Is the watch and wait approach adequate after comprehensive surgical staging in invasive Stage I epithelial ovarian cancer? The Norwegian Radium Hospital Experience

H. Oksefjell[1], B. Sandstad[2], C. Tropé[1]

[1]Department of Gynaecological Oncology, The Norwegian Radium Hospital, Montebello, Oslo
[2]Clinical Trials Unit, The Norwegian Radium Hospital, Montebello, Oslo and The Norwegian Cancer Association (Norway)

Summary

Objectives: The aim of this study on stage I epithelial ovarian cancer (EOC) was to see if our different treatment policies after 1995, when lymph node staging and paclitaxel were introduced, have affected the survival, try to define risk groups for relapse and who should get adjuvant chemotherapy (AC). *Methods:* A retrospective study based on record information from all patients with invasive EOC stage I operated at the Norwegian Radium Hospital (NRH) 1984-2001, in total 252 patients. *Results:* Total 5-year survival was 83 and 82%, respectively, in both time periods. We found age and histology to be significant prognostic factors for overall survival (OS) ($p < 0.01$). From 1995 survival was significantly better for those who had been properly staged than for the others ($p = 0.02$), with a 5-year survival rate of 87 vs 64%. Those who did not get chemotherapy but were staged, had a significantly better overall survival than those who were not ($p = 0.02$), with a 5-year survival of 93 vs 77%. In the period 1995-2001 the patients who received no adjuvant treatment lived longer than those who underwent chemotherapy and/or radiotherapy ($p = 0.03$). In the first period 17% had no adjuvant treatment vs 58% in the last. Patients in a high-risk group getting AC had a tendency toward better survival than those who did not ($p = 0.08$). *Conclusions:* Patients with Stage I low and medium risk EOC do not need AC if properly staged. For the high-risk group the optimal AC has not yet been established.

Key words: Early stage ovarian cancer.

Introduction

In Scandinavia the age-adjusted incidence of epithelial ovarian cancer (EOC) is among the highest in the world. In Norway the incidence has been reasonably stable over the past 20 years, approximately 14 per 100,000 women [1]. Worldwide EOC is the most common cause of death in gynaecological cancer. One of the main reasons for this is that more than 70% of cases are diagnosed after the tumour has already spread beyond the ovaries. Only about one-third of patients with EOC have localised disease confined to the ovaries or pelvis. The prognosis for these women is much better. In Norway the population-based overall relative 5-year survival rate improved between 1976 and 2000 from 80% to 91% for FIGO (Federation International of Obstetrics and Gynaecology) Stage I with tumour growth limited to the ovaries [1]. Still approximately 30-50% of women with early stage (FIGO Stage I-II) disease eventually relapse and succumb to their disease [2].

These suboptimal survival results have led to major efforts to identify prognostic factors, improve surgical staging, and develop adjuvant therapies that could improve patient outcome.

The retrospective study of Vergote *et al.,* from seven hospitals in six countries between 1980 and 1994, identified degree of differentiation as the most powerful prognostic indicator of disease-free survival, followed by rupture before surgery, rupture during surgery, FIGO 1973 sub-stage and age [3]. Other studies have reported DNA ploidy by image- or flow-cytometry as an independent prognostic factor for survival [4, 5]. A new study from 2007 pointed out the pretreatment value of CA-125 ≤ 30 U/ml as the strongest predictive factor to identify a subgroup of Stage I with extremely good survival [6]. Several molecular biologic parameters have been tested and some like p53 have shown promising prognostic importance, but will have to be further investigated [7, 8]. Patients with Stage I EOC who suffer a relapse after surgery do so because of sub-clinical metastases at time of surgery, most commonly in the peritoneal cavity but occasionally in extraperitoneal locations such as the lymph nodes. Therefore an accurate surgical staging is crucial in the assessment of prognosis of Stage I EOC. With a second laparotomy with lymph node staging of improperly staged patients, presumed to be early-stage EOC, and with a high-risk profile for relapse, approximately 28% were found to have positive nodes and had to be upstaged to Stage III C in our experience [9] which is similar to Trimbos *et al.* [10], Young *et al.* [11], and Zanetta *et al.* [12].

Patients with a statistically significant risk for having persistent disease should be treated with adjuvant chemotherapy (AC). However, only a fraction of the patient population treated has micro metastatic disease and can potentially benefit from the treatment. Therefore the role of AC in patients with Stage I EOC remains controversial [13].

A review of 22 prospective randomised studies has discussed adjuvant treatment for early-stage EOC [13].

Revised manuscript accepted for publication January 30, 2008

The two prospective trials, the International Collaborative Ovarian Neoplasm I (ICON I) and Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION), and the combined analysis of the two trials from 2003, add important information on AC but leave some critical issues unsolved [10, 14, 15]. It was concluded that platinum-based AC, six cycles, improved overall- and recurrence-free survival at five years in the combined group of patients with early-stage ovarian cancer defined by the inclusion criteria of the ICON1 and ACTION trials. The inclusion criteria were however different, and no data presented in the ICON 1 trial suggested that the low-risk subset of patients with well-differentiated histology and sub-Stages I A and I B- benefit from AC. In a long-time follow up of women in the ICON 1 study presented at ASCO 2007, there was clear evidence that AC reduces the risk of recurrence/death or death alone in high-risk patients but not in the medium and low-risk group. The high-risk group was defined as FIGO Stage I A grade 3, I B or IC grade 2 or 3, and clear cell tumours [16].

The sub analysis of the ACTION trial suggested that accurate surgical staging identifies patients who do not require AC [10]. The study has been criticised because only one-third of the patients were properly staged.

At present the combination of paclitaxel and carboplatin (PC) is generally accepted as the standard chemotherapy for EOC and carboplatin has been shown to be as good as cisplatin with fewer side-effects [16-19]. A randomised phase III trial GOG 157 on 457 early-stage EOC, where about 70% of the patients had complete surgery, concluded that three cycles compared to six cycles of PC do not significantly alter the recurrence rate in high-risk early-stage EOC but are associated with less toxicity [20]. Therefore three cycles of PC is today in most parts of the world considered as the standard AC in high-risk Stage I EOC [13].

The Norwegian Radium hospital (NRH) is one of four cancer centres sharing the main responsibility for cancer treatment in Norway and the hospital mainly serves as a referring hospital for the south-eastern parts of the country including about 60% of the Norwegian population. Most patients with Stage I EOC are operated on at local hospitals except for patients considered as complicated cases, e.g., high-risk patients who are referred to NRH for primary surgery. If the surgery was not radical enough at the local hospital or they had to be evaluated for intraabdominmal P32 [21], or inclusion in the NSGO (Nordic Society of Gynecologic Oncology) prospective randomised study in Stage I EOC [5], they were referred and reoperated on immediately at NRH.

The aim of our study was to evaluate the treatment of patients with Stage I EOC during the two time periods, 1984-1994 and 1995-2001, to see if our different surgical and chemotherapy treatment policies during the periods have affected survival. From this we would try to define risk groups for relapse and which patients who would benefit from AC or not.

Materials and Methods

All patients with histological verified invasive Stage I EOC operated on at NRH between 1984 and 2001 were included in this retrospective study, a total of 252 patients. This is about half the patients with Stage I EOC referred to NRH in that period. The second half had their primary surgery at local hospitals and were referred to NRH for further planning and chemotherapy. All patients with borderline tumours were excluded from the beginning. Data were collected from patient records found via the hospital code registry for diagnosis and operation. No patients were lost in follow-up.

Registered parameters included age at start of treatment, period of diagnosis, histological subgroups, and degree of differentiation. Types of chemotherapy were subdivided in four groups: 1 = single platinum, 2 = platinum in combination with non-paclitaxel chemotherapy, 3 = all regimens with paclitaxel single or in combination and 4 = others (antracyclins, cyclophosphamide, thiotepa and fluorouracil). Before 1995 mostly single platinum was used as AC. Paclitaxel was introduced around the mid-nineties and followed by the combination platinum/paclitaxel. Staging of the patients was performed according to the system developed by FIGO in 1988. Before that staging was done retrospectively from the records. Histological classification was done according to criteria defined by the World Health Organisation (WHO). Clear cell tumours were not graded. All histological sections were reviewed by the specialised pathologists at NRH. We registered if the patient was reoperated on or primarily operated on at NRH and if lymph node staging was done. Number of nodes removed was registered. In the eighties, patients were randomised to cisplatin or radioactive phosphorus or whole abdominal irradiation as adjuvant treatment [21]. From 1992 to 1997 patients with a high-risk profile of Stage I EOC were randomized to six courses of adjuvant carboplatin or no adjuvant treatment at all [5]. NRH's surgical staging procedures in EOC have been followed from the mid-nineties [13]. From about the same period in inadequately Staged I EOC we chose a high-risk group for re-laparotomy to be all grade 3 and undifferentiated tumours, all aneuploid tumours, all clear cell adenocarcinomas and patients with elevated CA-125 values for a second laparotomy within three weeks for a complete restaging procedure. Gynaecologists at the referring hospitals do not do lymph node dissection. The ICON 1 classification for low-, medium- and high-risk Stage I epithelial ovarian cancer was used for grouping our patients. Low-risk (Stage I A grade 1, non-clear cell), medium-risk (Stage I A grade 2 and Stage I B or IC grade 1, non-clear cell), and high-risk (Stage I A grade 3, Stage I B or IC grade 2 or grade 3 and all clear cell) [16]. Time of final status (alive, dead or emigrated) was registered as January 2007.

Statistical analysis

Overall survival was estimated using the Kaplan-Meier method and groups were compared with log-rank tests. The five-year survival was estimated. Some of the most important suggested factors were far from proportional hazards, making them unsuitable for inclusion in the Cox proportional hazards regression model. We therefore decided to present results of univariate survival analysis only; p values ≤ 0.05 were regarded as statistically significant. Data analysis was performed using SPSS 15.0.

Table 1. — *Characteristics of patients with invasive Stage I EOC (n) and five-year total survival (%) for different treatment periods.*

Characteristics	All		1984-1994		1995-2001	
	n	≥ 5-year survival	n	≥ 5-year survival	n	≥ 5-year survival
All	252	83	155	83	97	82
Age (years):						
≤ 39	54	94	39	95	15	93
40-49	55	91	32	91	23	91
50-59	77	82	45	76	32	91
60-69	47	79	27	85	20	70
70+	19	42	12	50	7	29
Histology:						
Serous	58	83	34	82	24	83
Mucinous	53	87	36	86	17	88
Endometrioid	62	89	41	90	21	86
Clear cell	45	69	20	65	25	72
Mixed	23	91	16	88	7	100
Non-classified	11	73	8	75	3	67
Differentiation:						
Well	95	87	64	89	31	84
Moderate	58	76	44	73	14	86
Poor	43	81	24	83	19	79
Sub-stages:						
A	158	85	110	85	48	85
B	23	74	19	74	4	75
C	70	80	26	81	44	80
Chemotherapy:						
Single platinum	94	83	72	89	22	64
Platinum combined	6	83	3	100	3	67
Paclitaxel combined	14	86	–	–	14	86
Others	5	80	5	80	–	–
Radiotherapy:						
No	180	85	88	86	92	84
Extern	12	75	8	88	4	50
P32	49	78	49	78	–	–
Chemotherapy ± radiotherapy:						
None	80	89	24	83	56	91
Chemo	100	82	64	88	36	72
Radio	50	74	48	75	2	50
Both	11	91	9	100	2	50
Lymph node staging:						
No	157	82	143	83	14	64
Yes	89	88	7	100	82	87
Chemotherapy:						
No	133	83	75	77	58	90
Yes	119	83	80	89	39	72

Table 2. — *Characteristics of patients with Stage I EOC, with and without lymph node staging, 1984-2001.*

Characteristics	Lymph node staging			
	Yes		No	
	n	%	n	%
Age:				
≤ 39	16	18	38	24
40-49	22	25	30	19
50-59	29	33	47	30
60-69	17	19	29	19
70+	5	6	13	8
Histology:				
Serous	22	25	36	30
Mucinous	16	18	37	24
Endometrioid	18	20	39	25
Clear cell	24	27	21	13
Mixed	6	7	16	10
Non-classified	3	3	8	5
Differentiation:				
Well	27	49	66	49
Moderate	12	22	44	33
Poor	16	29	25	19
Sub-stages:				
A	50	57	105	67
B	3	3	18	12
C	35	40	34	22
Chemotherapy:				
Single platinum	17	55	73	87
Platinum combined	3	10	3	4
Paclitaxel combined	11	36	3	4
Others	0		5	6
Chemotherapy ± radiotherapy:				
None	56	63	23	16
Chemotherapy	29	33	69	47
Radiotherapy	2	2	47	32
Both	2	2	7	5
Chemotherapy:				
Yes	31	35	84	54
No	58	65	73	47

Table 3. — *Treatment frequencies (n) and 5-year OS (%) for EOC Stage I with and without lymph node staging or AC.*

	Lymph node staging			
	Yes		No	
	n	%	n	%
Chemotherapy				
Yes	84	86	73	77
No	31	77	58	93

Results

Patient characteristics are shown in Table 1. The 252 patients with invasive cancer had a 5-year survival rate of 83%. Most patients were between 50 and 70 years in both periods. The last period contained proportionately fewer patients below 39 years and more between 50 and 70 years. The best overall and 5-year survival rates were found for the group below 39 years, and the worst for the oldest group over 70 (Table 1, Figure 1). The difference was significant ($p < 0.001$).

There was a nearly equal distribution of patients between the main histological subgroups, and univariate analysis showed a significant difference ($p < 0.01$) overall (OS) between the groups (Figure 2). The OS and 5-year survival rates were best for the endometrioid and mucinous group and worst for the clear cell and non-classified group. The serous group did not do so well either. The last period contained relatively more patients with clear cell cancers than the first period relatively (Table 1).

Table 1 shows no difference in 5-year survival in the well, moderate, and poorly differentiated tumours, and the difference in OS was not significant in univariate analysis.

As for the sub-stages no significant differences were found in OS and 5-year survival. Most patients with Stage IC were found in the last time period and most with Stage I A in the first period.

Fig. 1

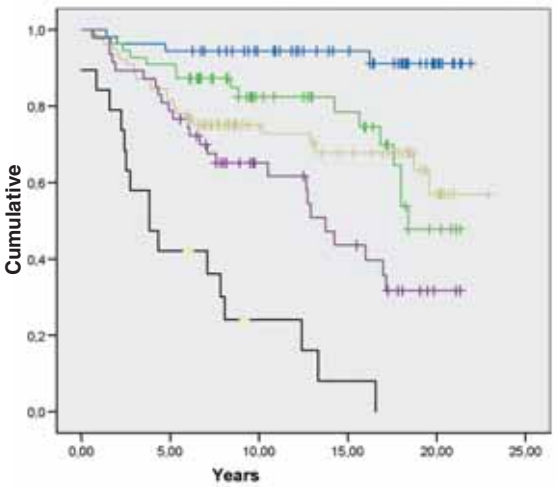

Fig. 2

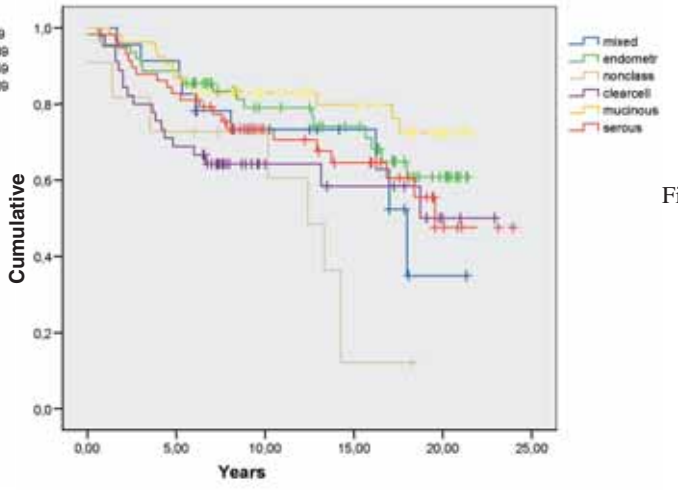

Fig. 3

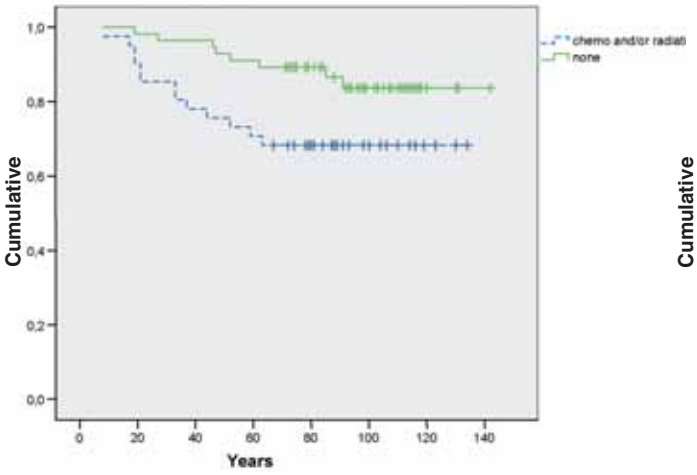

Fig. 4

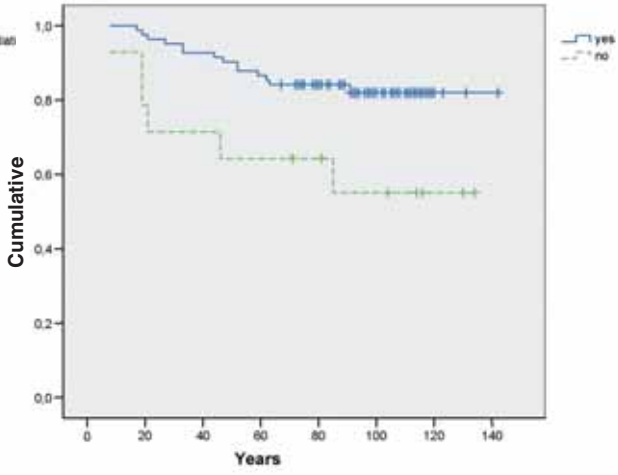

Fig. 5

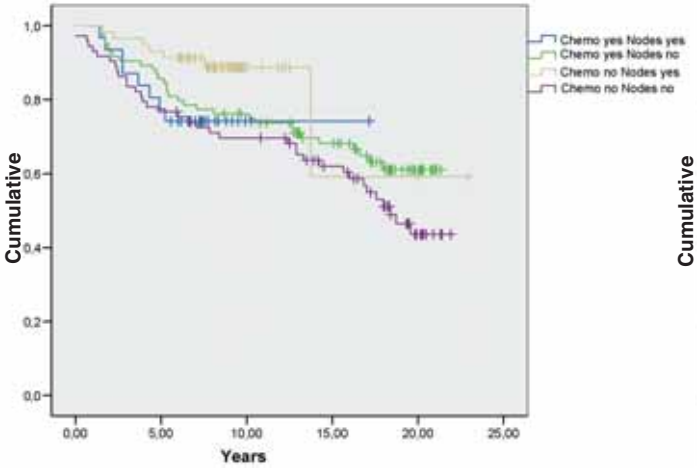

Fig. 6

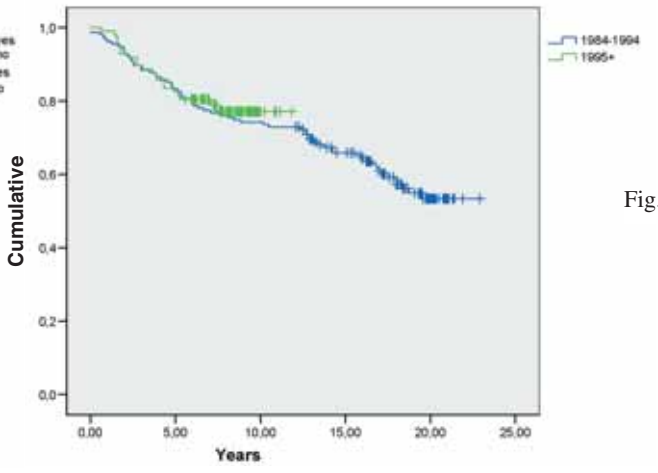

Figure 1. — Stage I EOC. OS for different ages ($p < 0.01$).
Figure 2. — Stage I EOC. OS for different histological groups ($p < 0.01$).
Figure 3. — Stage I EOC. OS with adjuvant treatment or not ($p = 0.03$).
Figure 4. — Stage I EOC. OS with lymph node staging or not ($p = 0.02$).
Figure 5. — Stage I EOC. OS combining lymph node staging and adjuvant chemotherapy ($p = 0.05$).
Figure 6. — Stage I EOC. OS for different treatment periods ($p = 0.68$).

No significant difference in survival was found between the chemotherapy groups or between those who got AC and those who did not (Table 1). For the last period however, there was a tendency towards better OS for those who did not get AC compared to those who did get it (p = 0.06). In the first period the 5-year survival was best for those who received AC.

Intraperitoneal radioactive phosphorus was in use in the first period and a few patients received external abdominal and pelvic irradiation adjuvant to surgery in both periods. A few patients even received combined chemo- and radiotherapy as shown in Table 1. For the whole cohort no significant difference in survival was observed in the groups who received either radiotherapy or chemotherapy, or no adjuvant treatment at all. However from 1995 we found a significantly better OS for those who received no adjuvant treatment compared to those who had cytostatica and/or radiotherapy (p = 0.03) (Figure 3) with a 5-year survival of 91% (Table 1).

Only 17% of the patients had no adjuvant treatment in the first time period compared to as much as 58% in the last period.

Lymph node staging was mostly performed after 1995 and in 85% of the cases. We found a tendency towards better OS for all patients that had been properly staged compared to those who had not (p = 0.08). After 1995 the OS difference was significant (p = 0.02) (Figure 4). Table 2 shows the characteristics of the patients with and without lymph node sampling. There were more patients with clear cell, poorly differentiated and Stage IC tumours among those who had lymph node staging, and 63% vs 16% had no adjuvant treatment at all. Thirty-six percent versus 4% however received paclitaxel in combination.

There was no significant difference in survival for those who received or did not receive AC. By combining AC and lymph node staging however, we found a significantly better survival for those who did not have AC but had lymph node staging than for those who had not been staged (p = 0.02). Comparing the four combined groups (Figure 5), also shows a difference which is significant (p = 0.05).

Table 3 shows the 5-year survival rates for the AC and lymph node staging groups, and the same condition is demonstrated with a 5-year survival rate of 93% for those who did not undergo AC but were staged and 77% for those who were not staged.

The OS was not significantly better when 15 or more lymph nodes were removed compared to less than 15.

When comparing the two treatment periods 1984-1994 and 1995-2001, no significant difference in OS was demonstrated between the periods (p = 0.68) (Figure 6).

When defining three different risk groups as in the ICON I study, we found no significant difference in OS in the high-risk group between those who received AC and those who did not (p = 0.6). The same nonsignificant difference was demonstrated for the medium- and low-risk groups. Table 4 shows more characteristics for the different risk groups.

Table 4. — *Characteristics and number of patients in the different risk groups of invasive EOC Stage I.*

Characteristics	Risk groups		
	Low	Medium	High
Age (years):			
≤ 39	24	14	11
40-49	18	10	21
50-59	13	20	38
60-69	8	11	23
Histology:			
Serous	15	15	24
Mucinous	31	16	2
Endometrioid	17	22	18
Clear cell	0	0	45
Mixed	4	7	4
Nonclassified	0	1	7
Differentiation:			
Well	67	28	0
Moderate	0	33	24
Poor	0	0	43
Lymph node staging:			
No	46	44	55
Yes	20	15	42

Low risk: Stage I A, diff grade 1, non-clear cell. Medium risk: Stage I A, grade 2 and Stage I B or c, grade 1, non-clear cell. High risk: Stage I A, grade 3, I B or c grade 2 or 3 and all clear cell.

Discussion

The results of this retrospective study taking place between 1984 and 2001 are influenced by the two randomised studies described that the department took part in during that time [5, 21]. In the last period more patients were reoperated on for proper staging and more were also referred for primary surgery at NRH because they were considered preoperatively as high-risk patients. The 5-year survival rate for the whole cohort of 83% is almost the same as reported from Norway for the same period [1]. Age and the histological types as prognostic factors for overall survival are also comparable with Vergote *et al.* [3]. The distribution between the histological groups and survival showed the same tendencies and is in accordance with others that found nodal disease more frequent in serous and clear cell tumours than in mucinous and endometrioid types and best survival for mucinous and endometrioid types [3, 10, 22, 23]. For the degree of differentiation and sub-stages we did not find significant differences in univariate analysis opposed to Vergote *et al*. [3], but we saw the same tendencies.

Two prospective observational studies have been published, Trimbos *et al*. [24] and Monga *et al*. [25] in which patients did not receive AC after surgery. These studies demonstrated the natural course for patients with Stage I EOC and emphasised the importance of proper staging of EOC [13]. On the basis of these findings we started systematic lymph node staging from about 1995, and from that time we found a significant better survival for the patients who had lymph node sampling than those who did not in accordance with the optimally staged patients in the observation arm of the ACTION study [10] (Figure 4). The group that was properly staged also consisted of

more patients with a poor prognosis and more who did not receive any adjuvant therapy. Comparing the survival with or without AC alone we found no significance in contrast to the conclusion of the ICON 1 and the combination of ICON 1 and ACTION study [14, 15]. By combining AC and lymph node staging we found the significantly best survival for the patients who did not receive AC but had been properly staged compared to those who were not. This is in accordance with the conclusion of the ACTION study which says that the benefit of AC appears to be limited to patients with non-optimal staging. The poor survival of the improperly staged patients with no AC can be explained by the fact that many of them could be Stage III C as we have shown earlier [9].

By using the risk groups of the long-time follow-up of ICON 1 study in our work, we got nearly the same results as them, showing that AC reduces the risk of death in the high-risk group of patients but not in the medium- or low-risk groups [16]. However, none of the ICON I patients were properly staged. For selected patients who were staged incompletely at the time of initial surgery, completion of the staging procedure with either laparoscopy or laparotomy is another reasonable approach before a final decision can be made regarding the need for AC.

No significant difference in survival was found between the chemotherapy groups, but the numbers in some of the groups are small.

After 1995 we found the best significant survival for "the no-adjuvant-treatment-at-all-group".

We could not demonstrate better OS for the last period, but there were relatively less young patients, more patients with serous and clear cell and poorly differentiated tumours and patients with Stage IC EOC after 1995. This result makes the effect of AC in adequately staged high-risk patients more doubtful given that no statistically significant effect of AC was shown in this group in the ACTION trial [10]. We believe many world leading gynaecologic oncologists may consider AC even in properly high-risk patients Stage I as over-treatment [11, 26, 27]. Tropé *et al*. [5] and Bolis *et al*. [28] have shown that salvage treatment was more effective in the optimally staged observation arm. They suggested that salvage treatment should be postponed until the time of recurrence. In a small select group of very high-risk patients we consider the use of three cycles of adjuvant PC [13, 20].

In a Norwegian study [29] including 70 (54%) Stage I patients, 22% had chronic fatigue. Five-year survivors of Stage I EOC had more somatic and mental morbidity, more fatigue, poorer quality of life, and used more medication and health services than controls (compared with an age representative sample of the general female population). The relative risk for developing secondary malignancies is increased from 3.3 to 6.5 after platinum therapy depending on dose [30]. This supports our belief that the use of AC should be reduced for patients who are likely to be long-term survivors [13].

We have demonstrated however that a lot of patients avoided stressing AC and probably got a better quality of life the last time period compared to the first time period and even with better survival.

All this should indicate that there are two groups of patients with low- and medium-risk Stage I invasive EOC that do not need AC treatment, and according to what we have found it is important that these patients undergo a proper staging operation and do not belong to the high-risk group defined above. We also mean that it is better to centralise the patients to get the primary surgery done by a gynaecological oncologist to avoid a second restaging laparotomy.

Acknowledgments

We thank the scientific secretary, Mrs. Gry Seppola for technical and organizational help, and the financial support from Inger and John Fredriksen's Foundation for Ovarian Cancer Research. We also thank Anne Birgitte Jacobsen at the Clinical Trials Unit, The Norwegian Radium Hospital for supporting the construction of the electronic database, and we thank our specialized pathologists for reviewing all the histological sections.

References

[1] Norway Institute of Population-Based Cancer Research: Cancer in Norway 2005. Cancer Registry of Norway Institute of Population-Based Cancer Research, 2006

[2] Ozols R.F., Rubin S.C., Thomas G.M., Robboy S.J.: "Epithelial ovarian cancer". In: Hoskins W.J., Perez C.A., Young R.C. (eds.) Principles and Practice of Gynaecologic Oncology, 3rd edition. Philadelphia, Lippincott, Williams & Wilkins, 2000, 981.

[3] Vergote I., De Brabanter J., Fyles A., Bertelsen K., Einhorn N., Sevelda P. *et al.*: "Prognostic importance of degree of differentiation and cyst rupture in Stage I invasive epithelial ovarian carcinoma". *Lancet,* 2001, *357,* 176.

[4] Kristensen G.B., Kildal W., Abeler V.M., Kaern J., Vergote I., Tropé C.G. *et al*: "Large-scale genomic instability predicts long-term outcome for women with invasive Stage I ovarian cancer". *Ann. Oncol.,* 2003, *14,* 1494.

[5] Trope C., Kaern J., Høgberg T., Abeler V., Hagen B., Kristensen G. *et al.*: "Randomized study on chemotherapy in Stage I high-risk ovarian cancer with evaluation of DNA-ploidy as prognostic instrument". *Ann. Oncol.,* 2000, *11,* 281.

[6] Obermair A., Fuller A., Lopez-Varela E., van Gorp T., Vergote I., Eaton L. *et al.*: "A new prognostic model for FIGO Stage I epithelial ovarian cancer". *Gynecol. Oncol.*, 2007, *104,* 607.

[7] Anttila M.A., Ji H., Juhola M.T., Saarikoski S.V., Syrjänen K.J.: "The prognostic significance of p53 expression quantitated by computerized image analysis in epithelial ovarian cancer". *Int. J. Gynecol. Pathol.,* 1999, *18*, 42.

[8] Skirnisdottir I., Seidal T., Gerdin E., Sorbe B.: "The prognostic importance of p53, bcl-2, and bax in early Stage epithelial ovarian carcinoma treated with adjuvant chemotherapy". *Int. J. Gynacol. Cancer*, 2002, *12,* 265.

[9] Oksefjell H., Sandstad B., Tropé C.: "Ovarian cancer Stage IIIC. Consequences of treatment level on overall and progression-free survival". *Eur. J. Gynaecol. Oncol.*, 2006, *27,* 209.

[10] Trimbos J.B., Vergote I., Bolis G., Vermorken J.B., Mangioni C., Madronal C. *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,* 113.

[11] Young R.C., Decker D.G., Wharton J.T. *et al.*: "Staging laparotomy in early ovarian cancer". *JAMA*, 1983, *250,* 3072.

[12] Zanetta G., Rota S., Chiari S., Bonazzi C., Bratina G., Torri V. *et al.*: "The accuracy of staging: An important prognostic determinator in Stage I ovarian carcinoma: A multivariate analysis". *Ann. Oncol.,* 1998, *9,* 1097.

[13] Trope C., Kaern J.: "Adjuvant chemotherapy for early-stage ovarian cancer: Review of the literature". *J. Clin. Oncol.,* 2007, *25*, 2909.

[14] International Collaborative Ovarian Neoplasm Trial 1: "A randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer". *J. Nat. Cancer Inst.,* 2003, *95,* 125.

[15] 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,* 105.

[16] Swart A.C. on behalf of ICON collaborators: "Long-term follow-up of women in a randomized trial of adjuvant chemotherapy for early stage ovarian cancer (ICON 1)". ASCO 2007; abstract nr 5509 (oral presentation).

[17] McGuire W.P., Hoskins W.J., Brady M.F., Kucera P.R., Patridge E.E, Look K.Y. *et al.*: "Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with Stage III and IV ovarian cancer". *N. Engl. J. Med*., 1996, *334*, 1.

[18] du Bois A., Luck H.J., Meier W., Adams H.P., Mőbus V., Costa S. *et al.*: "A randomized clinical trial of cisplatin/paclitaxel as first-line treatment of ovarian cancer". J. *Natl. Cancer Inst.,* 2003, *95*, 1320.

[19] Ozols R.F., Bundy B.N., Greer B.E., Fowler J.M., Clarke-Pearson D., Burger R.A. *et al.*: "Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected Stage III ovarian cancer: a Gynecologic Oncology Group study". *J. Clin. Oncol.,* 2003, *21*, 3194.

[20] Bell J., Brady M.F., Young R.C., Lage J., Walker J.L., Look K.Y. *et al.*: "Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynaecologic Oncology Group study". *Gynecol. Oncol.,* 2006, *102*, 432.

[21] Vergote I.B., Vergote-De Vos L.N., Abeler V.M., Aas M., Lindegaard M.W., Kjørstad K.E. *et al.*: "Randomized trial comparing cisplatin with radioactive phosphorus or whole abdominal irradiation as adjuvant treatment of ovarian cancer". *Cancer,* 1992, *69,* 741.

[22] Onda T., Yoshikawa H., Yokota H., Yasugi T., Taketani Y.: "Assessment of metastasis to aortic and pelvic lymph nodes in epithelial ovarian carcinoma". *Cancer*, 1996, *78*, 803.

[23] Baiocci G., Raspagliesi F., Grosso G., di Re F., Fontanelli R.: "Early ovarian cancer: Is there a role of systematic pelvic and paraaortic lymphadenectomy?". *Int. J. Gynecol. Cancer,* 1998, 8, 103.

[24] Trimbos J.B., Schueler J.A., van der Burg M., Hermans J., van Lent M., Heintz A.P.M. *et al.*: "Watch and wait after careful surgical treatment and staging in well-differentiated early ovarian cancer". *Cancer,* 1991, *67*, 597.

[25] Monga M., Carmichael J.A., Shelley W.E., Kirk M.E., Krepart G.V., Jeffrey J.F. *et al.*: "Surgery without adjuvant chemotherapy for early epithelial ovarian carcinoma after comprehensive surgical staging". *Gynecol. Oncol.,* 1991, *43,* 195.

[26] Vergote I., Trimbos B.J.: "Treatment of patients with early epithelial ovarian cancer". *Curr. Opin. Oncol.,* 2003, *15,* 452.

[27] Colombo N., Pecorelli S.: "What have we learned from ICON1 and ACTION?". *Int. J. Gynecol. Cancer,* 2003, *13* (suppl. 2), 140.

[28] Bolis G., Colombo N., Pecorelli S., Torri V., Marsoni S., Bonazzi C. *et al.*: "Adjuvant treatment for early epithelial ovarian cancer: Results of two randomized clinical trials comparing cisplatin to no further treatment or chromic phosphate (32P)-GICOG: Gruppo Interregionale Collaborativo in Ginecologia Oncologica". *Ann. Oncol.*, 1995, *6,* 887.

[29] Liavaag A.H., Dorum A., Fossa S.D., Tropé C., Dahl A.A.: "A controlled study of fatigue, quality of life, somatic and mental morbidity in epithelial ovarian cancer survivors: How lucky are the lucky ones?". *J. Clin. Oncol.,* 2007, *25,* 2049.

[30] Travis L.B., Holowaty E.J., Bergfeldt K., Lynch C.F., Kohler B.A., Wiklund T. *et al.*: "Risk of leukemia after platinum-based chemotherapy for ovarian cancer". *N. Engl. J. Med.,* 1999, *340*, 351.

Address reprint requests to:
H. OKSEFJELL, M.D.
Department of Gynaecological Oncology
The Norwegian Radium Hospital,
Montebello N-0310 Oslo (Norway)
e-mail: halldis.oksefjell@radiumhospitalet.no