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Ovarian cancer Stage IIIC. Consequences of treatment level on overall and progression-free survival

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Summary

Background: Maximum cytoreduction at primary surgery has been found to be one of the strongest prognostic factors for survival of ovarian cancer. The aim of the study was to investigate the influence of hospital level (primary vs secondary care centre), number and timing of surgery and chemotherapy on how radical the surgery was at primary treatment of epithelial ovarian cancer Stage IIIC.

Material and Methods: A retrospective study based on record information from all patients with epithelial ovarian cancer Stage IIIC treated at the Norwegian Radium Hospital (NRH) 1985-2000, in total 776, subdivided into four groups: 1) Local primary surgery, no direct re-operation at NRH, no interval debulking; 2) local primary surgery, no direct re-operation, but interval debulking after 3-4 courses of chemotherapy at NRH; 3) local primary surgery, direct re-operation at NRH, no interval debulking; 4) primary surgery at NRH. Lymph node biopsies at re-operation in early stages and upgrading of stage where necessary were registered.

Results: Whether surgery was radical or not was an independent prognostic factor for overall and progression-free survival. The treatment group was an independent prognostic factor for overall, but not for progression-free survival. Group 3 had significantly the best overall and progression-free survival ($p = 0.01$ and 0.05). For macroscopically radical surgery both overall and progression-free survival were found significantly better for groups 3, 4 and 1 than for group 2. Most lymph node biopsies were performed during the last period and 28% were upgraded from Stage I and II to IIIC. More patients were referred for primary surgery at NRH during the last 5-year period during which overall survival and time to progression were significantly better.

Interpretation: Whether primary surgery is radical or not is a significant prognostic factor for survival and primary surgery is best performed by specialists in gynaecological oncology.

Key words: Ovarian cancer; Treatment level; Survival.

Introduction

Worldwide, epithelial ovarian cancer is one of the most frequently occurring types of cancer in women and the most common cause of death in gynaecological cancer. Age-adjusted incidence of ovarian cancer in Scandinavia is among the highest in the world. In Norway the incidence has been reasonably stable over the last 20 years, approximately 14 per 100,000 women. This equates to around 480 new cases diagnosed annually [1]. There are no good screening methods for early detection of cancer development. This leaves circa 70% of women with newly discovered ovarian cancer with advanced disease at the time of diagnosis (FIGO staging). Even though the 5-year survival rate over the last 20 years has gradually improved for all stages, from 39% in the period 1975-1979 to 43% in the period 1990-1994, it is still disappointingly low [2, 3]. More than 90% of ovarian cancer is epithelial.

In 1975 Griffith [4] published data indicating a survival benefit where residual tumours were successfully reduced to < 1.5 cm with surgery. These findings have been verified by a number of other authors including a large study from The Norwegian Radium Hospital published in 1971, where also the significance of debulking surgery was pointed out. In that study though, the comparisons were made between complete and incomplete tumour removal, and no adjustments were made for prognostic and other possibly confounding factors [5]. Bristow *et al.* published the effect of a relevant meta-analysis study 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 receive optimal tumour reduction [6]. Eisenkop *et al.* showed in a study from 2003 that macroscopically radical cytoreduction was significantly more important for survival than the spreading of metastatic disease before surgery [7]. By cytoreductive surgery it is meant maximum surgical reduction of tumour tissue without an absolute requirement that macroscopic surgery is radical. A common definition has been that the largest residual tumour should be less than 1 to 2 cm in diameter.

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In advanced cancer with suboptimal primary surgery, some patients receive three to four courses of chemotherapy before a new attempt of optimal surgical cytoreduction. In a randomised study patients with suboptimal cytoreduction at primary surgery were randomised to either interval debulking or no new surgery after three courses of chemotherapy. The study demonstrated significantly better survival in the intervention group [8, 9]. Another study showed no better overall or progression-free survival at secondary cytoreductive surgery after cisplatin and paclitaxel courses following maximum primary cytoreductive surgery [10].

Many studies have demonstrated better survival for women with ovarian cancer operated on by gynaecologists rather than general surgeons [11-15]. Junor *et al.* found that patients with Stage III disease and remaining residual tumour over 2 cm had a better prognosis when operated on by specialists in gynaecological oncology compared to general gynaecologists [13]. Olaitan *et al.* [14] confirmed these findings. For the same group a better survival rate has also been found at university hospitals vs non-teaching hospitals [15, 16]. In a doctoral thesis in 2003 S. Tingulstad demonstrated significantly better survival rates for patients with advanced ovarian cancer referred for primary surgery at a regional hospitals vs case-controls primarily operated on at local/central hospitals (26% vs 4% 5-year survival, $p = 0.01$) [13].

The Norwegian Radium Hospital (NRH) is one of four cancer centres with 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 62% of the Norwegian population. The aim of the study was to investigate the influence of hospital level (primary vs secondary centre), number and timing of surgery and chemotherapy on how radical the surgery was at primary treatment of epithelial ovarian cancer Stage IIIC and its survival. Thereafter to discuss possible changes in prognosis related to changes in treatment strategy.

Material and Methods

All patients with histologically verified epithelial ovarian cancer Stage IIIC treated at NRH during the 16-year period from 1985-2000 were included in this study, a total of 814. Fifteen with borderline tumours were excluded as well as 23 with delayed primary surgery due to neoadjuvant chemotherapy. That left 776 patients to be analysed. Data was collected from patient records found via the hospital code registry for diagnosis and operation. Nineteen records of all stages were not found, but an unknown number out of those were not epithelial ovarian cancer and would have been excluded. Registered parameters included age, FIGO-stage, histological type and degree of differentiation, time and hospital level for primary surgery, whether final surgery was radical at primary treatment or not and type of chemotherapy. Types of chemotherapy were subdivided into four groups (group 1 = single cisplatin, group 2 = platinum in combination with other non-paclitaxel cytotoxic drugs, group 3 = all regimes with paclitaxel and group 4 = others). Chemotherapy was given either as three to four courses after primary surgery before interval debulking, or as six to nine courses (most commonly) 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 1988). Histological classification was done by special gynaecological pathologists at NRH according to criteria defined by the World Health Organisation (WHO).

Patients were grouped as follows: 1) Local primary surgery, no direct re-operation at NRH, no interval debulking, 2) local primary surgery, no immediate re-operation at NRH, but interval debulking after three to four courses of chemotherapy, 3) local primary surgery, direct re-operation at NRH, no interval debulking and 4) primary surgery at NRH.

For all stages directly re-operated on at NRH it was noted whether lymph node biopsies were taken for correct staging, and whether the re-operation caused a higher staging ("restaging") or not. Times for completed primary treatment, for first sign of progression and for final status (dead, alive, emigrated) at the end of registration in autumn 2004 were registered. Data for final status was 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 the log-rank test. The factors that were significant in the log-rank test were included in the Cox proportional hazards regression model. The model was then restricted by backward elimination. The number of patients alive and the number of patients alive and progression-free after two years and five years was estimated.

Data analysis was performed using SPSS 12.0; p values ≤ 0.05 were regarded as significant.

Results

Patient characteristics are shown in Table 1. By applying univariate analysis, significant differences were found in both overall and progression-free survival between the different age groups. In multivariate analysis with five other prognostic variables a decreasing survival rate with age was found (data not shown).

The majority of the patients had a serous papillary-type cancer. However, the number of patients in some of the histological groups was too low for survival comparison.

In all the treatment groups the majority of patients had poorly differentiated cancer. In group 3 the proportion of highly differentiated cancer was significantly higher than in the other groups. Degree of differentiation was significant in univariate analysis, but was not a significant factor in the multivariate model. Patients with highly differentiated cancer seemed to have a better overall survival. Of those directly re-operated on at NRH, a higher percentage of cases of poorly

Table 1. — *Characteristics of 776 women with Stage IIIC epithelial ovarian cancer operated on at different levels:*
1. Local primary surgery, no direct re-operation at NRH, no interval debulking
2. Local primary surgery, no direct re-operation at NRH, interval debulking
3. Local primary surgery, direct re-operation at NRH, no interval debulking
4. Primary surgery at NRH.

Characteristics	Number of patients (%)	1	2	3	4	p value
Age (years):						
≤ 39	36 (5)	11 (3)	8 (5)	7 (10)	10 (5)	
40-49	125 (16)	55 (17)	26 (16)	15 (21)	29 (14)	
50-59	210 (27)	85 (26)	56 (34)	21 (30)	48 (23)	0.06
60-69	240 (31)	98 (30)	52 (31)	14 (20)	76 (37)	
≥ 70	157 (20)	77 (24)	25 (15)	13 (19)	42 (21)	
Histology:						
Serous	582 (76)	245 (75)	134 (81)	39 (56)	164 (80)	
Mucinous	22 (3)	12 (4)	2 (1)	6 (9)	2 (1)	
Endometroid	40 (5)	20 (6)	7 (4)	5 (7)	8 (4)	
Clearcell	31 (4)	12 (4)	5 (3)	5 (7)	9 (4)	
Mixed	27 (4)	9 (3)	4 (2)	5 (7)	9 (4)	
Undifferentiated	20 (3)	10 (3)	3 (2)	5 (7)	2 (1)	
Not classified	42 (6)	17 (5)	10 (6)	5 (7)	10 (5)	
Differentiation:						
1 Well	48 (7)	16 (5)	7 (4)	14 (23)	11 (6)	
2 Moderate	214 (30)	98 (32)	47 (30)	9 (15)	60 (31)	< 0.01
3 Poor	442 (62)	183 (59)	103 (65)	37 (61)	119 (62)	
Residual disease:						
No macroscopic tumor	194 (25)	59 (18)	71 (43)	29 (41)	35 (17)	< 0.01
Rest ≤ 2 cm	220 (29)	81 (25)	55 (33)	17 (24)	67 (33)	
Rest > 2 cm	353 (46)	185 (57)	41 (25)	24 (34)	102 (50)	
Chemotherapy:						
Platinum single	193 (26)	77 (24)	48 (29)	12 (18)	56 (28)	
Platinum comb	246 (33)	101 (32)	77 (46)	26 (38)	42 (21)	
Paclitaxel comb	268 (36)	123 (39)	39 (23)	20 (29)	86 (43)	< 0.01
Others	44 (6)	17 (5)	3 (2)	10 (15)	14 (7)	
Period:						
1985-1990	181 (24)	63 (19)	46 (28)	20 (29)	52 (25)	
1991-1995	268 (35)	103 (32)	77 (46)	26 (37)	62 (30)	< 0.01
1996-2000	319 (42)	160 (49)	44 (26)	24 (34)	91 (44)	

Table 1 shows an increasing number of treated patients from 1985 to 2001. More patients were referred for primary surgery at NRH (25% vs 44%), but there were also more receiving only chemotherapy at NRH following primary surgery performed at local hospitals (19% vs 49%). Comparing 1996-2001 with earlier periods significantly better overall and progression-free survival rates were found ($p < 0.01$) and using regression analysis, the 5-year period itself was found to be an independent prognostic factor both for overall and progression-free survival.

Figures 1 and 2 show overall and progression-free survival for the four treatment groups, and Table 3 shows 2- and 5-year overall and progression-free survival for the groups. Patients directly re-operated on at NRH (group 3) lived significantly longer (RR = 0.66) with a median survival rate of 3.2 years, whereas those not directly re-operated on but interval debulked (group 2) lived the shortest (RR = 1.33); median survival rate 1.5 years. RR was calculated in comparison to group 4. Using multivariate analysis (Table 2) the treatment group was found to be an independent prognostic factor for overall but not for progression-free survival.

For patients described as having been macroscopically radically operated on a significant difference in overall and progression-free survival was found among the groups ($p < 0.01$ and $p = 0.01$). Patients in groups 1, 3 and 4 lived significantly longer than patients in group 2 (Figure 3).

An overview of lymph node biopsies at direct re-operation together with if they caused a registered higher staging of the disease or not is shown in Table 4. Lymph node biopsies were almost exclusively taken in the last 5-year period and for 23 out of 81 (28%) re-operations with lymph node biopsies, a restaging of FIGO Stage I and II to IIIC was the result.

Discussion

Only indirect documentation exists on the effect of cytoreductive surgery. However, retrospective studies have consistently identified surgical cytoreduction as an independent prognostic factor [6].

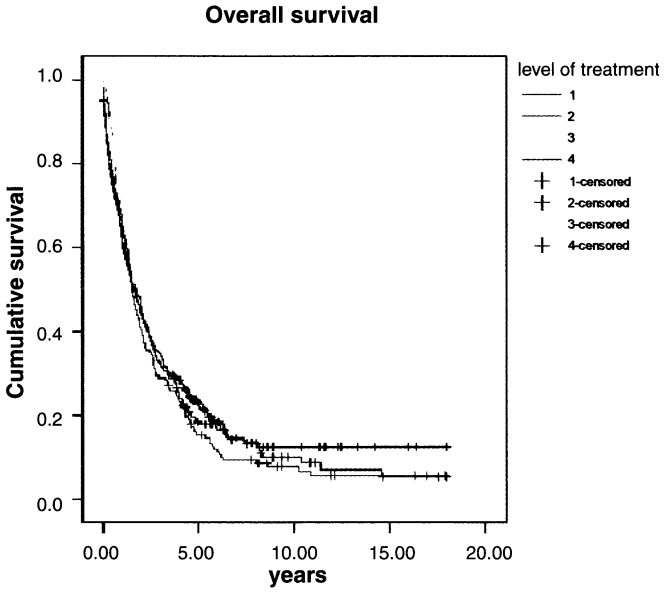
The strength of the conclusions drawn is limited by the retrospective design of this study. The current documentation does not reveal whether the observed effect of cytoreduction is a direct cause of the surgical intervention or an indirect result of successful surgery selecting patients with a favourable biological profile.

compared to highly differentiated cancers were alive after two years. Moreover, for group 3 compared to the other treatment groups a strikingly high percentage of those with poorly differentiated cancers were alive after five years and also without disease after two and five years (data not shown).

Multivariate analysis demonstrated that radical surgery was an independent prognostic factor for both overall (Table 2) and progression-free survival (not shown). Macroscopically most were radically operated on in group 2 (43%) and group 3 (41%) compared to 18% for group 1 and 17% for group 4. Still, the overall and progression-free survival rates were significantly worse for group 2 and best for group 3. The same apparently paradoxical situation was found for the 2- and 5-year survival rates (curve 1 and 2, Table 3). Few cases in group 2 received chemotherapy containing paclitaxel (23%) compared to the other groups.

Type of chemotherapy was significant in univariate analysis, and patients receiving paclitaxel seemed to have the best total- and progression-free survival. Type of chemotherapy was also found to be an independent prognostic factor for overall survival. Compared to other regimes paclitaxel was most often given to patients who were primarily operated on at NRH (43%), but compared to the other treatment groups, group 1 received most paclitaxel courses (46%).

Fig. 1



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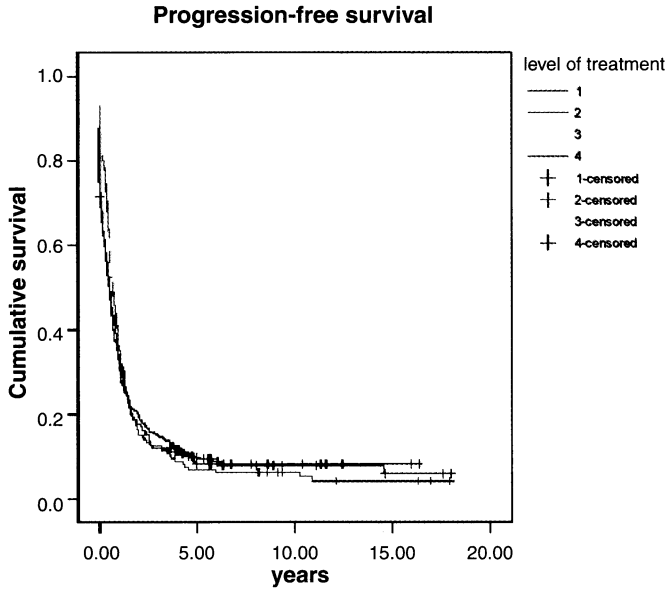
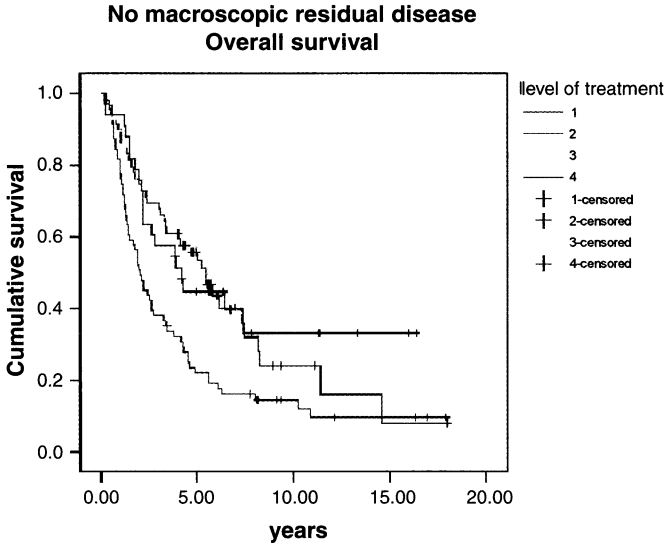


Fig. 3



Figures 1, 2, 3 — Epithelial ovarian cancer Stage IIIC.

1. Local primary surgery, no direct re-operation at NRH, no interval debulking.
2. Local primary surgery, no direct re-operation at NRH, interval debulking.
3. Local primary surgery, direct re-operation at NRH, no interval debulking.
4. Primary surgery at NRH.

It is clear that the prognosis is best for those being directly re-operated on (group 3) and worst for those receiving chemotherapy before re-operation with interval debulking (group 2), but the reasons for this are uncertain. One reason can be that more patients in group 3 were upgraded to Stage IIIC after lymph node staging, and Stage IIIC with only positive nodes has a better prognosis than intraabdominal Stage IIIC.

Many patients were radically operated in groups 2 and 3, 43% and 41%, respectively. Radical surgery was a strong prognostic factor in our material, and is in agreement with previous findings [4-6]. This would indicate that surgery is best performed by specialists in gynaecological oncology as described earlier [11-15]. Our material could not however demonstrate that radical surgery gives a significantly better survival rate when primary surgery or direct re-operation takes place at NRH and not at the local hospital as we supposed (Figure 3). The reason for this and that the overall survival for those primarily operated at NRH was not significantly better than for those only being operated on at their local hospital, and that there were fewer patients operated on at NRH with no residual disease, can be seen as a result of an extensive selection of patients with advanced Stage IIIC referred for primary surgery at NRH. That Group 2 (Figure 3), which had the worst prognosis, also contained the highest number of patients with no residual disease, is difficult to explain since interval debulking was also performed by specialists in gynaecological oncology. Both 2- and 5-year overall and progression-free survival rates for the radically operated cases in this group are shorter than for the other radically operated cases (data not shown). We know though, that patients with the most advanced Stage IIIC most

Table 2. — *Prognostic factors for overall survival in patients (776) with epithelial ovarian cancer in FIGO Stage IIIC.*

Potential factors	Log-rank tests	Cox-regression	Relative hazards	95% CI	
	p value	p value			
Treatment group		< 0.01			
Group 1		0.96	0.99	0.81	1.22
Group 2	0.01	0.02	1.33	1.04	1.69
Group 3		0.02	0.66	0.46	0.93
Group 4		reference	1.0		
Age in years		< 0.01			
≤ 39		< 0.01	0.30	0.18	0.49
40-49		< 0.01	0.61	0.45	0.82
50-59	< 0.01	0.06	0.77	0.59	1.01
60-69		< 0.01	0.65	0.50	0.83
≥ 70		reference	1.0		
Chemotherapy		< 0.01			
Platinum single	< 0.01	< 0.01	0.57	0.38	0.83
Platinum combined		< 0.01	0.51	0.34	0.74
Paclitaxel combined		< 0.01	0.40	0.26	0.63
Others		reference	1.0		
Residual disease		< 0.01			
No macroscopic tumor	< 0.01	< 0.01	0.39	0.31	0.49
≤ 2 cm		0.01	0.76	0.63	0.93
> 2 cm		reference	1.0		
Period		0.09			
1985-1989	< 0.01	0.10	1.27	0.95	1.70
1990-1995		0.03	1.31	1.03	1.67
1996-2000		reference	1.0		
Degree of differentiation	0.01				

Pearson's chi-square test.

Table 3. — *Overall and progression-free survival for 776 patients with epithelial ovarian cancer, Stage IIIC operated on at different levels (1-4) (see Table 1).*

Treatment group	% patients alive ≥ 2 years		% patients alive ≥ 5 years		p value survival (curves)	
	Overall	Prog free	Overall	Prog free	Overall	Progr free
1	44	20	18	7		
2	40	15	15	7	0.01	0.05
3	60	31	32	18		
4	46	18	16	7		

Table 4. — *Lymph-node staging and upgrading of FIGO-stage in patients with epithelial ovarian cancer primarily operated on at local hospitals and re-operated immediately at NRH, divided in periods.*

Period			Upgrading to IIIC		Total
			no	yes	
1984-1989	Lymph-node staging	no	113	11	124
		yes	1	0	1
	Total		114	11	125
1990-1995	Lymph-node staging	no	36	4	40
		yes	4	7	11
	Total		40	11	51
1996-2001	Lymph-node staging	no	7	3	10
		yes	58	23	81
	Total		65	26	91

often receive chemotherapy before re-operation to possibly make the tumour more "operable". Possibly, bulky tumour masses with poor central blood supply may reduce chemotherapy sensitivity and eventually increase risk of chemo-resistant disease development. Large tumours provide a rather low growth fraction and higher numbers of spontaneous mutations and this will increase absolute numbers of resistant cells in tumour colonies [17]. Not finding better survival might be due to chemotherapy making the disease subclinical, only to reappear more quickly. Van der Burg *et al.* found improved survival, but one cannot generally recommend planned interval debulking from their study, since it does not compare optimal primary surgery with optimal interval debulking [8, 9]. The GOG-study did not demonstrate better survival with interval debulking after primary maximum cytoreduction with < 1 cm residual tumour [10]. Our treatment group 2 is inhomogeneous containing both primarily optimally and sub-optimally operated patients, with an unknown but likely high amount of residual tumour tissue. With only a few patients in this group receiving chemotherapy containing paclitaxel, this is probably also an important reason for poor survival rates, even though many in this group macroscopically were left with no residual disease. In Norway interval debulking was mostly performed in periods before the start of paclitaxel usage (Table 1).

Paclitaxel was most used during the last 5-year period and gave a clear survival benefit. An increasing proportion of patients were referred for primary surgery at NRH. That most paclitaxel-courses were given to patients primarily operated on at local hospitals may explain the fact that the short-term survival for this group was approximately the same as for group 4.

For overall survival and time to first sign of progression to have become significantly better with time is partly explained by the addition of paclitaxel and partly by better surgery. By more consequently taking lymph node biopsies at re-operation and at primary surgery, a more correct staging is achieved and treatment is more adequate. This must be part of the reason that group 3 has done so well.

The main conclusion is that the quality of surgery is an important prognostic factor for survival. Primary surgery for ovarian cancer is best performed by specialists in gynaecological oncology. A further increase in centralisation to teaching hospitals for primary surgery of ovarian cancer will probably give patients an additional survival benefit. The only way to show that is to do prospective studies.

The above-mentioned conclusion is supported by an evidence-based review [18] and by a prospective registration study by Paulsen *et al.* [16] who showed improved short-time survival for Stage IIIC ovarian cancer patients operated on primarily at teaching hospitals. All patients in Stage IIIC and operated on in Norway from 2002 are registered via

the Norwegian cancer registry. The hospitals were grouped as teaching or non-teaching hospitals. The surgeons were classified as specialised gynaecologists, general gynaecologists and general surgeons. Follow-up time ranged from 455-820 days. Of the women operated on at university hospitals 79% were alive after 450 days vs 62% at non-university hospitals ($p = 0.02$). Applying multivariate analysis for correction of prognostic factors demonstrated a hazard ratio of 1.83 when patients were operated on at a non-teaching hospital. Women undergoing surgery by specialists compared to general gynaecologists had a 20% improved survival ($p < 0.01$).

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