stage, patient age, lymph-vascular space involvement and myometrial invasion were significantly related to survival at univariate analysis, but only pathological stage and patient age were independent prognostic variables at multivariate analysis (23). Conversely, Murphy *et al.* (25) detected no correlation between recurrence rate and tumor stage, myometrial invasion, peritoneal cytology, cervical extension, or involvement of extrauterine sites. Carcangiu and Chambers (67) found that myometrial invasion, lymph-vascular space involvement, the admixture of endometrioid features, as well as the predominant histological pattern (named papillary *versus* nonpapillary) did not influence the survival of patients with pathological stage I-II clear cell carcinoma of the endometrium. This histological type appears to be associated with a high risk of venous thromboembolism (69, 70). Lee *et al.* (70) reviewed 29 patients with clear cell endometrial carcinoma and 58 controls with high-grade endometrial cancer matched for

stage, age and date of diagnosis, and found that venous thromboembolism occurred in 34.5% of the former *versus* 13.8% of the latter (OR=3.68, $p=0.032$). Among patients with clear cell carcinoma, venous thromboembolism had an adverse effect on survival, with an HR of 3.65 (95% CI=3.14-4.16; $p=0.011$).

Conclusion

Clear cell carcinoma accounts for only 2 to 5.5% of all endometrial carcinomas (21-25), and therefore the biological information on this malignancy is very limited. This tumor occurs in the older population and it has a poorer prognosis when compared with endometrioid carcinoma (20, 21, 23, 25, 26, 48, 54, 66). Patients with clear cell carcinoma often experience relapse in the pelvis, in para-aortic nodes and at distant sites, whereas they do not seem to have a high propensity to fail in the abdomen (20, 23, 25, 26, 48). Pelvic irradiation significantly reduces the risk of pelvic recurrence (25), whereas literature data on whole-abdomen irradiation have reported conflicting, inconclusive and generally disappointing results (54, 57, 61). The retrospective evaluation of a large series of patients with advanced or recurrent endometrial cancer undergoing chemotherapy showed a trend for a lower response rate for clear cell carcinoma compared with UPSC or endometrioid carcinoma, but histological type was not an independent predictor of response (65). Patients with stage Ia clear cell carcinoma who have undergone comprehensive surgical staging have a low risk of recurrence and do not need any further treatment, whereas patients with more advanced disease should receive some form of adjuvant postoperative therapy, although it is not clear which treatments are most effective (49, 53).

The guidelines of the Italian Society of Gynecologic Oncology recommended the use of adjuvant chemotherapy in patients with clear cell endometrial carcinoma in stage Ib or greater (71, 72), whereas Tropè *et al.* (49) advise pelvic irradiation plus brachytherapy in early-stage disease, and pelvic irradiation with or without para-aortic irradiation plus chemotherapy in advanced disease. A randomized multicenter

trial (Postoperative Radiation Therapy in Endometrial Carcinoma PORTEC 3) is currently ongoing, comparing pelvic irradiation 48.6 Gy (plus brachytherapy if cervical invasion) *versus* radiotherapy with concurrent (CDDP at 50 mg/m² for 2 cycles) and adjuvant chemotherapy (TAX at 175 mg/m²+CBDCA AUC 5 for 4 cycles) in patients with high-risk endometrioid carcinoma as well as in those with stage IB-III clear cell carcinoma or UPSC of the endometrium.

Patients with recurrent or metastatic disease not manageable with surgery or irradiation should receive chemotherapy with the same regimens used for endometrioid carcinoma, *i.e.* CDDP+DOX, CDDP+DOX+TAX, or CBDCA+TAX.

Adequate molecular characterization of clear cell carcinoma of the endometrium is strongly warranted in order to identify new biological prognostic variables of the disease and to develop novel molecular targeted therapies to use concomitantly or sequentially to chemotherapy during first-line treatment or as salvage therapy after the failure of conventional treatment.

Consideration should be given to extended thromboprophylaxis in women with clear cell endometrial carcinoma because these patients have a high risk of developing venous thromboembolism (69, 70). The assay plasma levels of thrombin-antithrombin III complex and D-dimer could be useful for early detection of patients with this severe complication (69, 72).

References

- Bokhman JV: Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* 15: 10-17, 1983.
- Prat J: Prognostic parameters of endometrial carcinoma. *Hum Pathol* 35: 649-662, 2004.
- Liu FS: Molecular carcinogenesis of endometrial cancer. *Taiwan J Obstet Gynecol* 46: 26-32, 2007.
- Lax SF: Molecular genetic changes in epithelial, stromal and mixed neoplasms of the endometrium. *Pathology* 39: 46-54, 2007.
- Prat J, Gallardo A, Cuatrecasas M and Catasús L: Endometrial carcinoma: pathology and genetics. *Pathology* 39: 72-87, 2007.
- Doll A, Abal M, Rigau M, Monge M, Gonzalez M, Demajo S, Colás E, Llauradó M, Alazzouzi H, Planagumá J, Lohmann MA, Garcia J, Castellvi S, Ramon y Cajal J, Gil-Moreno A, Xercavins J, Alameda F and Reventós J: Novel molecular profiles of endometrial cancer-new light through old windows. *J Steroid Biochem Mol Biol* 108: 221-229, 2008.
- Matias-Guiu X, Catusus L, Bussaglia E, Lagarda H, Garcia A, Pons C, Muñoz J, Argüelles R, Machin P and Prat J: Molecular pathology of endometrial hyperplasia and carcinoma. *Hum Pathol* 32: 569-577, 2001.
- Koul A, Willén R, Bendahl PO, Nilbert M and Borg A: Distinct sets of gene alterations in endometrial carcinoma implicate alternate modes of tumorigenesis. *Cancer* 94: 2369-2379, 2002.
- Holcomb K, Delatorre R, Pedemonte B, McLeod C, Anderson L and Chambers J: E-cadherin expression in endometrioid, papillary serous, and clear cell carcinoma of the endometrium. *Obstet Gynecol* 100: 1290-1295, 2002.
- Moreno-Bueno G, Sánchez-Estévez C, Cassia R, Rodríguez-Perales S, Díaz-Uriarte R, Domínguez O, Hardisson D, Andujar M, Prat J, Matias-Guiu X, Cigudosa JC and Palacios J: Differential gene expression profile in endometrioid and nonendometrioid endometrial carcinoma: STK15 is frequently overexpressed and amplified in nonendometrioid carcinomas. *Cancer Res* 63: 5697-5702, 2003.
- Santin AD, Bellone S, Van Stedum S, Bushen W, Palmieri M, Siegel ER, De Las Casas LE, Roman JJ, Burnett A and Pecorelli S: Amplification of *c-erbB2* oncogene: a major prognostic indicator in uterine serous papillary carcinoma. *Cancer* 104: 1391-1397, 2005.
- Catusus L, Gallardo A, Cuatrecasas M and Prat J: *PIK3CA* mutations in the kinase domain (exon 20) of uterine endometrial adenocarcinomas are associated with adverse prognostic parameters. *Mod Pathol* 21: 131-139, 2008.
- Yalta T, Atay L, Atalay F, Caydere M, Gonultas M and Ustun H: E-cadherin expression in endometrial malignancies: comparison between endometrioid and non-endometrioid carcinomas. *J Int Med Res* 37: 163-168, 2009.
- Bansal N, Yendluri V and Wenham RM: The molecular biology of endometrial cancers and the implications for pathogenesis, classification, and targeted therapies. *Cancer Control* 16: 8-13, 2009.
- Draetta G and Eckstein J: CDC25 protein phosphatases in cell proliferation. *Biochim. Biophys Acta* 1332: M53-M63, 1997.
- Ma ZQ, Chua SS, DeMayo FJ and Tsai SY: Induction of mammary gland hyperplasia in transgenic mice overexpressing human Cdc25B. *Oncogene* 18: 4564-4576, 1999.
- Wu W, Slomovitz BM, Celestino J, Chung L, Thornton A and Lu KH: Coordinate expression of Cdc25B and ER-alpha is frequent in low-grade endometrioid endometrial carcinoma but uncommon in high-grade endometrioid and nonendometrioid carcinomas. *Cancer Res* 63: 6195-6199, 2003.
- Vang R, Barner R, Wheeler DT and Strauss BL: Immunohistochemical staining for Ki-67 and p53 helps distinguish endometrial Arias-Stella reaction from high-grade carcinoma, including clear cell carcinoma. *Int J Gynecol Pathol* 23: 223-233, 2004.
- Silverberg SG and De Giorgi LS: Clear cell carcinoma of the endometrium. Clinical, pathologic, and ultrastructural findings. *Cancer* 31: 1127-1140, 1973.
- Kurman RJ and Scully RE: Clear cell carcinoma of the endometrium: an analysis of 21 cases. *Cancer* 37: 872-882, 1976.
- Webb GA and Lagios MD: Clear cell carcinoma of the endometrium. *Am J Obstet Gynecol* 156: 1486-1491, 1987.
- Christopherson WM, Alberhasky RC and Connelly PJ: Carcinoma of the endometrium: I. A clinicopathologic study of clear-cell carcinoma and secretory carcinoma. *Cancer* 49: 1511-1523, 1982.
- Abeler VM, Vergote IB, Kjørstad KE and Tropé CG: Clear cell carcinoma of the endometrium. Prognosis and metastatic pattern. *Cancer* 78: 1740-1747, 1996.
- Cirisano FD Jr, Robboy SJ, Dodge RK, Bentley RC, Krigman HR, Synan IS, Soper JT and Clarke-Pearson DL: Epidemiologic and surgicopathologic findings of papillary serous and clear cell endometrial cancers when compared to endometrioid carcinoma. *Gynecol Oncol* 74: 385-394, 1999.
- Murphy KT, Rotmensch J, Yamada SD and Mundt AJ: Outcome and patterns of failure in pathologic stages I-IV clear-cell carcinoma of the endometrium: implications for adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys* 55: 1272-1276, 2003.

- 26 Malpica A, Tornos C, Burke TW and Silva EG: Low-stage clear cell carcinoma of the endometrium *Am J Surg Pathol* 19: 769-774, 1995.
- 27 Kanbour-Shakir A and Tobón H: Primary clear cell carcinoma of the endometrium: a clinicopathologic study of 20 cases. *Int J Gynecol Pathol* 10: 67-78, 1991.
- 28 Blaustein's Pathology of the Female Genital Tract. Fifth Edition Kurman RJ (ed.): New York: Berlin, Heidelberg, Springer-Verlag 2002.
- 29 Fadare O, Liang SX, Ulukus EC, Chambers SK and Zheng W: Precursors of endometrial clear cell carcinoma. *Am J Surg Pathol* 30: 1519-1530, 2006.
- 30 Matias-Guiu X, Lerma E and Prat J: Clear cell tumors of the female genital tract. *Semin Diagn Pathol* 14: 233-239, 1997.
- 31 Sakuragi N, Hareyama H, Todo Y, Yamada H, Yamamoto R, Fujino T, Sagawa T and Fujimoto S: Prognostic significance of serous and clear cell adenocarcinoma in surgically staged endometrial carcinoma. *Acta Obstet Gynecol Scand* 79: 311-316, 2000.
- 32 Vang R, Whitaker BP, Farhood AI, Silva EG, Ro JY and Deavers MT: Immunohistochemical analysis of clear cell carcinoma of the gynecologic tract. *Int J Gynecol Pathol* 20: 252-259, 2001.
- 33 Arai T, Watanabe J, Kawaguchi M, Kamata Y, Nishimura Y, Jobo T and Kuramoto H: Clear cell adenocarcinoma of the endometrium is a biologically distinct entity from endometrioid adenocarcinoma. *Int J Gynecol Cancer* 16: 391-395, 2006.
- 34 Lax SF, Pizer ES, Ronnett BM and Kurman RJ: Clear cell carcinoma of the endometrium is characterized by a distinctive profile of p53, Ki-67, estrogen and progesterone receptor expression. *Hum Pathol* 29: 551-558, 1998.
- 35 Itamochi H, Kigawa J, Sugiyama T, Kikuchi Y, Suzuki M and Terakawa N: Low proliferation activity may be associated with chemoresistance in clear cell carcinoma of the ovary. *Obstet Gynecol* 100: 281-287, 2002.
- 36 Tong WM, Cortes U and Wang Z-Q: Poly(ADP-ribose) polymerase: a guardian angel protecting genome and suppressing tumorigenesis. *Biochim Biophys Acta* 1552: 27-37, 2001.
- 37 Miyamoto T, Kakizawa T and Hashizume K: Inhibition of nuclear receptor signalling by poly (ADP-Ribose) polymerase. *Mol Cell Biol* 19: 2644-2649, 1999.
- 38 Sartorius CA, Takimoto GS, Richer JK, Tung L and Horwitz KB: Association of the Ku autoantigen/DNA-dependent protein kinase holoenzyme and poly(ADP-ribose) polymerase with the DNA binding domain of progesterone receptors. *J Mol Endocrinol* 24: 165-182, 2000.
- 39 Ghabreau L, Roux JP, Frappart PO, Mathevet P, Patricot LM, Mokni M, Korbi S, Wang ZQ, Tong WM and Frappart L: Poly(ADP-ribose) polymerase-1, a novel partner of progesterone receptors in endometrial cancer and its precursors. *Int J Cancer* 109: 317-321, 2004.
- 40 Kato N and Motoyama T: Hepatocyte nuclear factor-1beta (HNF-1beta) in human urogenital organs: its expression and role in embryogenesis and tumorigenesis. *Histol Histopathol* 24: 1479-1486, 2009.
- 41 Schwartz DR, Kardia SL, Shedden KA, Kuick R, Michailidis G, Taylor JM, Misek DE, WR, Zhai Y, Darrach DM, Reed H, Ellenson LH, Giodano TJ, Fearon ER, Hanash SM and Cho KR: Gene expression in ovarian cancer reflects both morphology and biological behavior, distinguishing clear cell from other poor-prognosis ovarian carcinomas. *Cancer Res* 62: 4722-4729, 2002.
- 42 Le KH, Patterson AP, Wang L, Marquez RT, Atkinson EN, Baggerly KA, Ramoth LR, Rosen DG, Liu J, Hellstrom I, Smith D, Hartmann L, Fishman D, Berchuck A, Schmandt R, Whitaker R, Gershenson DM, Mills GB and Bast Jr RC: Selection of potential markers for epithelial ovarian cancer with gene expression arrays and recursive descent partition analysis. *Clin.Cancer Res* 10: 3291-3300, 2002.
- 43 Yamamoto S, Tsuda H, Aida S, Shimazaki H, Tamai S, and Matsubara O: Immunohistochemical detection of hepatocyte nuclear factor 1beta in ovarian and endometrial clear-cell adenocarcinomas and nonneoplastic endometrium. *Hum Pathol* 38: 1074-1080, 2007.
- 44 Kokawa K, Shikone T, Otani T, Nishiyama R, Ishii Y, Yagi S and Yamoto M: Apoptosis and the expression of Bcl-2 and Bax in patients with endometrioid, clear cell, and serous carcinomas of the uterine endometrium. *Gynecol Oncol* 81: 178-183, 2001.
- 45 Heatley MK: A high apoptotic index occurs in subtypes of endometrial adenocarcinoma associated with a poor prognosis. *Pathology* 29: 272-275, 1997.
- 46 Malik FA, Sanders AJ and Jiang WG: KAI-1/CD82, the molecule and clinical implication in cancer and cancer metastasis. *Histol Histopathol* 24: 519-530, 2009.
- 47 Briese J, Schulte HM, Sajin M, Bamberger C, Redlin K, Milde-Langosch K, Löning T and Bamberger AM: Correlations between reduced expression of the metastasis suppressor gene KAI-1 and accumulation of p53 in uterine carcinomas and sarcomas. *Virchows Arch* 453: 89-96, 2008.
- 48 Cirisano FD Jr, Robboy SJ, Dodge RK, Bentley RC, Krigman HR, Synan IS, Soper JT and Clarke-Pearson DL: The outcome of stage I-II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with endometrioid carcinoma. *Gynecol Oncol* 77: 55-65, 2000.
- 49 Tropé C, Kristensen GB and Abeler VM: Clear-cell and papillary serous cancer: treatment options. *Best Pract Res Clin Obstet Gynaecol* 15: 433-446, 2001.
- 50 Chan JK, Loizzi V, Youssef M, Osann K, Rutgers J, Vasilev SA and Berman ML: Significance of comprehensive surgical staging in noninvasive papillary serous carcinoma of the endometrium. *Gynecol Oncol* 90: 181-185, 2003.
- 51 Creasman WT, Kohler MF, Odicino F, Maisonneuve P and Boyle P: Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. *Gynecol Oncol* 95: 593-596, 2004.
- 52 Sutton G, Axelrod JH, Bundy BN, Roy T, Homesley H, Lee RB, Gehrig PA and Zaino R: Adjuvant whole abdominal irradiation in clinical stages I and II papillary serous or clear cell carcinoma of the endometrium: a phase II study of the Gynecologic Oncology Group. *Gynecol Oncol* 100: 349-354, 2006.
- 53 Kwon JS, Abrams J, Sugimoto A and Carey MS: Is adjuvant therapy necessary for stage IA and IB uterine papillary serous carcinoma and clear cell carcinoma after surgical staging? *Int J Gynecol Cancer* 18: 820-824, 2004.
- 54 Smith RS, Kapp DS, Chen Q and Teng NN: Treatment of high-risk uterine cancer with whole abdominopelvic radiation therapy. *Int J Radiat Oncol Biol Phys* 8: 767-778, 2000.
- 55 Craighead PS, Sait K, Stuart GC, Arthur K, Nation J, Duggan M and Guo D: Management of aggressive histologic variants of endometrial carcinoma at the Tom Baker Cancer Centre between 1984 and 1994. *Gynecol Oncol* 77: 248-253, 2000.

- 56 Hacker NF: Uterine cancer. In: Practical Gynecologic Oncology, Second edition. Berek NJ and Hacker NF (eds.). Baltimore: Williams and Wilkins, pp. 285-326, 1994.
- 57 Sigurdsson K, Sigurdardottir B, Steinsson S, Benediktsdottir K, Sigurvinnsson T and Sigvaldason H: Survival and prognostic factors of endometrial cancer patients in Iceland 1964-1985: can attendance at population-based Pap-smear screening affect survival? *Int J Cancer* 79: 166-174, 1998.
- 58 Photopoulos GJ, Carney CN, Edelman DA, Hughes RR, Fowler WC Jr, Walton LA: Clear cell carcinoma of the endometrium. *Cancer* 43: 1448-1456, 1979.
- 59 Carinelli SG and Senzani F: Clear cell carcinoma of endometrium. *Tumori* 65: 201-205, 1979.
- 60 Aquino-Parsons C, Lim P, Wong F and Mildenerger M: Papillary serous and clear cell carcinoma limited to endometrial curettings in FIGO stage Ia and Ib endometrial adenocarcinoma: treatment implications. *Gynecol Oncol* 71: 83-86, 1998.
- 61 Randall ME, Filiaci VL, Muss H, Spirtos NM, Mannel RS, Fowler J, Thigpen JT and Benda JA; Gynecologic Oncology Group Study: Randomized phase III trial of whole-abdominal irradiation *versus* doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 24: 36-44, 2006.
- 62 Hogberg T, Rosenberg P, Kristensen G, de Oliveira F, de Pont Christensen R, Sorbe B, Lundgren C, Salmi T, Andersson H and Reed NS: A randomized phase-III study on adjuvant treatment with radiation (RT) ± chemotherapy (CT) in early-stage high-risk endometrial cancer (NSGO-EC-9501/EORTC 55991) *J Clin Oncol* 25(18S): 274s, (abstract 5503), 2007.
- 63 Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, Kline R, Burger RA, Goodman A and Burks RT: Phase III trial of doxorubicin plus cisplatin with or without paclitaxel plus filgrastim in advanced endometrial carcinoma: a Gynecologic Oncology Group Study. *J Clin Oncol* 22: 2159-2166, 2004.
- 64 Takami M, Ohta Y, Nakayama Y, Fukai H, Matsumoto H, Takimoto T, Sakamoto H and Yamamoto T: A case of advanced clear cell carcinoma of the endometrium that responded remarkably to neoadjuvant chemotherapy of combination carboplatin plus weekly paclitaxel, *Gan To Kagaku Ryoho* 34: 457-460, 2007.
- 65 McMeekin DS, Filiaci VL, Thigpen JT, Gallion HH, Fleming GF and Rodgers WH; Gynecologic Oncology Group study: The relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials: a Gynecologic Oncology Group study. *Gynecol Oncol* 106: 16-22, 2007.
- 66 Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Heintz APM, Nyan HYS and Pecorelli S: Carcinoma of the corpus uteri. *Int J Gynecol Obstet* 95(Suppl 1): S105-S143, 2006.
- 67 Carcangiu ML and Chambers JT: Early pathologic stage clear cell carcinoma and uterine papillary serous carcinoma of the endometrium: comparison of clinicopathologic features and survival. *Int J Gynecol Pathol* 14: 30-38, 1995.
- 68 Alektiar KM, McKee A, Lin O, Venkatraman E, Zelefsky MJ, McKee B, Hoskins WJ and Barakat RR: Is there a difference in outcome between stage I-II endometrial cancer of papillary serous/clear cell and endometrioid FIGO Grade 3 cancer? *Int J Radiat Oncol Biol Phys* 54: 79-85, 2002.
- 69 Toyoda M, Satoh T, Takano K, Sato NO, Oki A, Tsunoda H and Yoshikawa H: Successful diagnosis of thromboembolism before surgery in a woman with clear cell adenocarcinoma of the endometrium. *Int J Clin Oncol* 10: 444-446, 2005.
- 70 Lee L, Garrett L, Lee H, Oliva E, Horowitz N and Duska LR: Association of clear cell carcinoma of the endometrium with a high rate of venous thromboembolism. *J Reprod Med* 54: 133-138, 2009.
- 71 Società Italiana di Ginecologia Oncologica: Manuale di Ginecologia Oncologica, UTET Torino 1998.
- 72 Raspagliesi F, Gadducci A and Franchi M: Requisiti minimi per il trattamento delle neoplasie ginecologiche. Società Italiana di Oncologia Ginecologica, EDITEAM Gruppo Editoriale, Cento (FE), 2007.
- 73 Kawasaki T, Shinoki N, Iwamoto S, Fujimura H, Yoshikawa N, Ohta Y, Ikeda M, Ariyoshi H, Shibuya T and Monden M: Diagnostic value of plasma thrombin- antithrombin III complex and D-dimer concentration in patients with varicose veins for exclusion of deep-vein thrombosis. *Thromb Res* 91: 101-104, 1998.

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