Original Articles

Improved survival for Stage IIIC ovarian cancer patients treated at the Norwegian Radium Hospital between 1984 and 2001

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Summary

Background: The aim of this study was to evaluate the treatment of FIGO Stage IIIC patients who were primarily treated completely or partially at the Norwegian Radium Hospital (NRH) during a 15-year period in order to discover possibilities for improvement of prognosis of advanced ovarian cancer.

Materials and Method: A retrospective study based on record information from all patients with epithelial ovarian cancer Stage IIIC treated at NRH from 1985-2000, in total 776 patients.

Results: We found age, amount of residual tumour after surgery for primary treatment and type of chemotherapy to be the most significant prognostic factors for overall survival. During the last 5-year period primary surgery was increasingly centralised, and surgery was improved with lymph node staging and use of paclitaxel. Survival was significantly better during the last 5-year period and after macroscopic radical surgery. Also progression-free survival was better with no macroscopic tumour remaining.

Interpretation: Improved survival during the last 5-year period is partly attributed to improved surgery and partly to the addition of paclitaxel. We believe that further centralisation of primary surgery for advanced ovarian cancer can contribute to a better prognosis.

Key words: Ovarian cancer; Survival.

Introduction

Worldwide ovarian cancer is one of the most frequently occurring types of cancer in women and the most common cause of death in gynaecological cancer [1]. In Scandinavia the age adjusted incidence of ovarian cancer is among the highest in the world [2]. The incidence in Norway has been reasonably stable over the past 20 years, approximately 14 per 100,000 women [2]. This equates to around 480 new cases diagnosed annually. Even though the 5-year survival rate over the past 20 years has gradually been improved for all stages, from 39% in the period 1975-79 to 43% in the period 1990-94, it is still disappointingly low [2, 3].

More than 90% of ovarian cancer is epithelial.

Many overviews of prognostic factors for patients with ovarian cancer have been published. Applying multivariate analysis, FIGO-stage and amount of residual tumour after primary surgery are the most frequently reported independent prognostic factors for survival. Factors such as age, histological type, degree of differentiation, preoperative CA125, ascites, DNA-ploidy, general constitution and different molecular biological markers are reported as independent prognostic factors for survival [4-13].

Postoperative chemotherapy has traditionally held an important position in the treatment of advanced ovarian cancer.

The effect of non-platinum chemotherapy regimens after primary surgery in advanced ovarian cancer has not been documented [14, 15]. Available documentation shows significant improvement in survival with use of platinum agents in combination chemotherapy [14]. Cisplatin and carboplatin are equally effective, with carboplatin being significantly less toxic than cisplatin [15, 16]. Current data show significant differences in survival favouring the addition of paclitaxel to platinum [17, 18]. Due to the recent randomised controlled study (ICON3) there is debate over whether single-agent platinum is equivalent to combinations with paclitaxel. However, today, carboplatin plus paclitaxel is the standard first-line therapy [19-21].

In 1975 Griffith [5] published data indicating a survival benefit where residual tumours were successfully reduced to less than 1.5 cm. These findings have been verified by a number of other authors. A recent review article shows the importance of qualified primary surgery [22].

Bristow *et al.* [11] published the effect of a meta-analysis on survival after maximum surgical tumour reduction followed by chemotherapy containing platinum. A total of 63 studies were included in the meta-analysis which concluded that the strongest prognostic factor for increased median survival is the number of patients in a cohort who achieve optimal tumour reduction. Eisenkop *et al.* showed in a study from 2003 that macroscopically radical cytoreduction was significantly more important for survival than

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the spreading of metastatic disease before surgery [12]. By cytoreductive surgery it is meant maximum surgical reduction of tumour tissue without an absolute requirement that surgery is radical macroscopically. A common definition has been that the largest residual tumour should be less than 1-2 cm in diameter [4, 5, 7, 11].

Many studies have demonstrated a better prognosis for patients with advanced disease when operated on by specialists in gynaecological oncology compared to general gynaecologists [23-26]. Tingulstad *et al.* demonstrated significantly better survival rates for patients with advanced ovarian cancer referred for primary surgery at Trondheim teaching hospital compared to case-controls who received primary surgery at local or central hospitals (26 % vs 4 % 5-year survival), and 21 months vs 12 months median survival, p = 0.01 [23]. This is supported by Paulsen *et al.* [25] who showed in a prospective population based registration study improved short-time survival for Stage IIIC ovarian cancer patients undergoing surgery primarily at teaching hospitals. The recent review article from Toronto seems to confirm the importance of being operated on by gynaecological oncologists [26].

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. All the patients with Stage I-IIIC epithelial ovarian cancer are referred to NRH to decide further treatment. If the primary surgery at the local hospital seems radical enough, patients only receive adjuvant chemotherapy. If the surgery was not radical enough they are reoperated immediately if it seems possible but if not, they receive three to four courses of chemotherapy at first and then interval debulking surgery is done before further chemotherapy. Some patients are referred for primary surgery at NRH. Earlier this used to be those whose operation seemed to be difficult, but in the last time period (1996-2001) more patients were referred for primary surgery at NRH also in early stages. Since about 1995 we consequently did lymph node staging either primarily or at the re-operation in the early stages. We have shown that 28.4% of suggested Stage I or II by immediate re-operation were upgraded to Stage IIIC [27].

The aim of this study was to evaluate the treatment of FIGO Stage IIIC patients who were primarily treated completely or partially at the NRH in different time periods. Stage IIIC has been chosen to best demonstrate the effect of surgery.

Materials and Methods

All patients with histological verified epithelial ovarian cancer Stage IIIC treated at NRH during the 16-year period 1984-2001 were included in this study, a total of 814. Advanced cancer was chosen to better evaluate the effect of surgery. Fifteen with borderline tumours were excluded as well as 23 with delayed primary surgery due to neoadjuvant chemotherapy. This left 776 patients to be analysed. Data were collected from patient records found via the hospital code registry for diagnosis and operation.

Registered parameters were: age at start of treatment (≤ 49, 50-59, 60-69 and ≥ 70 years), period of diagnosis (1984-90, 1991-1995, 1996-2001), histological subgroups (serous, mucinous, endometroid, clear-cell, mixed, undifferentiated and non-classified), degree of differentiation (high, medium, poor and unclassified), and amount of residual disease after final surgery for primary treatment (macroscopically radical surgery, residual tumour ≤ 2 cm and residual tumour > 2 cm). Types of chemotherapy were subdivided into four groups: 1 = single cisplatin, 2 = cisplatin in combination with non-paclitaxel chemotherapy, 3 = all regimes with paclitaxel single or in combination and 4 = others (antracyclins, cyclophosphamide, thiotepa and fluorouracil). Chemotherapy was given either as three or four courses after primary surgery before interval debulking, 25%, 29% and 14% of the patients for the first to the third period respectively, or as six to nine courses postoperatively, or both. Staging of the ovarian cancer patients was performed according to the system developed by the International Federation of Gynaecology and Obstetrics (FIGO) in 1988. Before 1988 the staging was done retrospectively from the records. Histological classification was done according to criteria defined by the World Health Organisation (WHO).

Times for completed primary treatment, for first sign of progression and for final status at the end of registration autumn 2004 (alive, dead or emigrated) were registered. Data for final status were collected from the Cancer Registry with permission.

Statistical analysis

Associations between categorical variables were assessed using chi-square tests. Overall survival and progression-free survival was estimated using the Kaplan-Meier method and groups were compared with log-rank tests. The suggested most important prognostic factors were then included in the Cox proportional hazards regression model. The number of patients alive after three years was estimated and the median survival time calculated; p values ≤ 0.05 were regarded as significant. Data analysis was performed using SPSS 13.0.

Results

Patient characteristics are shown in Table 1. Most patients were between 50 and 70 years in all periods, but the last period included a considerably higher number of women over 70 years of age. The best overall survival rates were found in women under 50 years and the worst for those over 70 years for all three periods. The difference was significant for all periods (Table 2).The median- and 3-year survival was also better for the youngest and worse for the oldest women, but increased with time for all age groups.

The majority of the patients had serous papillary-type cancer. No significant differences in overall survival rates were found between the subtypes, but in many of the subgroups the number of patients was too low for reliable statistics.

The majority of patients had poorly differentiated cancer in all three periods. Median- and 3-year survival was best for those with well differentiated and lowest for those with poorly differentiated cancer in all periods. Median survival increased from one, one to two and four

Table 1. — *Characteristics of 776 patients with epithelial ovarian cancer Stage IIIC and ≥ 3-year total survival and median survival for different treatment periods.*

Chaacteristics	1984-1990 Survival			1991-1995 Survival			1996-2001 Survival		
	No.	≥ 3 yrs. %	median years	No.	≥ 3 yrs %	median years	No.	≥ 3 yrs %	median years
Age (years)									
≤ 49	42	43	1.4	61	41	2.0	58	52	3.4
50-59	44	20	0.9	80	34	2.0	88	45	2.4
60-69	71	28	1.1	83	29	1.3	85	44	2.7
≥ 70	21	24	0.8	46	13	0.8	83	25	1.5
Histology									
Serous	125		1.1	213		1.5	240		2.5
Mucinous	6		1.5	6		0.4	10		0.2
Endometroid	14		1.2	13		1.5	13		–
Clearcell	10		0.5	10		0.3	9		1.0
Mixed	6		1.1	8		1.3	13		1.1
Undifferentiated	4		1.5	6		1.2	10		0.8
Unclassified	10		1.0	14		1.1	19		4.9
Differential grade									
High	15	60	4.0	15	60	3.9	16	56	3.4
Medium	49	31	1.1	86	31	1.5	79	41	2.5
Poor	99	25	1.1	148	30	1.4	192	40	2.4
Unclassified	3	33	2.7	6	17	1.1	6	17	0.3
**Residual disease*									
0	43	51	3.0	71	52	3.8	80	63	5.1
≤ 2 cm	39	36	1.5	76	29	1.2	104	38	2.3
> 2 cm	96	17	0.7	122	18	0.8	129	30	1.7
Chemotherapy									
Platinum single-agent	83	23	1.0	61	18	0.8	49	24	1.5
Platinum combined	68	35	1.2	159	33	1.5	21	45	2.1
Paclitaxel combined	0	–		36	44	2.1	232	46	2.7
Others	23	30	0.6	7	29	1.7	6	0	0.1

*residual disease after interval debulking and/or primary surgery patients in some of the groups are missing because of variable registration in the records.

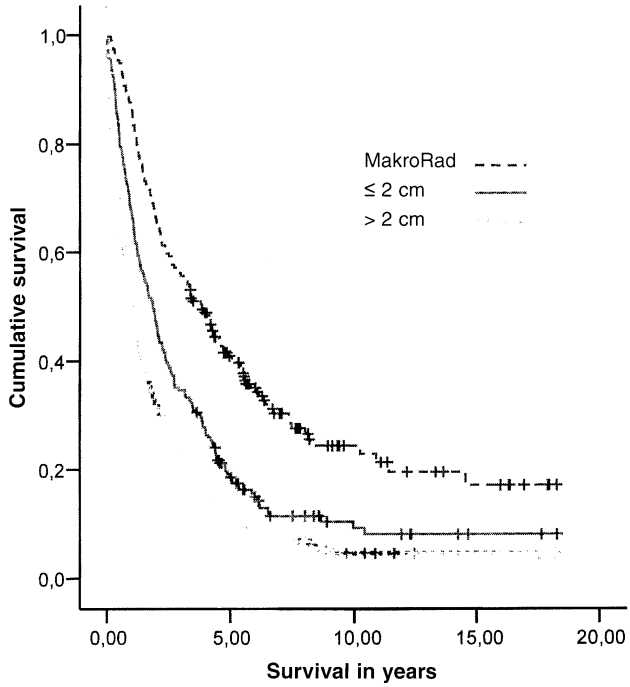
years from the first to the last period for those with poorly differentiated cancer. The degree of differentiation was not an independent prognostic factor for survival (Table 2).

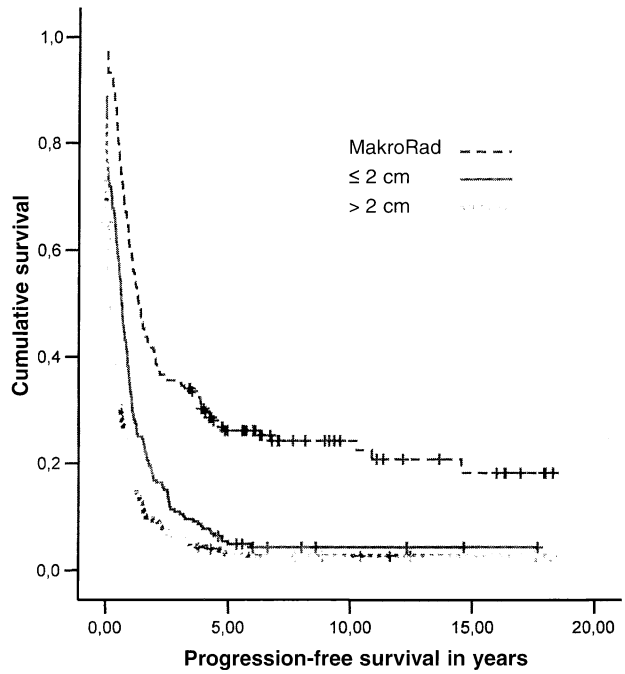
Macroscopically, only about 26% received radical surgery after interval debulking and/or primary surgery and that did not change with time. Most patients had residual disease > 2 cm in all periods which decreased from the first to last period from 53.6% to 42.0% (Table 1). Figures 1 and 2 show overall and progression-free survival in relation to how radical surgery was performed. The difference was significant in both cases ($p < 0.01$). When adjusting for other prognostic variables, patients who underwent radical surgery lived significantly longer ($p < 0.01$) than patients who had residual tumour ≤ 2 and > 2 for all periods except for the first period when tumour was ≤ 2 cm (Table 2). Overall median survival for patients who macroscopically were radically operated on increased from three years from 1984-1990, 3.8 years from 1991-1995 to 5.1 years from 1996-2001. For residual tumours ≤ 2 cm and > 2 cm the median survival increased from the first to the last period (1.5 and 0.7 years to 2.3 and 1.7 years). Where surgery was radical a total of 51% were alive more than three years in the first period and 63% in the last period, and where residual disease was > 2 cm, 17% and 30% were alive, respectively (Table 1).

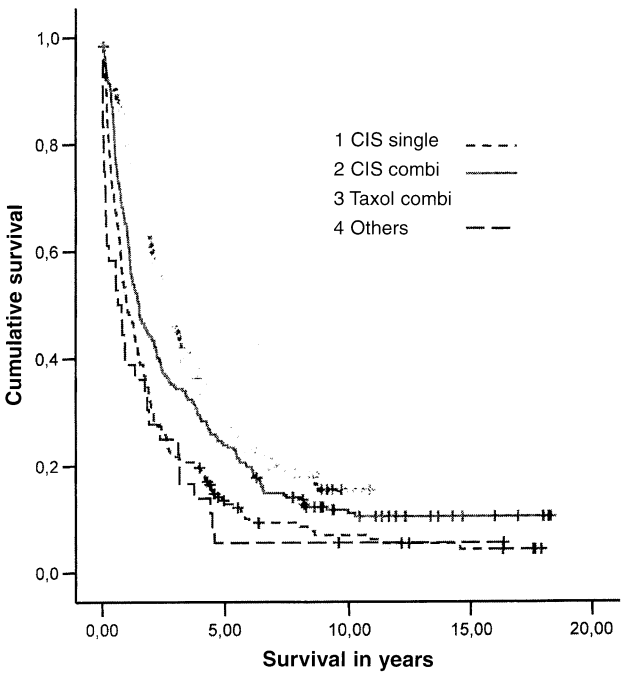
Figure 3 demonstrates overall survival for the different regimes of chemotherapy. Most patients were in the paclitaxel group and their prognosis was significantly better ($p < 0.01$) with a median survival of 2.7 years vs 1.5 years for cisplatin-based combinations, 1.1 years for single-agent cisplatin and 0.65 years for the rest. The 3-year survival rates were 44% and 33% for the paclitaxel group and the cisplatin-based combination-group, respectively, in the second period and 46% and 45% in the last period. The median survival time for the two chemotherapy groups mentioned was 2.7 years for the paclitaxel group and 2.1 for the other in the last period. Type of chemotherapy was an independent prognostic factor for overall, but not progression-free survival (data not shown). Chemotherapy with paclitaxel dominated the last 5-year period when few platinum combinations were given [21] compared to single platinum [49] (Table 1).

Overall survival for the three treatment periods is shown in Figure 4 demonstrating the significantly better survival in the last period. Using multivariate analysis, the time period was found to be an independent prognostic factor both for progression-free and overall survival (data not shown). Overall median survival rates for the three periods increased with time and were 1.1, 1.4 and 2.4 years, respectively.

From 1985 to 2000 the number of patients almost doubled (Table 1), and an increasing number of patients were referred for primary surgery at NRH (data not shown).







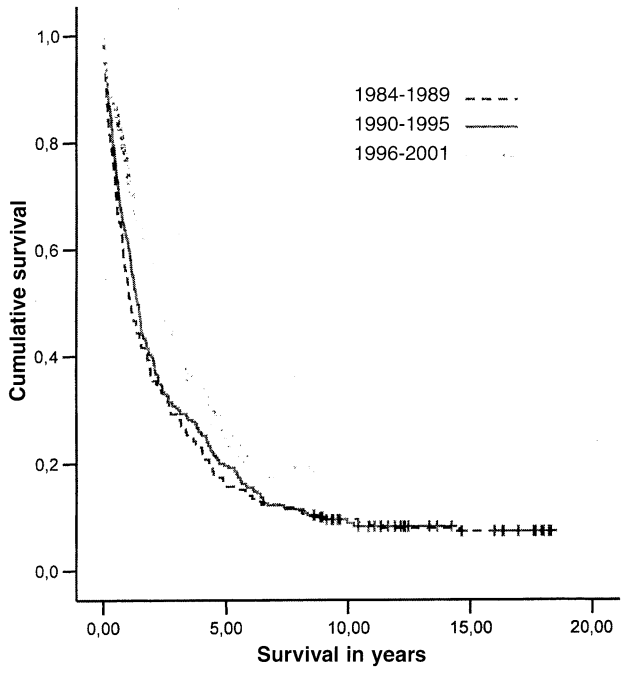


Figure 1. — Kaplan-Meier survival curves for epithelial ovarian cancer Stage IIIC for size of residual disease after interval debulking and/or primary surgery, + censored ($p < 0.01$).
Figure 2. — Kaplan-Meier progression-free survival curves for epithelial ovarian cancer Stage IIIC for size of residual disease after interval debulking and/or primary surgery, + censored ($p < 0.01$).
Figure 3. — Kaplan-Meier survival curves for epithelial cancer Stage IIIC for different chemotherapy treatment groups, + censored ($p < 0.01$).
Figure 4. — Kaplan-Meier survival curves for epithelial ovarian cancer Stage IIIC for different treatment periods, + censored ($p < 0.01$).

Table 2. — *Hazard ratios and 95% confidence interval (CI) for overall survival in patients with epithelial ovarian cancer Stage IIIC for three time periods (Cox regression).*

	Factors	p-values		Hazard ratios	95% CI	
Period	*Age (years)*	*0.08*			Lower	Upper
	≤ 49 category			1.0		
	50-59		0.23	1.34	0.83	2.16
	60-69		0.40	1.22	0.77	1.92
	≥ 70		0.01	2.25	1.20	4.21
	Differential grade	*0.36*				
	High category			1.0		
	Medium		0.14	1.65	0.86	3.20
1984-1990	Poor		0.07	1.77	0.95	3.32
	Unclassified		0.51	1.56	0.42	5.64
	**Residual disease*	*< 0.01*				
	0 category			1.0		
	≤ 2 cm		0.09	1.52	0.93	2.50
	> 2 cm		< 0.01	2.17	1.41	3.34
	Chemotherapy	*0.28*				
	Platinum single-agent category			1.0		
	Platinum combined		0.26	0.82	0.57	1.16
	Others		0.43	1.22	0.74	2.03
	Age	*0.08*				
	≤ 49 category			1.0		
	50-59		0.05	1.45	1.0	2.12
	60-69		0.42	1.18	0.79	1.74
	≥ 70		0.04	1.79	1.03	3.10
	Differential grade	*0.13*				
	High category			1.0		
	Medium		0.06	2.01	0.98	4.10
1991-1995	Poor		0.03	2.20	1.10	4.41
	Unclassified		0.55	1.41	0.46	4.33
	**Residual disease*	*< 0.01*				
	0 category			1.0		
	≤ 2 cm		< 0.01	1.94	1.34	2.81
	> 2 cm		< 0.01	2.29	1.60	3.27
	Chemotherapy	*0.22*				
	Platinum single-agent category			1.0		
	Platinum combined		0.70	0.92	0.61	1.40
	Paclitaxel + combined		0.08	0.62	0.36	1.06
	Others		0.71	1.18	0.49	2.82
	Age	*0.09*				
	≤ 49 category			1.0		
	50-59		0.24	1.30	0.84	2.00
	60-69		0.30	1.26	0.82	1.93
	≥ 70		0.01	1.77	1.12	2.80
	Differential grade	*0.31*				
	High category			1.0		
	Medium		0.12	1.77	0.87	3.62
1996-2001	Poor		0.13	1.70	0.85	3.38
	Unclassefied		0.08	2.76	0.90	8.48
	**Residual disease*	*< 0.01*				
	0 category			1.0		
	≤ 2 cm		< 0.01	2.00	1.34	2.99
	> 2 cm		< 0.01	2.65	1.81	3.90
	Chemotherapy	*< 0.01*				
	Platinum single-agent category			1.0		
	Platinum combined		0.47	0.78	0.40	1.53
	Paclitaxel + combined		0.31	0.81	0.54	1.22
	Others		< 0.01	4.40	1.78	10.90

* Residual disease after interval debulking and/or primary surgery.

Discussion

This study demonstrated that the amount of residual tumour after interval debulking and/or primary surgery and type of chemotherapy, age and time period are the most significant prognostic factors for survival of epithelial ovarian cancer FIGO Stage IIIC. This is in agreement with conclusions from earlier studies [4-12]. We did not find any significant difference in survival whether the patient had an interval debulking in addition to the primary surgery or not [27]. The amount of residual tumour proved itself to be an independent prognostic factor for overall survival and so did type of chemotherapy for the last time period. When the surgery was macroscopically radical, the time to first relapse was also significant. The longest survival, the hazard ratio and median survival results show that there is also something to be gained by leaving less than 2 cm tumour. A disappointingly low number of patients received radical surgery in all time periods but we possibly left less tumour in the last period as there were 12% fewer patients with residual tumour > 2 cm in the last compared to the first period. Median survival time increased with time independent of amount of tumour left but mostly for the radically operated patients. Taking into account that an increasing number of patients were over 70 years (who should have the poorest prognosis) and had an increased median survival appears to show some improvement. That the prognosis was better for the youngest age group and worse for the oldest has been demonstrated by many authors [8, 11].

In patients with advanced ovarian cancer there is little doubt that primary surgical debulking represents a cornerstone in the improvement of survival and quality of life [4-12]. The definition of optimal debulking varies between 0 and 2 cm for the maximum diameter of residual tumour. It is impossible to register the number of residual lesions. The maximum diameter of the residual tumour is also a rough measure of residual tumour, nonetheless, it provided valuable prognostic information also in this study.

Surgery should be as radical as possible and proper staging is important for the decision on adjuvant chemotherapy.

At a second operation lymph node staging is increasingly performed in early stages because lymph node staging is not performed by general gynaecologists at local hospitals. In the last time period, lymph node staging was performed in 81 patients and out of those 23 were upgraded to Stage IIIC [27]. Stage IIIC due to retroperitoneal lymph nodes has a better prognosis than abdominal Stage IIIC. This is in agreement with earlier findings, i.e., that patients operated on by specialists in gynaecological oncology have a better prognosis than those operated on by general gynaecologists [23-26].

We have shown that patients receiving paclitaxel in single or in combined agents have significantly longer survival (Figure 3) with 0.6 years longer median survival than those receiving combination platinum in the last two time periods (Table 1). Paclitaxel was most used during the last 5-year period and the survival benefit was also demonstrated by McGuire *et al.* and Piccart *et al.* [17, 18]. The 3-year survival rate was also 11% better in the second period but in the last period there was surprisingly no difference. This could be due to the relatively few patients getting cisplatin in combination in the last period and few getting paclitaxel in the second period. The increasing number of patients over 70 years in the last period could be another explanation and regimes containing paclitaxel add more benefit to short-term than to long-term survival.

We have shown that overall survival was significantly better in the last time period (Figure 5). This may be partially because of improved cytoreduction. Our opinion is also that surgical radicality is better described by gynaecological-oncologists which explains the unchanged number of radically operated patients with time. Improved prognosis could also be due to stage migration because of more lymph node staging as mentioned above. However this means that these patients get adjuvant chemotherapy which in turn improves the prognosis.

Primary surgical debulking in Stage IIIC patients with ovarian cancer is currently accepted as the standard therapy in Norway, the United States and in a great majority of European countries. Debulking surgery prior to chemotherapy maximises the probability of avoiding chemotherapy resistance by reducing the number of resistant clones and therefore improves disease outcome. Neoadjuvant treatment should be evaluated in prospective randomised clinical trial protocols and can be used for patients with medical contraindications for primary cytoreduction.

As earlier described, we found that poorly differentiated tumours had a poorer prognosis than well differentiated tumours, but in our study, as opposed to Makar et al's, the degree of differentiation was not an independent prognostic factor for either time period when adjusted for our other chosen factors [8].

An increasing number of patients are referred to NRH for primary surgery. That overall and progression-free survival rates have improved significantly with time is partly explained by the addition of paclitaxel and partly by better surgery.

This report demonstrates that type of chemotherapy, amount of residual tumour after primary surgery and time period were independent prognostic variables for overall survival. We believe that further centralisation of primary surgery with lymph node staging of advanced ovarian cancer can contribute to a better prognosis.

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