Chapter 4

Clear cell carcinoma compared to serous carcinoma in early ovarian cancer: same prognosis in a large randomized trial

P.J.Timmers
A.H. Zwinderman
I. Teodorovic
I. Vergote
J.B. Trimbos

Int J Gynecol Cancer 2009; 19(1): 89-93

ABSTRACT

Background*:* An analysis was performed comparing survival of patients with clear cell carcinoma (CCC) to patients with serous adenocarcinoma (SAC) in early ovarian cancer. Furthermore, a literature search was done in order to clarify the clinical and histopathological features of clear cell tumors of the ovary.

Methods: Between November 1990 and March 2000, 448 patients with ovarian cancer FIGO stages I-IIa were enrolled in the EORTC ACTION trial, a randomized study comparing adjuvant chemotherapy to observation after surgical treatment in patients with early ovarian cancer. Patients in the chemotherapy group received platinum-based chemotherapy for at least 4 courses.

Results: 63 patients with clear cell carcinoma (14.1%) were compared to 156 patients with serous tumors (34.8%). The median age was 54 years in the CCC group and 56 years in the SAC group. The treatment arms were well balanced between both groups. A significant difference was found in the FIGO stage Ic with capsule rupture, 28/63 (44.4%) in the CCC patients and 29/156 (18.6%) in the SAC patients ($P < 0.001$). Recurrences occured in 25% of the patients and this was similar between the CCC group and the SAC group. No significant difference was found in overall survival (OS) between patients with clear cell carcinoma and serous carcinoma in both treatment arms together. In the observation arm the 5-year disease-free survival (DFS) was 71% in the CCC group versus 61% in the SAC group, whereas in the chemotherapy arm the 5-year DFS was higher in the SAC group compared to the CCC group (78% versus 60%). Both differences were not statistically significant.

Conclusions: The present study showed no worse prognosis in patients with clear cell carcinoma as compared to patients with serous carcinoma in early ovarian cancer. Poorer overall survival in the CCC group receiving adjuvant chemotherapy in relation to the SAC group might be explained by possible chemoresistance of clear cell tumors.

INTRODUCTION

Clear cell carcinoma (CCC) of the ovary is generally considered to be a tumor with poor prognosis and distinct clinical characteristics compared to other epithelial ovarian cancers [1]. It is often associated with endometriosis and nulliparity is frequently described [2,3]. The incidence of CCC various from 4 to 12% of all ovarian cancers. These tumors were first described by Pelham in 1899 as hypernephroma of the ovary in view of their resemblance to renal cell carcinoma. Later, terms as mesonephromas [4] and hypernephroid carcinoma of the ovary were used. In 1944, Saphir and Lackner [5] were the first authors who suggested the term clear cell adenocarcinoma. Different hypotheses were made indicating these tumors to be from germ cell origin of the endodermal sinus and those who refuted this theory suggested a Müllerian origin. The latter is now generally accepted as the nature of this tumor. Histopathologic findings of CCC consist of four cell types, typical clear or hobnail, eosinophilic and flattened cells in a papillary, solid, or tubulocystic architectural pattern. Since the World Health Organization in 1973 defined CCC as a separate histologic cell type [6] a number of studies have been performed to clarify the behaviour of this tumor. Several studies have shown a high incidence of FIGO stage I tumors [7-13], poorer prognosis compared to serous adenocarcinomas of the ovary [10,14,15] and resistance to platinum-based chemotherapy [1,13,16]. Most of these trials are retrospective cohort studies and often lack a sufficient number of patients.

The purpose of the current study was to compare clinical characteristics, response to platinum-based chemotherapy and survival of patients with clear cell carcinoma (CCC) versus serous adenocarcinoma (SAC) randomized in a large multicenter trial of early ovarian cancer.

PATIENTS AND METHODS

Between November 1990 and March 2000, 448 patients were entered in the EORTC ACTION trial, a randomized clinical study on the role of platinum containing adjuvant chemotherapy in early ovarian cancer FIGO stages Ia and Ib (grade II-III), stages Ic and IIa (grade I-III) and all stages I-IIa clear cell epithelial cancer of the ovary. Randomization between platinum containing chemotherapy and no adjuvant treatment was performed after surgical treatment consisting of total abdominal hysterectomy and bilateral salping-oophorectomy (TAH plus BSO) and staging. Patients randomized to receive chemotherapy were treated within six weeks after surgery for at least four consecutive

courses. In the observation arm no further treatment was given until a histologically or cytologically proven relapse. The same regimen of chemotherapy according to the institution had to be given in case of recurrent disease in the observation arm as in the adjuvant chemotherapy group. Analysis of the results was on an intention-to-treat basis. A detailed description of the design of the ACTION trial is given in three recently published papers by Trimbos et al. [17,18,19].

Analysis

Overall survival and disease-free survival times were defined as the period between randomization and death or relapse. Disease-free and overall survival curves were generated using the method of Kaplan-Meier [20]. Comparisons of the survival distributions were made with the log-rank test. The chi-square or Fisher's exact test were used to evaluate differences in proportions. The Statistical Package for Social Science (SPSS) was used for statistical analysis. Significance was defined as a *P*-value < 0.05.

Furthermore a review of the literature was done in order to evaluate the prognosis of clear cell carcinoma in early ovarian cancer. Papers were selected from journals in English language literature by a Pubmed search over the last thirty years. Only studies which met the following criteria were included:

1) patients with FIGO stage I-II epithelial ovarian carcinoma
2) a minimum of 10 patients with clear cell early ovarian carcinoma in the study group
3) a registrered median survival or a survival curve in the final publication

RESULTS

Of the 448 patients included in the ACTION trial, 156 (34.8 %) were serous adenocarcinomas (SAC) and 63 (14.4%) were clear cell carcinomas (CCC). The median follow-up period was 5.1 years. Table 1 shows the clinical characteristics of the 219 patients from both the SAC and CCC group. There was a significant difference in FIGO stage ($P < 0.001$), 44.4% of the CCC were FIGO stage Ic because of capsule rupture and this was the case in 18.6% in the SAC group. The time of capsule rupturing was the same in both groups, in 24 patients (85.7%) during surgery in the CCC group versus in 26 patients (89.6%) in the SAC group. Tumors were limited to one ovary (Stage Ia) in 36.5% (23/63) of the CCC cases and 33.3% (52/156) of the SAC patients. Only 1 patient (1.6%) in the CCC group had a tumor extending to both ovaries (Stage Ib) compared to 15 patients (9.6%) in the SAC group and 2 patients (3.2%) had pelvic extension (Stage II) of the CCC cases versus 15 (9.6%) in the SAC patients. Differentation grade was

also significantly different in both groups ($P < 0.001$), 33 of the 63 CCC were poorly differentiated (52.4%) against 49 of the 156 in the SAC group (31.4%). No differences were noted between CCC and SAC patients for the variables age, pre-treatment CA 125 values and site of progression. The treatment arms were well balanced between the two groups.

During the follow-up period 56 relapses were found, 16 (25.4%) in the CCC group and 40 (25.6%) in the SAC group. In both groups together 47 patients died, 16 of the deaths occurred in the CCC group, the other 31 in the SAC patients.

Table 1. Patient Characteristics

	Clear cell N=63	**Serous N=156**	***P*-value**
Age	54 (10)	56 (11)	0.74
Treatment arm			
Observation	27 (42.9%)	72 (46.2%)	0.76
Chemotherapy	36 (57.1%)	84 (53.8%)	
CA 125			
Normal	18 (28.6%)	43 (27.4%)	
Abnormal	33 (52.4%)	70 (45.2%)	0.43
Not done	12 (19%)	43 (27.4%)	
Type of staging			
Optimal	25 (39.7%)	45 (28.8%)	
Modified (protocol)	18 (28.6%)	53 (34%)	0.27
Minimal	17 (27%)	41 (26.3%)	
Inadequate	3 (4.8%)	17 (10.9%)	
FIGO Stage			
Ia	23 (36.5%)	52 (33.3%)	
Ib	1 (1.6%)	15 (9.6%)	
Ic ovarian surface	2 (3.2%)	22 (14.1%)	<0.001
Ic capsule rupture	28 (44.4%)	29 (18.6%)	
Ic ascites/washing	7 (11.1%)	23 (14.7%)	
IIa	2 (3.2%)	15 (9.6%)	
Time rupture			
During surgery	24 (85.7%)	26 (89.6%)	0.88
Before surgery	4 (14.3%)	3 (10.4%)	
Differentation grade			
Well	2 (3.2%)	22 (14.1%)	
Moderately	23 (36.5%)	84 (53.8%)	<0.001
Poorly	33 (52.4%)	49 (31.4%)	
Unknown	5 (7.9%)	1 (0.6%)	
Progression			
No	47 (74.6%)	116 (74.4%)	0.84
Yes	16 (25.4%)	40 (25.6%)	

Overall survival rate for the SAC group and the CCC group was not significantly different (Figure 1; *P* = 0.2). The overall survival (OS) by treatment arm is shown in Figure 2 and 3 (*P* = 0.8 and *P* = 0.04 respectively). In the observation arm the OS showed no difference between the CCC patients and the SAC patients. In the chemotherapy arm however a significant difference in OS between the CCC and SAC group was found. Figure 4 shows the DFS in both groups (*P* = 0.9). The 5-year disease-free survival in the chemotherapy arm of patients with serous adenocarcinoma was 78% versus 60% for patients with clear cell carcinoma (Figure 5; *P* = 0.1), whereas in the observation arm the 5-year disease-free survival was higher in the CCC group compared to the SAC group (71% versus 61%: Figure 6; *P* = 0.2). The DFS curve of the CCC patients was higher in the observation arm and lower in the chemotherapy arm compared to the SAC patients. Adjuvant chemotherapy significantly improved DFS in patients with serous adenocarcinoma (Figure 7; *P* = 0.01). In clear cell carcinoma patients no difference in DFS was found between the observation arm and chemotherapy arm (Figure 8; *P* = 0.4).

The sixteen papers meeting the criteria of the Pubmed search, are summarized in Table 2. The 5-year survival of patients with FIGO stage I clear cell ovarian carcinoma ranged from 49-93% and from 29-88.9% for those patients with FIGO stage II clear cell ovarian cancer. The 5-year survival for stage I and II clear cell carcinoma was significantly different, 74.1% versus 49.4%, respectively. In Table 3 the survival figures are shown for patients with serous early ovarian carcinoma from different studies, resulting in a 5-year survival of 76.6% (range 67%-87%) for FIGO stage I patients and 73.5% (range 68-80%) for FIGO stage II serous tumors.

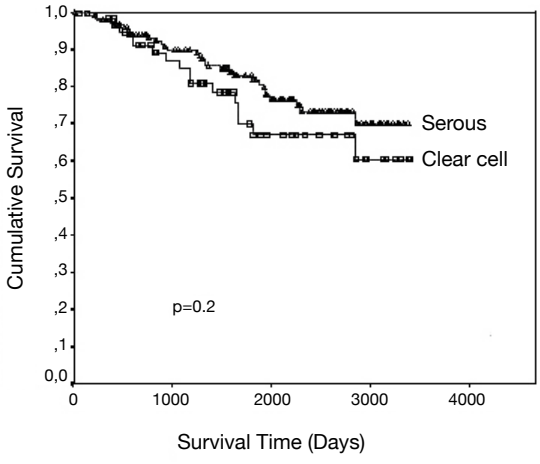

Figure 1. Kaplan-Meier curves for OS in patients with early ovarian cancer. Patients with clear cell carcinoma (n = 63) and patients with serous carcinoma (n = 156).
P = 0.2 using the log-rank test.

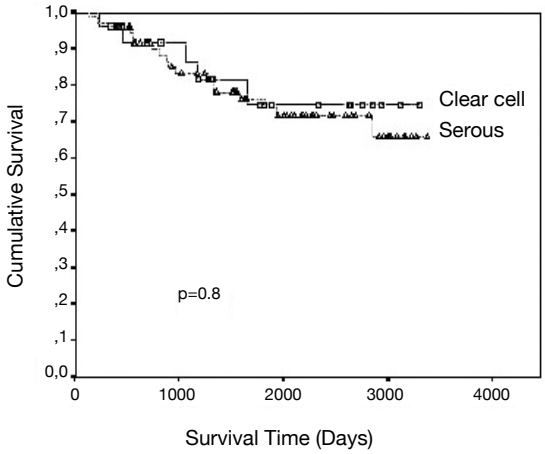

Figure 2. Kaplan-Meier curves for OS in patients with early ovarian cancer. Patients in the observation arm with clear cell carcinoma (n = 26) and patients with serous carcinoma (n = 74). Patients in the observation were observed until adjuvant chemotherapy was indicated.
P = 0.8 using the log-rank test.

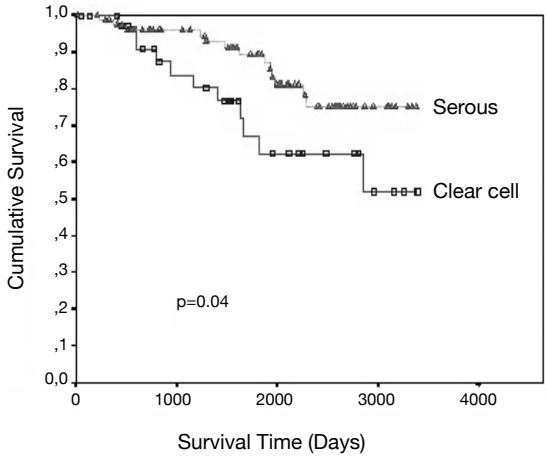

Figure 3. Kaplan-Meier curves for OS in patients with early ovarian cancer. Patients in the chemotherapy arm with clear cell carcinoma (n = 37) and patients with serous carcinoma (n = 82). Patients in the chemotherapy arm received immediate adjuvant chemotherapy.
P = 0.04 using the log-rank test.

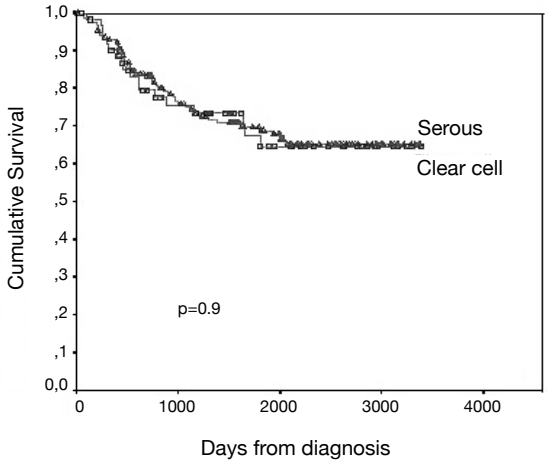

Figure 4. Kaplan-Meier curves for DFS in patients with early ovarian cancer. Patients with clear cell carcinoma (n = 63) and patients with serous carcinoma (n = 156).
P = 0.9 using the log-rank test.

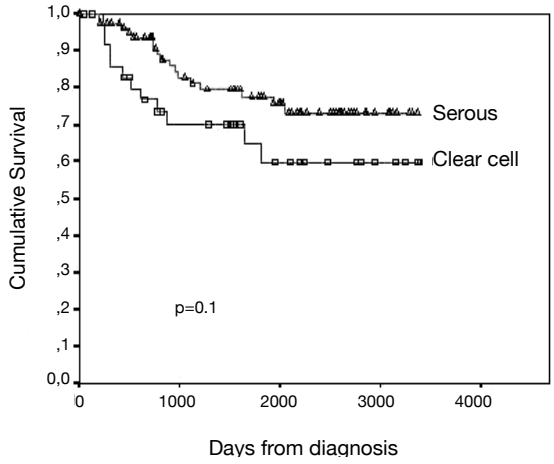

Figure 5. Kaplan-Meier curves for DFS in patients with early ovarian cancer. Patients in the chemotherapy arm with clear cell carcinoma (n = 37) and patients with serous carcinoma (n = 82). Patients in the chemotherapy arm received immediate adjuvant chemotherapy.
P = 0.1 using the log-rank test.

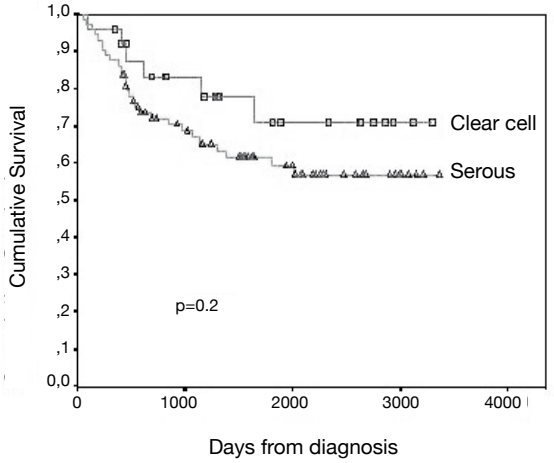

Figure 6. Kaplan-Meier curves for DFS in patients with early ovarian cancer. Patients in the observation arm with clear cell carcinoma (n = 26) and patients with serous carcinoma (n = 74). Patients in the observation were observed until adjuvant chemotherapy was indicated.
P = 0.2 using the log-rank test.

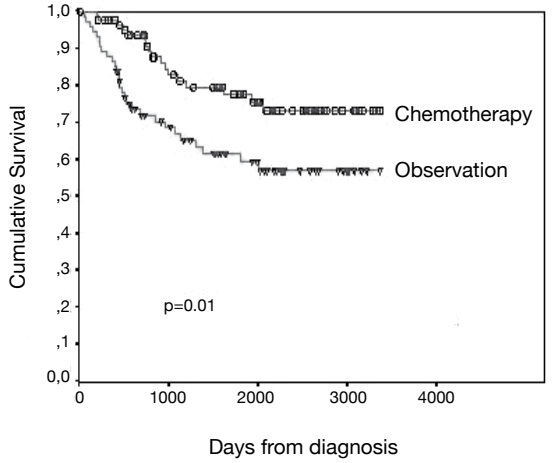

Figure 7. Kaplan-Meier curves for DFS in patients with early ovarian cancer. Patients with serous carcinoma in the chemotherapy arm (n = 82) and patients in the observation arm (n = 74). Patients in the chemotherapy arm received immediate adjuvant chemotherapy and patients in the observation arm were observed until adjuvant chemotherapy was indicated.
P = 0.01 using the log-rank test.

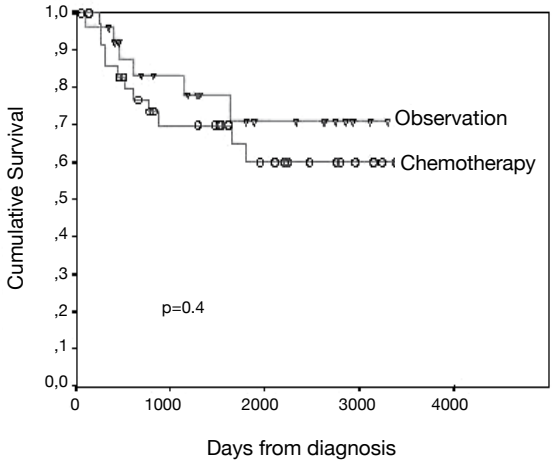

Figure 8. Kaplan-Meier curves for DFS in patients with early ovarian cancer. Patients with clear cell carcinoma in the chemotherapy arm (n = 37) and patients in the observation arm (n = 26). Patients in the chemotherapy arm received immediate adjuvant chemotherapy and patients in the observation arm were observed until adjuvant chemotherapy was indicated.
P = 0.4 using the log-rank test.

Table 2. Survival rate for Clear Cell Adenocarcinoma of the Ovary

		Clear cell 5-year survival	
Author	**Number of patients**	**FIGO stage I**	**FIGO stage II**
Czernobilsky et al. 1970 [2]	? (<12)	80%	na*
Aure et al. 1971 [13]	? (<59)	72%	na
Norris et al. 1971 [36]	? (<40)	61%	na
Shevschuk et al. 1981 [25]	? (<21)	87%	na
Brescia et al. 1989 [14]	15	93%	na
Crozier et al. 1989 [10]	38	49%	60%
Jenison et al. 1989 [7]	29	50%	29%
Kennedy et al. 1989 [6]	15	68%	42%
Montag et al. 1989 [1]	29	55%	29%
O'Brien et al. 1993 [9]	55	65%	40%
Ahmed et al. 1996 [35]	25	90.2%	na
Recio et al. 1996 [37]	37	67%	46%
Behbakht et al. 1998 [11]	27	85%	na
Kita et al. 2000 [12]	28	86%	60%
Sugiyama et al. 2000 [38]	59	80%	88.9%
Vergote et al. 2001 [34]	185	72.7%	na
Present series	63	63%	na
Total	**605**	**74.1%**	**49.4%**

*na: not applicable

Table 3. Survival rate for Serous Adenocarcinoma of the Ovary

		Serous 5-year survival	
Author	**Number of patients**	**FIGO stage I**	**FIGO stage II**
Aure et al. 1971 [13]	?	67%	na*
Swenerton et al. 1985 [39]	76	70%	na
Jenison et al. 1989 [7]	22	87%	80%
Sugiyama et al. 2000 [38]	52	86%	72.7%
Vergote et al. 2001 [34]	430	75.9%	na
Present series	156	74%	68%
Total	**706**	**76.6%**	**73.5%**

*na: not applicable

DISCUSSION

The results from this trial are based on one of the largest series in early ovarian cancer patients FIGO stage I-II. Most of the previous studies were retrospective with a small number of patients and often too few events to draw valid conclusions.

Clinical features

The clinical characteristics of clear cell carcinoma (CCC) have been widely explored. The age distribution, median 55 years, of the patients in the present study is similar to that reported by other groups. Nulliparity of greater than 50% has been reported in all series of clear cell carcinoma with the exception of those by Doshi and Fine (17 and 45% respectively) [21,22]. The frequency of concurrent endometriosis in published series of clear cell carcinoma varies from 8-55% compared to less than 5% in serous ovarian carcinoma [13,14,23]. Many authors described that the presence or absence of endometriosis did not appear to affect overall or progression-free survival [11,12].

Many investigators have stated that the percentage of patients with stage I-II disease in CCC is significantly higher compared with SAC patients, ranging from 53-66% in patients with CCC [7-13]. In a study of clear cell tumors versus matched controls consisting of serous ovarian tumors, 66% of the clear cell tumors were early-stage compared to 40% of the serous tumors [8]. One of the reasons for more stage I disease in the CCC patients may be a higher frequency of symptoms and signs at presentation resulting in earlier detection. In the literature no studies reported a primary peritoneal variant of the clear cell tumor, while mucinous and serous primary peritoneal cancers have been described.

Another argument for the fact that clear cell tumors stay localized until they become a pelvic cyst is the finding in a study of Okhawa et al. [24] that clear cell tumors remain attached to the mesothelial layer while serous tumors invade rapidly into this cell layer. Only 2 patients (3.2%) in our study group of CCC had pelvic extension, while 15/156 (9.6%) in the SAC group had FIGO stage IIa. It is also unusual to encounter bilateral involvement among stage I ovarian clear cell carcinoma patients. In the literature only 4.2% of stage I patients have been noted to have bilateral involvement and we observed this in 1 of the 63 patients (1.6%) in the CCC group versus 15 (9.6%) in the SAC group.

In the current study almost half of the patients in the CCC group had FIGO stage Ic, with 44.4% capsule rupture versus 18.6% in the SAC group. A possible explanation for this biologic phenomenon might be a larger tumor size of CCC as described in many series [7,12,13,24,25], and therefore more often capsule rupture before or during surgery.

In our study no difference was found in DFS and OS between the CCC and SAC group although almost half of the patient in the CCC group had FIGO stage Ic because of capsule rupturing compared to 18.6% in the SAC group.

Grading

One of the difficulties of managing clear cell carcinomas is the histologic grading. Different grading systems are used for ovarian cancer. The FIGO grading system [26] is primarily based on architectural features like the GOG grading system [27] which also in a lesser extent considers nuclear features, but varies on the histologic type being graded. Both grading systems cannot be used for clear cell carcinoma of the ovary. The WHO grading system [6] is dependent on observer's impressions derived possibly from both architectural and nuclear features, but not defined in a quantitative manner. Silverberg [28] proposed a universal grading system for all invasive ovarian carcinomas, based on the Nottingham system for grading all types of mammary carcinoma. Using this system tumors are graded architecturally as grade I-III according the (predominant) architectural pattern (glandular, papillary, solid), nuclear as grade I-III (slight, moderate, marked) and also on mitotic index. The efficacy of this grading system was tested in different series and seems to be valuable in predicting survival. They also found that histopathologic typing in ovarian cancer was less of prognostic significance for survival compared to grading, but better at predicting tumor responsiveness to chemotherapy. Ovarian clear cell cancer can be adequately graded by the Silverberg system.

Chemoresistance

In our study 16/63 (25.4%) recurrences were found in the CCC group and a similar percentage was found in the SAC group 40/156 (25.6%), with a median time to

recurrence of 28 months. Reviewing the literature, different numbers of recurrences are described. In a series of Bekbakht et al. [12], 10/27 (37%) patients with stage I clear cell carcinoma who received adjuvant platinum-based chemotherapy relapsed from which 7/13 (54%) were stage Ic tumors. In comparison, Hreshchyshyn et al. [29] reported a 6% recurrence rate in patients with stage I epithelial ovarian cancer treated with postoperative chemotherapy. The high relapse rate in clear cell carcinoma may be related to chemoresistance. In support of this concept, clear cell carcinoma cell lines were found to exhibit resistance to cisplatin in cell culture [16]. In a study of Kita et al. [13] 5 of the 10 patients with stage II disease had macroscopic residual disease from which 60% died within 9 months after initial surgery and adjuvant cisplatin based chemotherapy, also suggesting chemoresistance. In order to clarify the underlying mechanism of cisplatin resistance in clear cell carcinoma Itamochi [30] conducted a study in 11 CCC and 5 SAC cell lines. They found that the doubling time for CCC cells was significantly longer than that for SAC cell lines (61.4 vs 29.8 hour), suggesting that the resistance of CCC to cisplatin may be caused by low cell proliferation. In our study the disease-free survival (DFS) showed an advantage in the observation arm in the CCC group, while in the chemotherapy arm the DFS was higher in the SAC group. Both differences were not statistically significant but showed a trend and could be partly explained by a possible chemoresistance of the clear cell tumors. A significant difference was found in the SAC group in favor of the adjuvant chemotherapy arm while in the CCC group no survival difference was shown between the observation arm and chemotherapy arm**.**

Prognosis

Regardless of the high recurrence rate for clear cell carcinoma , overall survival is not significant lower than the survival of patients with serous ovarian cancer in the present study. In the current study, more patients in the CCC group were optimally staged (39.7%) versus the SAC group (28.8%). Therefore, we performed a separate analysis for only the optimally staged patients. Even if we look at the optimally staged CCC and SAC patients the outcome was the same, no significant difference could be found in DFS (P = 0.76) and OS (P = 0.28). Furthermore, the survival benefit in the chemotherapy arm of the SAC group compared to the CCC group disappeared (P = 0.11). Five-year survival rates in stage I-II clear cell carcinoma varied from 50-73% in reported series. Many studies were conducted on histologic type as prognostic factor. A number of studies gave patients with clear cell carcinoma of the ovary favorable prognosis compared to serous carcinoma of the ovary [10,14,15]. On the other hand, a same amount of studies regarded clear cell carcinoma as having a worse prognosis than other epithelial cancers [8,31,32]. Jenison et al. [8] noted that 22 patients with stage I clear cell ovarian carcinoma demonstrated a significantly worse estimated 5-year survival than did 11

patients with serous carcinoma (50% vs 87%, $P < 0.001$). Most of the studies however showed no difference in survival for patients with clear cell ovarian cancer compared to other histologic types of ovarian cancer. Our study also lends support to the postulation that clear cell carcinoma has a relatively good prognosis. Zanetta [33] analysed 351 patients with stage I ovarian cancer and could not find a significant difference in DFS and OS comparing clear cell tumors versus other histologic cell types. In a recent study of Vergote et al. [34] on 1545 FIGO stage I ovarian cancer patients histologic type was not of prognostic value, observing a 5-year survival of 72.7% in clear cell carcinoma patients versus 75.9% in patients with serous adenocarcinoma. In the multivariate analyses the degree of differentation was identified as the most powerful prognostic indicator but in this study clear cell carcinoma were not graded [34].

We conclude that although clear cell ovarian carcinomas do have unique clinical features, they have similar prognosis compared to serous ovarian cancer in early stages. The role of chemoresistance needs further study in these type of tumors.

REFERENCES

1. Goff BA, Sainz de la Cuesta R, Muntz HG, et al. Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease. Gynecol Oncol 1996; 60: 412-417.
2. Montag AG, Jenison EL, Griffiths CT, Welch WR, Lavin PT, Knapp RC. Ovarian clear cell carcinoma. A clinicopathologic analysis of 44 cases. Int J Gynecol Pathol 1989; 8(2): 85-96.
3. Czernobilsky B, Silverman BB, Enterline HT. Clear cell carcinoma of the ovary. A clinicopathologic analysis of pure and mixed forms and comparison with endometrioid carcinoma. Cancer 1970; 25: 762-772.
4. Schiller W. Mesonephroma ovarii. Am J Cancer 1939; 35: 1-21.
5. Saphir O, Lackner JE. Adenocarcinoma with clear cells (hypernephroid) of ovary. Surg Gynecolog Obstet 1944; 79: 539-543.
6. Serov SF, Scully RE, Sobin LH. Histological Typing of Ovarian Tumours. In International Histological Classification of Tumours, no 9. Geneva, World Health Organization, 1973: 17-54.
7. Kennedy AW, Biscotti CV, Hart WR, Webster KD. Ovarian clear cell adenocarcinoma. Gynecol Oncol 1989; 32: 342-349.
8. Jenison EL, Montag AG, Griffiths CT, et al. Clear cell adenocarcinoma of the ovary: a clinical analysis and comparison with serous carcinoma. Gynecol Oncol 1989; 32: 65-71.
9. Yoonessi M, Weldon D, Satchidand SK, Crickard K. Clear cell ovarian adenocarcinoma. J Surg Oncol 1984; 27: 289-297.
10. O'Brien ME, Schofield JB, Tan S, Fryatt I, Fisher C, Wiltshaw E. Clear cell epithelial ovarian cancer (mesonephroid): bad prognosis only in early stages. Gynecol Oncol 1993; 49: 250-254.
11. Crozier MA, Copeland LJ, Silva EG, Gershenson DM, Stringer CA. Clear cell carcinoma of the ovary: a study of 59 cases. Gynecol Oncol 1989; 35: 199-203.
12. Behbakht K, Randall TC, Benjamin I, Morgan MA, King S, Rubin SC. Clinical characteristics of clear cell carcinoma of the ovary. Gynecol Oncol 1998; 70: 255-258.
13. Kita T, Kikuchi Y, Kudoh K, et al. Exploratory study of effective chemotherapy to clear cell carcinoma of the ovary. Oncology reports 2000; 7: 327-331.
14. Aure JC, Hoeg K, Kolstad P. Mesonephroid tumors of the ovary: clinical and histopathologic studies. Obstet Gynecol 1971; 37: 860-867.
15. Brescia RJ, Dubin N, Demopoulos RI. Endometrioid and clear cell carcinoma of the ovary.

Factors affecting survival. Int J Gynecol Path 1989; 8: 132-138.
16. Gorai I, Nakazawa T, Miyagi E, Hirahara F, Nagashima Y, Minaguchi H. Establishment and characterization of two human ovarian clear cell adenocarcinoma lines from metastic lesions with different properties. Gynecol Oncol 1995; 57(1): 33-46.
17. Trimbos JB, Vergote I, Bolis G, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma. European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. J Natl Cancer Inst 2003; 95(2): 113-125.
18. Trimbos JB, Parmar M, Vergote I, et al. International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early stage ovarian carcinoma. J Natl Cancer Inst 2003; 95(2): 105-112.
19. Trimbos JB, Timmers P. Chemotherapy for early ovarian cancer. Curr Opin Obstet Gynecol 2004; 16(1): 43-48.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457-481.
21. Doshi N, Tobon H. Primary clear cell carcinoma of the ovary. An analysis of 15 cases and a review of the literature. Cancer 1977; 39: 2658-2664.
22. Fine G, Clarke HD, Horn RC. Mesonephroma of the ovary. A clinical, morphological, and histogenic appraisal. Cancer 1973; 31: 398-410.
23. Russel P. The pathologic assessment of ovarian neoplasms. Introduction to the common "epithelial" tumors and analysis of benign "epithelial" tumors. Pathology 1979; 11: 5-26.
24. Ohkawa D, Amasaki H, Terashima Y, et al. Clear cell carcinoma of the ovary. Light and electron microscopic studies. Cancer 1977; 40: 3019-3029.
25. Shevchuk MM, Monsanto BW, Fenoglio CM, Richart RM. Clear cell carcinoma of the ovary: A clinicopathologic study with review of the literature. Cancer 1981; 47: 1344-1351.
26. International Federation of Gynecology and Obstetrics. Classification and staging of malignant tumours in the female pelvis. Acta Obstet Gynecol Scand 1971; 50: 1-7.
27. Benda JA, Zaino R. GOG Pathology Manual. Buffalo, NY, Gynecologic Oncology Group, 1994.
28. Silverberg SG. Histopathologic grading of ovarian carcinoma: a review and proposal. Int J Gynecol Pathol 2000; 19: 7-15.
29. Hreshchyshyn MM, Park RC, Blessing JA, et al. The role of adjuvant therapy in Stage I ovarian cancer. Am J Obstet Gynecol 1980; 138: 139-145.
30. Itamochi H, Kigawa J, Sugiyama T, et al. Low proliferation activity may be associated with chemoresistance in clear cell carcinoma of the ovary. Obstet Gynecol 2002; 100(2): 281-287.
31. Tammela J, Geisler JP, Eskew PN Jr, Geisler HE. Clear cell carcinoma of the ovary: poor prognosis compared to serous carcinoma. Eur J Gynaec Oncol 1998; 19: 438-440.
32. Rubin SC, Wang GY, Curtin JP, et al. Platinum based chemotherapy of high risk stage I epithelial ovarian cancer following comprehensive surgical staging. Obstet Gynaecol 1993; 82: 143-147.
33. Zanetta G, Rota S, Chiari S, et al. The accuracy of staging: An important prognostic determinator in stage I ovarian carcinoma. A multivariate analysis. Ann Oncol 1998; 9(10): 1097-1101.
34. Vergote I, De Brabander J, Fyles A, et al. Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma. Lancet 2001; 357: 176-182.
35. Ahmed FY, Wiltshaw E, A'Hern RP, et al. Natural history and prognosis of untreated stage I epithelial ovarian carcinoma. J Clin Oncol 1996; 14: 2968-2975.
36. Norris HJ, Robinowitz M. Ovarian adenocarcinoma of mesonephric type. Cancer 1971; 28: 1074-1081.
37. Recio FO, Piver MS, Hempling RE, Driscoll DL. Lack of improved survival plus increase in thromboembolic complications in patients with clear cell carcinoma of the ovary treated with platinum versus nonplatinum–based chemotherapy. Cancer 1996; 78: 2157-2163.
38. Sugiyama T, Kamura T, Kigawa J, et al. Clinical characteristics of clear cell carcinoma of the ovary. Cancer 2000; 88: 2584-2589.
39. Swenerton KD, Hilsop TG, Spinelli J, Le Riche JC, Yang N, Boyes DA. Ovarian carcinoma: a multivariate analysis of prognostic factors. Obstet Gynecol 1985; 65: 264-270.