EJGO European Journal of Gynaecological Oncology

Clear cell endometrial cancer: a CTF multicentre Italian study

T. Maggino[1], P. Zola[2], E. Sartori[3], L. Fuso[4], C. Papadakis[1], A. Gadducci[5], F. Landoni[6]

[1] Department of Obstetrics and Gynecology, Dell'Angelo Hospital, Venice
[2] Department of Gynecologic Oncology, University of Turin, Turin; [3] Obstetrics and Gynecology Institute, University of Brescia, Brescia
[4] Department of Obstetrics and Gynecology, Mauriziano Hospital, Turin; [5] Obstetrics and Gynecology Institute, University of Pisa, Pisa
[6] Gynecological Oncology European Institute of Oncology, Milan (Italy)

Summary

Endometrial clear cell carcinoma (CCC) is a rare entity and only accounts for 1-6% of all endometrial cancers. CCC is considered an aggressive subtype of endometrial cancer with worse prognosis compared with type I cancer and more frequent relapses at distant and extrapelvic sites. These characteristics require specific treatment modalities, but rarity of the disease does not allow to identify evidence based indications for therapies. Objective of the present study is to analyse a series of cases treated in a multicentre Italian setting. *Materials and Methods:* Sixty-five endometrial CCC were treated in the period 1990-2010 in the participating institutions. Slides of the pathological specimens were reviewed by a single pathologist of each institution and debatable cases were collegially reviewed. Clinical records were collected by a common database. Demographic, surgical pathological, and follow-up data were registered. *Results:* All patients received primary surgery. Stage of disease according FIGO 2009 was as follow: 1a: 16.9%, 1b: 35.4%, 2: 9.2%, 3a: 9.2%, 3b: 3.1%, 3c: 16.9%, 4a: 3.1%, and 4b: 6.1%. Adjuvant post-operative treatment was adopted in 53.8% of cases. A relapse was detected in 29.2% of cases with a majority of extrapelvic sites (68.4%). Five-year survival rate was significantly related to stage of disease with an excellent prognosis for Stage Ia e Ib disease with a complete staging. In these cases adjuvant treatment does not show significant improvement of survival. Relapsed cases show a response rate to treatment in 26% of cases (predominantly chemotherapy). *Conclusion:* CCC requires extensive surgical staging. Stage I disease completely staged does not require adjuvant therapy. More advanced stages require adjuvant chemotherapy.

Key words: Clear cell endometrial cancer; Post-treatment relapses; Clinical outcome.

Introduction

Uterine cancer is the most common gynaecological malignancy in Western countries. It is estimated that in the United States 47,130 new diagnosis were reported in 2012 [1]. In Italy 7.465 new cases were registered in 2011 by the Consortium of the Tumour Registry (AIRTUM) [2]. The vast majority of uterine cancers originate from the endometrium and only a limited number, about 8%, are sarcomas. Endometrial cancers include endometrioid cancer (Type 1) and non-endometrioid cancer (Type 2). Type 2 endometrial cancers include serous papillary carcinomas (UPSC) and clear cell carcinomas (CCC), accounting respectively 7-10% [3, 4] and 1-6% of all endometrial carcinomas [4-6].

Clear cell tumours, like UPSC, are an aggressive subtype of endometrial carcinomas with a tendency to relapse outside the pelvis. Both CCC and UPSC develop more frequently in post-menopausal women but are not associated with estrogen use, obesity, and are more common in black women [7].

Survival of women with CCC is generally worse than those with low-grade but similar to high-grade endometrioid tumors [8]. CCC is more likely to present with extrauterine spread compared to low-grade endometrioid histology [9, 10].

Due to its rarity, it has been difficult to study CCC in controlled clinical trials, making the development of evidence-based management challenging [5].

The aims of the present study are to investigate patterns of care, treatment failures, and survival rates in patients treated for endometrial CCC in a multicentre retrospective Italian study.

Materials and Methods

Clinical records of endometrial CCC patients were treated in the period 1990-2010 in five Italian institutions (Obstetrics and Gynecology, Institute University of Brescia, Pisa, Turin, European Institute of Oncology-Milan, and Venice Mestre Hospital) where reviewed. Significant information concerning demographic, clinical, surgical, pathological, and data derived from follow-up programs where collected in a common database. Sixty-five cases of CCC were collected after a pathological revision of histological material that had been performed by a single pathologist in the local institution and subsequent collegial revision of the slides for questionable cases. All patients received the treatment in the participating institutions and surgery was the primary treatment in all cases.

The patients were restaged retrospectively according to International Federation of Gynaecology and Obstetrics (FIGO) classification 2009. Post-operative treatment was given according to local protocols and was established on the basis of pathological

Revised manuscript accepted for publication April 3, 2015

Table 1. — *Patients characteristics at diagnosis (65 cases).*

Age (yrs), Median (range)	64 (± 10.7)
Parity n (%)	
Unknown	2
Nulliparous	11 (17.46)
Parous	52 (82.54)
Diabetes (%)	
Unknown	1
Yes	4 (6.25)
Hypertension (%)	
Unknown	1
Yes	26 (40.62)
Menopause	57 (87.69)
HRT	
Unknown	2/57 (3.51)
No	51/57 (89.47)
Yes	4/57 (7.02)
Biopsy *vs.* definitive histology n (%)	
Agreement	35 (53.85)
Disagreement	20 (30.77)
Unknown	10 (15.38)
Preoperative Ca125	
Unknown	17
Positive (>35 UI)	11/48 (22.92)

findings, age, and general conditions. All patients were followed-up until they died or until December 2011. The medium follow-up was 133 months (range 6-216 months).

Statistical methods

The SAS statistical package (release 8.2) was used for computations. The time from surgery to death or last observation was defined as overall survival. The cumulative probability of survival was estimated by the products-limit method. The long-rank R test was used to compare the homogeneity of survival functions across strata defined by categories of prognostic variables.

Results

Patients characteristics at presentation are summarized in Table 1. All the patients received primary surgery, 62 patients by laparotomy (95.3%) and three by laparoscopy (4.6%).

Type of hysterectomy was: standard Type I (Piver and Rutledge) in 48 cases (73.85%) and Type II in 17 cases (26.15%). Additional surgical procedures to hysterectomy are listed in Table 2. Among the 55 cases in which the histotype was available for revision, both in biopsy and definitive surgical specimen, an agreement was registered in 63.6% of cases. Lymph-node metastases were observed in seven out of 51 cases submitted to lymphadenectomy (13.7%).

Tumor stage according to FIGO classification 2009 was as follows: Stage 1a: 11 (16.9%), Stage 1b: 23 (35.4), Stage 2: six (9.2%), Stage 3a: six (9.2%), Stage 3b: two (3.1%), Stage 3c: 11 (16.9%), Stage 4a: two (3.1%), and Stage 4b: four (6.1%). Residual tumour after surgery was described in six patients (9.2%). Adjuvant postoperative treatment was adapted in 35 patients (53.8%).

Table 2. — *Additional surgical procedures during total hysterectomy (65 cases).*

	n.	%
Bilateral salpingo-oophorectomy	62	95.4
Pelvic lymphadenectomy	51	78.5
Para-aortic lymphadenectomy	19	29.2
Omentectomy	28	43.0
Peritoneal biopsies	12	18.5
Appendectomy	9	13.8
Bowel resection	2	3.0
Peritoneal washing	52	80.0

Table 3. — *Patient characteristics at recurrence (19 cases).*

	n.	%
Presence of symptoms		
Yes	5	26.3
No	14	73.7
Sites of recurrence		
Vaginal	5	26.3
Pelvic	1	5.3
Peritoneal	4	21.0
Distant	5	26.3
Multiple	4	21.0
Positive findings at the time of recurrence*		
Clinical	9	47.3
Abnormal imaging	15	78.9
CA125 increase	4	21.0

*Some patients may have presented multiple positivity.

Adjuvant treatment was radiotherapy (external beam ± brachytherapy) in seven out of 35 patients (20.0%), chemotherapy in 16 patients (45.7%), and radio-chemotherapy in 12 patients (35.6%). Chemotherapy regimens consisted in combination of carboplatin-taxol in 14 patients, taxol-epirubicin-platinum in ten patients, and single carboplatin in four patients.

A relapse was detected during the follow up in 19 patients (29.2%). Characteristics of recurrences are detailed in Table 3. The majority of recurrences were extra-pelvic (13 out of 19: 68.4%) at peritoneal, distant or multiple sites. In 47.3% of cases the relapse was clinically detectable but only in 28.3% were symptomatic.

The five-year survival rate was significantly related to the disease stage. Early stages (Ia and Ib) had an excellent prognosis compared with all other stages (Figure 1). Among patients with Stage I and II with complete surgery, the survival rate did not show a significant difference according to different types of adjuvant treatment and no treatment at all (Figure 2).

Time of relapses showed that the events occurred mainly during the 36th month following primary treatment (Figure 3). Therapy at recurrence (19 cases) was radiotherapy in five (26.3%) cases, chemotherapy in ten (52.6%) cases, radiochemotherapy in three (15.7%) cases, and hormonal therapy in one case (5.2%).

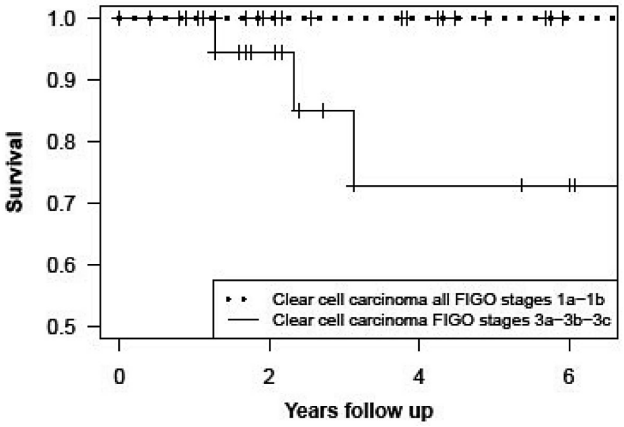

Figure 1. — Clear cell carcinoma: survival rate by stage of disease (FIGO 2009).

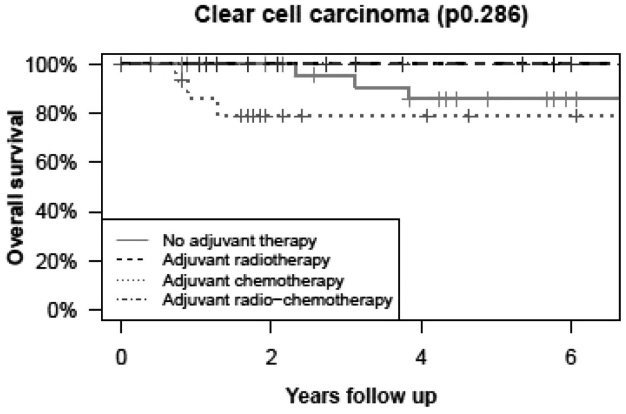

Figure 2. — Clear cell carcinoma: survival rate by type of adjuvant treatment (Stages I-II).

Response rate in relapsed cases after radiological assessment was: complete response in four cases (21.0%), partial response in one (5.3%) case, stable disease in one (5.3%) case, and progression of the disease in 12 cases (63.1%).

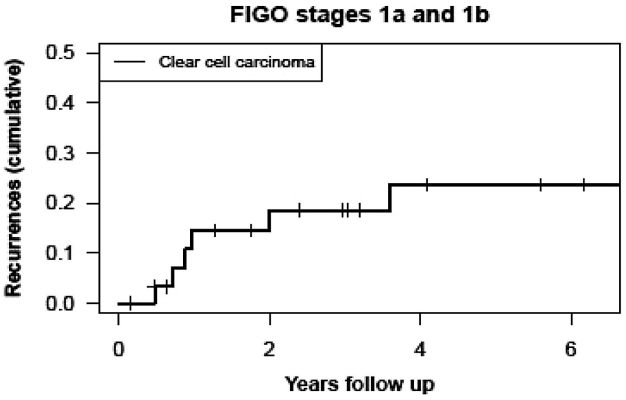

Figure 3. — Clear cell carcinoma: time of relapse.

Discussion

Endometrial CCC is a rare entity and only accounts for 1-6% of all endometrial cancer (11-13). The present case series confirmed that CCC is rarely associated with diabetes, hypertension, and use of hormonal replacement therapy as usually described for common endometrial cancer [3, 4, 7]. Preoperative biopsies are reliable to detect the definitive histotype in the majority of cases (35 out of 55 evaluable cases in this series: 63.6%) which reflect data referred by other studies [14].

Comprehensive surgical staging is advocated in endometrial CCC as subclinical extrauterine spread is frequent [15]. In the present series, 52.3% of patients were confirmed to have a Stage I disease after intensive surgical staging. Among patients with more advanced disease (25 cases with Stages III and IV), 19 (76%) had a complete resection of the disease.

Based on the limited available evidence and the present experience, it may be concluded that optimal cytoreduction of metastatic disease appears to be feasible and of benefit in patients with this disease [5].

The impact of clear cell histology in comparison to other high-risk endometrial cancer histologies such as UPSC is controversial [9, 7, 16].

The present series confirmed that Stage I CCC after comprehensive surgical staging had an excellent prognosis significantly better of what described in the present authors' recent report on UPSC treated in the same period in their institutions [17]; this is in agreement with the series described by Thomas *et al.* (15) in which patients with true Stage I disease after intensive surgical staging and without adjuvant treatment showed no hematologic, lymphatic or peritoneal failures at median follow up of 44 months. Since UPSC and CCC are thought to have poorer survival than type I endometrial cancer, presumably due to early metastatic occurrence, it is important to evaluate this lesions in light of those who are intensively surgically staged [9]. This consideration has an important role in the evaluation of debatable results of adjuvant therapy in Stage I disease and in general in CCC [5, 9, 18, 19].

All the studies reported in literature are small, retrospective, with heterogeneity of patients including various types of high-risk endometrial cancer and treated with various modalities of radiation therapy. The present results confirm the indication of various studies [5, 9, 15] that adjuvant pelvic radiotherapy does not appear to have a beneficial effect either in Stage I correctly staged CCC, due to the good prognosis of this disease, nor in high-risk apparent Stage I disease due to the sites of relapse which account for 68.4% of extrapelvic diseases. These assess-

ments induced to consider chemotherapy as post-surgical adjuvant treatment in CCC.

Small and retrospective studies have suggested a potential role of adjuvant administration of platinum-based chemotherapy in this setting [20-23]. All these studies included a heterogeneous group of patients with endometrial cancer including CC type at various stages of disease or at relapse. Based on the available data, the combination of carboplatin and paclitaxel ± doxorubicin appears to have efficacy in the treatment of women with advanced endometrial CCC and in relapsed patients and should be considered at present the schedule of reference [5].

In conclusion: endometrial CCC has a worse prognosis compared to type I histology due to the high percentage of extrauterine occult diffusion at presentation. This implies the need of intensive surgical staging aiming to identify correctly Stage I disease, which does not require adjuvant treatment; on the other hand, more advanced disease requires adjuvant treatment due to the high percentage of recurrent disease also in extrapelvic sites. This implies the need of administering combination chemotherapy including carboplatinum and placlitaxel.

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Address reprint requests to:
T. MAGGINO, M.D.
Department of Obstetrics and Gynecology
Dell'Angelo Hospital
Via Paccagnella, 11
30174 Zelarino-Venice (Italy)
e-mail: tiziano.maggino@ulss12.ve.it