Outcome of uterine clear cell carcinomas compared to endometrioid carcinomas and poorly-differentiated endometrioid carcinomas

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Summary

Objectives: Our aim was to compare the survival between patients with clear cell carcinoma (CC) and patients with endometrioid carcinoma (EC). *Methods:* Through the population-based Geneva Cancer Registry, we identified 1,380 resident women diagnosed with uterine cancer between 1970 and 2000. We excluded those with papillary serous endometrial carcinoma and uterine sarcomas. We categorized patients as CC (n = 32, 2.8%) or EC (n = 1,145, 97.2%). Uterine cancer-specific survival rates were calculated by Kaplan-Meier analysis. We used Cox proportional hazards analysis to compare uterine cancer mortality risks between groups, and adjusted these risks for other prognostic factors. *Results:* CC patients presented with a more advanced stage at diagnosis than EC patients (p = 0.002). Compared to women with EC, women with CC had a significantly greater risk of dying from their disease (hazard ratio [HR] 2.9, 95% confidence interval (95% CI) 1.7-4.9). After adjustment for age, stage and adjuvant chemotherapy, the risk of dying from uterine cancer was still significantly higher for CC patients (HR 2.0, 95% CI 1.2-3.4). By univariate analysis, the risk of dying of endometrial cancer was not significantly higher in CC patients than in patients with poorly-differentiated EC (HR 1.3, 95% CI 0.7-2.3). *Conclusion:* This population-based investigation shows that patients with CC have a poorer outcome than those with EC. Studies to determine the role of adjuvant treatment in CC patients are needed.

Key words: Adjuvant chemotherapy; Endometrioid carcinoma; Clear cell carcinoma; Survival.

Introduction

Uterine clear cell carcinoma (CC) is recognized as a distinct histological variant of endometrial carcinoma, and accounts for 2-4% of all endometrial adenocarcinomas [1-3]. Only a few series have reported on the management and clinical outcome of CC, and most of them regrouped CC with other potentially high-risk histologies such as uterine papillary serous carcinoma [3-10]. Moreover, most studies included a small number of patients with limited follow-up.

The prognosis of CC is still controversial as it is unclear if the worse prognosis is due to a more advanced stage at diagnosis or a more aggressive histological cell type. Giri et al. have suggested a favourable outcome in patients with clear-cell tumours, similar to classical adenocarcinomas in theirs behaviour and response to therapy [11]. Other authors observed that CC is an aggressive carcinoma with a poor outcome similar to uterine papillary serous carcinoma [1, 3, 8, 11]. One of the reasons for the poor prognosis of CC is that it generally presents at a more advanced stage at diagnosis than other uterine cancers. However, when analysing different stages separately, it is still not clear if CC behaves more aggressively than other endometrial cancers. Therefore, it is difficult to determine if CC patients should be considered as a high risk and if they should be treated in a different manner than patients with endometrioid carcinoma (EC).

In this population-based study, we aimed to elucidate whether CC is really associated with a worse outcome, while taking other prognostic factors into account.

Materials and Methods

The current investigation was performed with information from the population-based cancer registry of the Swiss canton of Geneva (approximately 420,000 inhabitants). The registry records of all incident cases of malignant neoplasms occurring in the Canton's resident population were accessed. Information was collected from various sources (i.e., pathology reports, medical files from public hospitals and private physicians), and is considered very accurate, confirmed by the very low percentage (< 1%) of cases recorded from death certificates only [12].

Recorded data included socio-demographic information, diagnostic circumstances, modalities of diagnostic assessment, and tumour characteristics (coded according to the International Classification of Diseases for Oncology) [13]. The cause of death was established from clinical records according to the World Health Organisation's classification. In addition to passive follow-up (routine examination of death certificates and hospital records), active follow-up was performed routinely each year through the files of the Cantonal Population Office, which is in charge of registration of the resident population. The Geneva Cancer Registry regularly assesses survival. The incidence index date refers to the date of confirmation of diagnosis

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or to the date of hospitalisation if it precedes the diagnosis and is related to the disease. Active follow-up was last done in December 2004.

We identified all 1,380 patients diagnosed with uterine cancer between January 1970 and December 2000, who were residents in the Swiss canton of Geneva. We excluded patients with uterine sarcoma (n = 127), uterine papillary serous carcinoma (n = 76) or endometrial cancer diagnosed at autopsy (n = 17). The study finally included 1,160 patients.

Disease stages were recorded according to the 1988 International Federation of Gynaecology and Obstetrics (FIGO) staging system: Stage I, tumour confined to the uterus; Stage II, tumour invading the cervix; Stage III-IV tumour associated with positive peritoneal cytology or with macroscopic or histological involvement of the serosa or adnexa or tumour invading the vagina, mucosa of the bladder, bowel, regional lymph node or distant metastases. Tumour grade was only coded for EC patients, because FIGO tumour grading is not applicable to CC; these tumours are generally considered as high-grade tumours [6]. We classified differentiation as good (grade 1), moderate (grade 2), poor (grade 3), or unknown. Information on grade was only available after 1985. Types of surgery included hysterectomy (with or without salpingo-oophorectomy) and no surgery. Radiotherapy and chemotherapy were categorized as yes *versus* no.

Statistical methods: We compared women with CC or EC in terms of age, stage and treatment by the chi-square test for heterogeneity. Five- and 10-year disease-specific survival rates were calculated according the actuarial method, taking only deaths from uterine cancer as terminal events. Cox's proportional hazard analysis was used to compare the risk of dying from endometrial cancer between CC and EC patients adjusted for all other prognostic factors. Subgroup analysis was then performed in which we compared survival and endometrial cancer mortality risks between CC patients and patients with poorly-differentiated EC. Statistical analysis was carried out with SPSS (version 11.5) and differences were considered statistically significant if the 2-sided p value was < 0.05.

Results

Of the 1,160 patients included in the study, 32 (2.8%) had CC. The characteristics of the 32 CC and 1,128 EC patients are summarised in Table 1. Patients with CC were somewhat older than EC patients (70 *versus* 66 years, respectively, p = 0.052). Patients with CC had a more advanced stage at diagnosis (p < 0.001). Only 52% had Stage I disease at diagnosis, whereas 77% of EC patients had Stage I. Twenty-seven percent of CC patients had disease outside the uterus (Stages III-IV) *versus* 16% of EC patients. Of the EC patients with valid information on tumour grade, 445 (59%) had well-differentiated tumours, 193 (26%) moderately-differentiated tumours, and 116 (15%), had poorly- or undifferentiated tumours.

There were no significant differences in surgical treatment between CC and EC patients. Six (19%) CC patients and 134 (12%) EC patients (difference not significant) did not undergo surgery. Four (67%) CC patients and 58 (43%) EC patients who did not have surgery presented disease spread beyond the uterus (Stage III or IV) at the time of diagnosis. Also, patients who did not have surgery were significantly older than operated women: mean age of the unoperated CC and EC patients was 75 years and 80 years, respectively.

Table 1. — *Characteristics of uterine cancer patients according to histology (clear cell vs endometrioid carcinoma).*

	Clear cell carcinoma n = 32 (2.8%)	Endometrioid carcinoma n = 1,128 (97.2%)	p-value*
Mean age at diagnosis (years)	70.3	66.5	0.052**
Differentiation			
Good	–***	445 (59%)	
Moderate	–	193 (26%)	
Poor/undifferentiated	–	116 (15%)	
Unknown	–	374 (-)	
FIGO Stage			
I	15 (52%)	742 (77%)	< 0.001
II	6 (21%)	75 (8%)	
III	1 (3%)	73 (7%)	
IV	7 (24%)	78 (8%)	
Unknown	3 (–)	160 (–)	
Surgical procedure			
Hysterectomy/BSO ± LN	26 (81%)	981 (88%)	0.608
No surgery	6 (19%)	134 (12%)	
Unknown	–	13 (–)	
Radiotherapy			
Yes	17 (53%)	623 (59%)	0.224
No	15 (47%)	425 (41%)	
Unknown	–	80 (–)	
Adjuvant chemotherapy			
Yes	3 (9%)	36 (13%)	0.056
No	29 (91%)	1,092 (97%)	

*p-value of the chi-square test for heterogeneity; **t-test; ***tumour grading was not applicable for clear cell carcinomas; BSO = bilateral salpingo-oophorectomy; LN = lymph node dissection.

Radiotherapy was equally frequently administered to CC patients as to EC patients (53 vs 59%, respectively). Adjuvant chemotherapy was, as expected, uncommon for both CC and EC patients (9% vs 13% respectively).

Figure 1 shows the disease-specific survival curves for CC and EC patients. Table 2 summarises the 5-year disease-specific survival rates for CC versus EC patients, for all patients together and for Stages I and II and Stages III and IV, separately. Important survival differences were observed. Overall, the 5-year disease-specific survival for CC patients was 50% vs 80% for EC patients. For patients with Stage I and II disease only, the survival differences persisted (5-year survival of 64% for CC patients vs 88% for EC patients). Also, for Stages III and IV, the survival difference between CC and EC persisted, but the number of CC patients in this category was rather low.

Patients with CC had a 3-fold increased risk of dying from endometrial cancer compared to EC patients (unadjusted hazard ratio [HR] 2.9, 95% confidence interval [CI]: 1.7-4.9) (Table 2). After adjustment for age and stage, the risk of dying from endometrial cancer was still significantly increased for CC patients (HR 2.0, 95% CI: 1.2-3.4). Further adjustment for treatment did not modify the results.

In subgroup analysis, we compared the characteristics, survival and mortality risks of CC patients and patients with poorly-differentiated EC. There was no significant difference in age between CC and poorly-differentiated EC patients (70.3 vs 67.4 years, respectively). Both groups had comparable stage distribution (25% of CC

and 27% of poorly-differentiated EC patients had Stage III or IV disease). Nineteen percent of CC versus 10% of poorly-differentiated EC patients did not undergo surgery (p = 0.25). CC patients less often received radiotherapy (53% vs 72%, p = 0.057). No differences in the use of adjuvant chemotherapy were observed.

The 5-year disease-specific survival of patients with poorly-differentiated EC was 58% (95% CI: 49%-67%), not significantly different from that of CC patients, 50% (95% CI: 32%-68%). The corresponding mortality risks are presented in Table 3. By univariate analysis, the risk of dying from endometrial cancer was not significantly higher in CC patients than in patients with poorly-differentiated EC (HR 1.3, 95% CI: 0.7-2.3). Adjustment for age and stage resulted in a HR of 1.1 (95% CI: 0.6-2.0). Further adjustment for therapy did not modify the results.

Table 2. — *Five-year endometrial cancer survival according to histology and FIGO stage*.

FIGO stage	Clear cell carcinoma			Endometrioid carcinoma		
	n	*ND	5-yr DSS (95% CI)	n	*ND	5-yr DSS (95% CI)
All stages	32	15	50% (32-68%)	1,128	208	81% (79-83%)
Stages I-II	21	7	64% (42-86%)	817	91	88% (86-90%)
Stages III-IV	8	6	25% (0-55%)	151	84	40% (32-48%)

*Number of deaths at 5 years; DSS = disease-specific survival.

Table 3. — *Effect of adjustment for age and stage on the risk of dying of endometrial cancer for patients with uterine clear cell cancer (CC) compared to all patients with endometrioid carcinoma (EC) and to patients with poorly differentiated EC*.

All patients	Unadjusted HR (95% CI)	HR (95% CI) adjusted for age and stage
EC	1 (reference)	1 (reference)
CC	2.9 (1.7-4.9)	2.0 (1.2-3.4)
CC versus poorly-differentiated EC		
EC	1 (reference)	1 (reference)
CC	1.3 (0.7-2.3)	1.1 (0.6-2.0)

HR = hazard ratio.

Discussion

CC is a well-established histopathological entity that comprises about 2-4% of endometrial carcinomas [1-3]. In our study, it represented 2.8% of all endometrial cancers, which is consistent with the three largest reports published in the literature, where the observed incidence rate was 3-3.1% [1, 2, 6].

A literature review revealed that the prognosis of this type of uterine cancer is still regarded as somewhat controversial, though many investigations suggest that it is an aggressive disease [1, 2, 8]. As a result, the optimal management of these patients remains undefined. The aim of our work was to compare the outcome of CC with EC in a population-based study after exclusion of uterine serous papillary carcinoma and uterine sarcomas which are well-known high-risk uterine cancers.

In our series, the uterine cancers were diagnosed at a later stage of disease compared to EC. High rates of recurrence have been observed in patients with CC, even in those with early-stage disease. The disease-specific

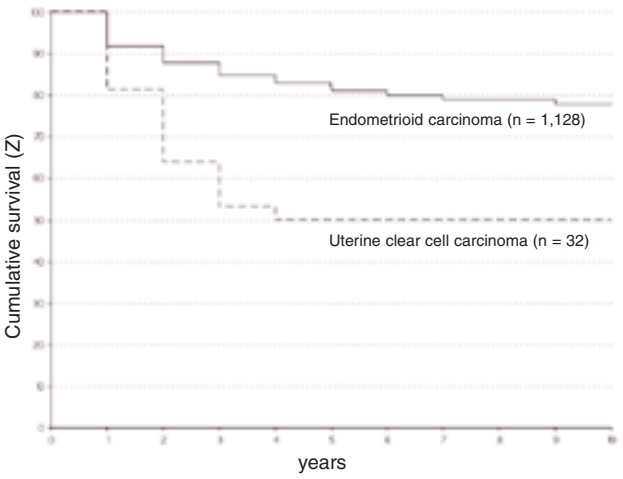

Figure 1. — Uterine cancer survival by histology (clear cell versus non-clear cell).
Note: Survival curves are derived from life table analysis and are not adjusted for other prognostic variables.

survival for Stages I-II was poorer for CC compared to EC (64% vs 88%). This is in agreement with most previous reports where the outcome of CC patients is generally inferior to that of endometrial cancer patients. However, ranges reported in the literature for 5-year survival rates in CC patients are large, between 59% and 72% for Stages I-II and 38-64% for Stages I-IV [2, 3, 5, 6, 14, 15]. The large difference in survival may be attributed to the fact that most published works have included small series recruited over a long period with possible variation in treatment modalities.

In our study, when only poorly-differentiated EC was compared to CC, a similar percentage of patients had extrauterine disease and the survival rate appeared to be similar between the two groups. This result points to a similar aggressive behaviour of CC and poorly-differentiated EC, in agreement with two previous studies, but the small sample size of these series limits the statistical power of the analysis and may have failed to show a difference [1, 2]. A recent large, population-based investigation has shown that CC and uterine papillary serous carcinoma have a worse outcome than grade 3 EC [2].

A shortcoming of our study was that surgical staging was performed at the discretion of the physicians (non-standardised surgical approach). The current trend is that CC needs comprehensive surgical staging similar to ovarian cancer, including peritoneal washing, omental- and peritoneal-blind biopsies, and pelvic and paraaortic lymphadenectomy. Therefore, the frequency of extrauterine metastasis in CC (and in EC) could be underestimated. On the other hand, our study is a population-based selection with long-term follow-up (median follow-up 8 years).

In conclusion, CC comprises a small percentage of endometrial carcinomas, presents with older age, advanced stage at diagnosis, and is associated with poor outcome. In the future, adjuvant chemotherapy and radio-

therapy need to be explored in patients with early-stage disease in an attempt to improve disease outcome. However, due to disease rareness, it will not be easy to recruit patients in an appropriately powered and randomised study, and only multicentre trials will be able to give a final response.

References

[1] Creasman W.T., Kohler M.F., Odicino F., Maisonneuve P., Boyle P.: "Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium". *Gynecol. Oncol.,* 2004, *95,* 593.

[2] Hamilton C.A., Cheung M.K., Osann K., Chen L., Teng N.N., Longacre T.A. *et al.*: "Uterine papillary serous and clear cell carcinomas predict for poorer survival compared to grade 3 endometrioid corpus cancers". *Br. J. Cancer*, 2006, *13,* 642.

[3] Cirisano F.D. Jr, Robboy S.J., Dodge R.K., Bentley R.C., Krigman H.R., Synan I.S. *et al.*: "The outcome of Stage I-II clinically and surgically staged papillary serous and clear cell endometrial cancers when compared with EC". *Gynecol. Oncol.,* 2000, *77*, 55.

[4] Webb G.A., Lagios M.D.: "Clear cell carcinoma of the endometrium". *Am. J. Obstet. Gynecol.*, 1987, *156,* 1486.

[5] Carcangiu M.L., Chambers J.T.: "Early pathologic stage clear cell carcinoma and uterine papillary serous carcinoma of the endometrium: comparison of clinicopathologic features and survival". *Int. J. Gynecol. Pathol.*, 1995, *14,* 30.

[6] Abeler V.M., Vergote I.B., Kjorstad K.E., Trope C.G.: "Clear cell carcinoma of the endometrium. Prognosis and metastatic pattern". *Cancer,* 1996, *78*, 1740.

[7] Photopulos G.J., Carney C.N., Edelman D.A., Hughes R.R., Fowler W.C. Jr, Walton L.A.: "Clear cell carcinoma of the endometrium". *Cancer*, 1979, *43*, 1448.

[8] Malpica A., Tornos C., Burke T.W., Silva E.G. *et al.*: "Low-stage clear-cell carcinoma of the endometrium". *Am. J. Surg. Pathol.*, 1995, *19,* 769.

[9] Murphy K.T., Rotmensch J., Yamada S.D., Mundt A.J.: "Outcome and patterns of failure in pathologic Stages I-IV clear-cell carcinoma of the endometrium: implications for adjuvant radiation therapy". *Int. J. Rad. Oncol. Biol. Phys.*, 2003, *55*, 1272.

[10] Alektiar K.M., McKee A., Lin O., Venkatraman E., Zelefsky M.J., McKee B. *et al.*: "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. Rad. Oncol. Biol. Phys.,* 2002, *54,* 79.

[11] Giri P.G., Schneider V., Belgrad R.: "Clear cell carcinoma of the endometrium: An uncommon entity with a favorable prognosis". *Int. J. Radiat. Oncol. Biol. Phys.*, 1981, *7,* 1383.

[12] Bouchardy C.: "Cancer Incidence in Five Continents". Vol VII. Lyon, France, International Agency for Research on Cancer, 1997, 666.

[13] WHO, ICD-O International Classification of Diseases for Oncology. 1976.

[14] Trope C., Kristensen G.B., Abeler V.M.: "Clear-cell and papillary serous cancer: treatment options". *Best. Pract. Res. Clin. Obstet. Gynaecol.*, 2001, *15,* 433.

[15] Kurman R.J., Scully R.E.: "Clear cell carcinoma of the endometrium: an analysis of 21 cases". *Cancer*, 1976, *37,* 872.

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