

Clear Cell Carcinoma of the Uterus.

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RÉSUMÉ

But : Le but de ce travail est de déterminer les particularités cliniques, pathologiques et d'étudier le mode et les facteurs prédictifs de récurrence des carcinomes à cellules claires (CCC) de l'endomètre.

Méthodes: Nous avons étudié les dossiers de patientes traitées à l'Institut Salah-Azaiz pour CCC de l'endomètre. Toutes les patientes étaient reclassées après revue des comptes rendus chirurgicaux et anatomopathologiques selon la classification de la FIGO. Nous avons comparé les stades cliniques et anatomopathologiques respectifs pour chaque patiente. Nous avons ensuite analysé les facteurs prédictifs d'extension extra-utérine et de récurrences.

Résultats: 12 patientes présentant un carcinome à cellules claires de l'endomètre ont été traitées à l'institut Salah-Azaiz. L'âge moyen est de 64 ans (50 à 84 ans). L'extension tumorale était sous-estimée par la classification clinique chez 9 patientes. 9 patientes avaient une extension extra-utérine au moment du diagnostic. L'envahissement myométrial n'était pas corrélé avec l'extension extra-utérine. Après un suivi moyen de 32 mois, 4 patientes ont présenté une récurrence : vaginale dans un cas, abdomino-pelvienne dans 2 cas et abdominale isolée dans un cas. La récurrence était localisée dans le champ d'irradiation dans un cas. Toutes les récurrences étaient précoces survenant pendant la première année après le traitement. Deux patientes ayant récidivé au niveau abdominopelvien ont progressé malgré le traitement associant la chirurgie et la radiochimiothérapie.

Conclusion: L'extension extra-utérine est souvent retrouvée au moment du diagnostic et n'est pas corrélée au degré d'envahissement myométrial. Les récurrences locorégionales sont fréquentes et non curables malgré l'association des traitements locorégionaux et systémiques.

SUMMARY

Aim : The aim of this study was to determine the characteristics and outcome of patients presenting with clear cell carcinoma (CCC) of the endometrium treated in a single institution.

Methods: We reviewed the records of patients treated in the Salah-Azaiz institute for CCC of the endometrium. A histopathological stage was retrospectively assigned to these patients according to the FIGO classification and was compared to the clinical stage. Pathological features were studied in order to determine predictive factors of extrauterine disease extension and failure patterns.

Results: 12 patients were included in the study. The mean age at diagnosis was 64 years (50 to 84 years). Upstaging after surgery was found in 9 patients. 9 patients had extrauterine extension. Deep myometrial invasion was not correlated with extrauterine extension. After a median follow up of 32 months, 4 patients presented with recurrences: one vaginal recurrence, two cases of pelvic and abdominal recurrence and abdominal recurrence in one patient. All recurrences occurred during the first year after surgery. Tumor recurrence was located within the radiation field in one case. Two patients with abdomino-pelvic recurrences progressed despite the association of surgery, radiation therapy and chemotherapy.

Conclusion: Extrauterine extension is frequent at diagnosis and not correlated to classical risk factors observed in endometrioid carcinoma. A complete surgical staging is necessary for adjuvant treatment. Locoregional and distant recurrences are frequent and have a poor outcome.

Mots-clés

Carcinome à cellules claires de l'endomètre, anatomopathologie, traitement, pronostic

Key - words

Clear cell carcinoma of the endometrium, pathology, treatment, prognosis

السرطان ذي الخلايا الواضحة في الرحم . دراسة حول 12 حالة وآستعراض للمقالات الطبية

الباحثون : هنتاتي . د - كشباتي . ل - بالعيد . أ - بن حسونة . ج - معالج . م .

الهدف من هذه الدراسة هو تحديد الخصائص السريرية والمرضية للسرطان ذي الخلايا الواضحة في الرحم . تشتمل دراستنا على 12 حالة . لاحظنا أن تطور الورم خارج الرحم كان كثير التواتر أثناء تشخيص المرضى والتنكسات الموضعية أيضا وهي الغالب لا يمكن معالجتها بالرغم من العلاج الموضعي والمجموعي .

الكلمات الأساسية : سرطان ذي الخلايا الواضحة للبطانة - تحليل تشريحي مرضي - علاج .

Clear cell carcinoma (CCC) is an uncommon subtype of endometrial carcinoma that has been described for the first time nearly a century ago, by De Bonnelle [1]. It was first thought to be a mesonephros tumor until 1967 where Scully and Barlow related the origin of this tumor to the müllerian epithelium [2]. The CCC of the uterus is a distinct variant and represents 0.8 to 6 % of endometrial carcinoma [1-9]. It is a particularly aggressive form of the uterine tumours characterised by a rapid and frequent extra-uterine spread. Although its natural history is not well established, some authors suggest that it may be similar to the ovarian epithelial carcinoma [7]. Published series are usually retrospective and limited in patients' number and the histopathological criteria are unclear. Nevertheless, most of the authors agree on the need of a complete surgical staging according to FIGO system. Adjuvant treatment varies from abstention to locoregional radiation therapy by pelvic/whole abdominal radiation +/- vaginal brachytherapy and chemotherapy [2, 6, 10].

The purpose of this study is to analyze the outcome and patterns of failure in patients presenting with CCC of the uterus treated in a single institution and to discuss implications for adjuvant radiation therapy and chemotherapy.

METHODS AND MATERIALS

We reviewed the records of patients presenting with CCC of the endometrium treated in Salah-Azaïz Institute. Clinical staging was used for all patients before treatment decision.

The treatment consisted of surgery, pelvic radiotherapy with or without vaginal brachytherapy. Surgery was performed at first in 8 cases. 3 patients had brachytherapy before surgery. 3 of the patients didn't have peritoneum cytology. The patient with clinical stage IV had a biopsy only.

8 patients received adjuvant pelvic radiation therapy. The surgical stage of these patients was IB-IVB. 6 patients out of 12 had brachytherapy.

We reviewed the type of surgery for all the patients. This treatment was considered complete if there has been a hysterectomy, lymph node sampling, bilateral oophorectomy, colpectomy and peritoneum cytology. If enlarged Lomboaortic lymph nodes or peritoneum nodes noticed during surgery, biopsies were performed.

All the cases were retrospectively assigned a new stage according to the FIGO 1988 surgical staging system after review of the histopathologic outcome.

We compared the clinical and surgical staging of the patients. We studied the relationship between myometrium infiltration and disease dissemination outside the uterus. Then we analysed the locoregional control and recurrences.

RESULTS

Patients and tumour characteristics are described in table 1. In all, 12 patients were diagnosed with CCC. The mean age at

diagnosis was 64 years (50 to 84 years). Postmenopausal status was found in 11 patients. The mean number of children was 3 (varying between 1 and 5). Only one patient was nulliparous. Oral contraception use was found in one case.

The clinical stage was IA in 4 cases, IB in 6 cases, II in one case and IV in one case. After histopathological review, these patients were retrospectively assigned a new stage according to the 1988 staging system (table 2). Upstaging after surgery was found in 3 patients with clinical IA stage (1 IB, 1 IIIC and 1 IVB). For the stage IB patients, the surgical stage was IIIA, IIIC and IVB in 1, 3 and 1 cases respectively. The last patient with clinical stage II was assigned stage IV after surgery. In all, upstaging after surgery was found in 9 cases out of 11. Surgical staging was not possible in one patient who had an incomplete surgery outside our institute.

Table 1: patient characteristics

Mean age	64 years (from 50 to 82 years)
Mean age at puberty	13 years
Median age at menopause	48 years
Mean number of children	3
Oral contraception use	1
Symptoms at diagnosis	
Bleeding	10
Leucorrhea	5
Pelvic pain	7
Others	2
Histology	
Clear cell carcinoma	9
Clear cell and endometrioid carcinoma	3
Tumour extension in the endometrium wall	
Confined to the endometrium	1
Myometrium invasion < 50%	6
Myometrium invasion > 50%	4
Extra-uterine invasion	
Pelvic node invasion	4
Ovarian invasion	4
Lomboaortic node invasion	2
Peritoneum cytology	6
Positive	4
Negative	2
Peritoneal metastases	2
Visceral metastases	1
Surgical stage*	
IA	1
IB	2
IIIA	1
IIIC	4
IVB	3

*: One patient had partial hysterectomy in an other hospital. No surgical staging was performed.

Table 2: Surgical staging versus clinical staging

Clinical stage	Stage IA	Stage IB	Stage II	Stage IVB
Surgical stage				
stage I				
IA	1			
IB	1	1		
Stage III				
IIIA		1		
IIIC	1	3		
Stage IV				
IVA			1	
IVB	1	1		1

In 3 cases among those with extrauterine extension, the myometrial invasion was limited to less than half of the myometrium depth.

After a median follow up of 32 months (3 to 239 months), 4 patients presented with recurrences. The pattern of recurrences is shown in table 3. One patient had a vaginal recurrence, intra-abdominal recurrence in 1 case and pelvic associated to intra-abdominal recurrence in 2 cases. The mean time to recurrence was 6 months (2 to 11 months) after surgery. Recurrences were located outside the radiation field in 2 cases (table). One of them presented pelvic recurrence within the radiation field. For this patient, the delay between surgery and radiation therapy was long (6 months). The other patient with pelvic and intra-abdominal was treated with surgery only.

The patient with vaginal recurrence was treated with surgical excision and brachytherapy. She was recurrence free at last follow up. Two patients with pelvic and peritoneal recurrences progressed despite a surgical-radiation therapy and chemotherapy. The other patient was given palliative treatment.

DISCUSSION

Clear cell carcinoma is a rare histological subtype of endometrium cancer. Because of the retrospective aspect of the published studies and the limited number of the cases in these series, the epidemiological aspects are not well established. In

our study, oral contraception and nulliparity were found in only 1 case out of 12. These findings suggest that the impact of sexual hormones on this histological type differs from endometrioid carcinoma. This correlates with the results of other studies where no association between exogenous estrogen and CCC of the uterus was found [6, 7].

Unlike clear cell carcinoma of the cervix and vagina in young women, where diethylstilbesterol exposure is incriminated, CCC of the uterus corpus are not related to this drug and appear in post-menopause period. Mean age at diagnosis is 68 years [11]. Unlike endometrioid carcinoma, CCC tends to spread rapidly outside the uterus. According to Creasman and al. study from the 25th annual report of FIGO, 46% of CCC and serous papilloma cancers were staged II-IV at diagnosis versus 21% of endometrioid carcinoma [8]. This correlates with the findings of our study where 9 patients from 12 (75%) were stage III-IV.

A complete surgical staging is necessary for CCC carcinoma before adjuvant treatment decision. This staging work up requires a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphnode sampling with a peritoneal cytology and a careful abdominal examination. A systematic para-aortic sampling is recommended by some authors because of the absence of correlation between node-diameter and histological lymph-node metastases [11, 12]. In our study, upstaging after surgery was found in 9 cases out of 12. This was also noticed in other published studies varying from 31 to 46% of the cases [5, 6].

Extrauterine metastases are more frequent in CCC than in low grade endometrioid carcinoma, and not correlated with myometrial depth invasion [5, 6]. Cirisano et al. found extrauterine metastases in 45% of CCC versus 17% of the endometrioid carcinoma grade 3 [5]. In our study, extrauterine extension was associated with a limited invasion of the myometrium in 3 cases out of 8. A statistical analysis of risk factors of extrauterine extension was not possible because of the small number of our cases.

One of our patients presented with lung and liver metastases at diagnosis. Distant metastases involving the lung and supra clavicular nodes were reported in the literature [4]. We suggest a systematic liver ultrasound or CT scan with a chest X ray in the initial disease work up.

Recurrences are frequent in CCC (22%) compared with endometrioid carcinoma (9%) [6]. In our study, one third of our

Table 3: characteristics of the patients with recurrences

Clinical stage	Surgical stage*	Treatment for primary disease	Site of recurrence	Treatment of the recurrence	Outcome
Stage IA	Stage IA	Surgery	Vagina	Surgical resection Radiation therapy	†NED
Stage IB	Stage IIIC	Surgery at first Pelvic radiation therapy	Peritoneum	Supportive care	Progression
Stage II	Stage IVA	Surgery Surgery at first	Peritoneum + pelvis	Surgery + pelvic radiation therapy	Progression
Stage IA	Stage IIIC	Pelvic radiotherapy** Brachytherapy	Peritoneum + pelvis	Chemotherapy	Progression

*: according to the FIGO 1988 staging system. **: the time interval between surgery and radiotherapy is 6 months. †: no evidence of disease at last follow up.

patients have relapsed. Most of these relapses were located in the peritoneum (3/4) followed by the pelvis (2/4). The abdomen and pelvis were also found to be the first sites of relapse in other series [2, 13]. One patient with pelvic recurrence was treated with surgery only for the primitive disease despite the tumour extension outside the uterus. One of our patients recurred within the radiation field. This can be explained by the long delay between surgery and radiation therapy (6 months). The other distant recurrences were outside the radiation field. All these recurrences appeared during the first year after surgery. There was no standard treatment for the pelvic and/or abdominal recurrences. Two of our patients with pelvic and abdominal recurrences had disease progression despite surgery, radiation therapy and chemotherapy, respectively.

Unlike vaginal recurrences which can be managed by local resection and brachytherapy and / or pelvic radiation therapy, the outcome of pelvic and distant recurrences remains very poor [2]. Distant recurrences were observed in other series despite adjuvant pelvic radiation therapy in stage IB and II CCC of the endometrium [7]. Lymphovascular invasion and surgical stage are independent risk factors of recurrences [6, 7, 11].

Survival in CCC seems to be similar to G3 if stratified by equivalent stage [4, 8]. 5-year survival rates for CCC and uterine papillary serous carcinoma are 60% for stage I, 50% for stage II and 5 to 10% for advanced stages [11]. Lymphovascular invasion, age (> 60 years) and stage are predictive factors of survival [3, 4, 6, 7]. The high frequency of advanced stages and the high rate of early recurrences in the peritoneum suggest an aggressive tumour biology and a poorer response rate to conventional treatments. Some authors propose an adjuvant

treatment with whole abdominal radiotherapy. However, recurrences after adjuvant whole abdominal radiotherapy are observed in 30 to 67% [14, 15]. Stewart et al. found that half of the recurrences were located within the irradiated field [14]. Distant metastases after adjuvant radiotherapy without chemotherapy are found in 14 % in stage I and 35 % in stage II [7]. The authors of the latter study recommend an adjuvant treatment associating a systemic treatment with chemotherapy to radiotherapy for stages IB-C and II with lymphovascular invasion and for stage III.

Stage IA should not be given an adjuvant treatment [2, 7]. For advanced stages, cytoreductive surgery is necessary. This can be illustrated by the results of a GOG study where median progression free survival in patients left with a residual tumor was 4.5 months only, despite a whole abdominal radiation [6]. Thomas et al. observed an improvement in progression free survival and overall survival in patients with no visible residual disease after cytoreduction [16].

CONCLUSION

CCC carcinoma of the endometrium is characterised by frequent extrauterine and distant metastases at diagnosis. A complete surgical staging is necessary before adjuvant treatment decision. Local and distant recurrences are frequent and occur during the first year after surgery. Adjuvant treatment combining radiotherapy and chemotherapy are to be investigated to limit locoregional and distant recurrences which have a poor outcome.

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