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REVIEW ARTICLE

Pattern of care and impact of participation in clinical studies on the outcome in ovarian cancer

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The purpose of this study was to evaluate the pattern and quality of care for ovarian cancer in Germany and analyze prognostic factors with emphasis on characteristics of treating institutions, hospital volume, and participation in clinical trials. This study utilized national survey including patients with histologically proven invasive epithelial ovarian cancer diagnosed in the third quarter of 2001 including descriptive analysis of pattern of surgical care and systemic treatment in early (FIGO I–IIA) and advanced (FIGO IIB–IV) ovarian cancer and both univariate and multivariate analysis of prognostic factors. One third of all patients diagnosed in the third quarter of 2001 in Germany, 476 patients, were included. Standard care according to German guidelines was provided to only 35.5% of patients with early ovarian cancer. Recommended chemotherapy was given to 78% in advanced disease. Multivariate analysis showed advanced stage, poor performance status, comorbidity, ascites, and treatment in an institution not participating in cooperative studies to be associated with inferior survival. Non-participation was associated with an 82% increase of risk (HR = 1.82; 95% CI, 1.27–2.61; $P = 0.001$). Hospital volume did not affect treatment outcome. Adherence to treatment guidelines showed remarkable variety among German hospitals, indicating options and need for improvement. Selecting an institution that participates in cooperative trials might be an option for individual patients seizing the chance for better quality of care even when individual factors might hamper enrollment in a study.

KEYWORDS: guideline, hospital volume, ovarian neoplasm, pattern of care, quality of care, study participation.

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Guidelines for the treatment of invasive epithelial ovarian cancer are comparable in most countries and are available for Germany as well[1]. Despite the availability of standard guidelines throughout Europe, treatment results differ markedly among the countries participating in the EUROCARE studies, even if age

adjusted survival analyses were performed[2]. One quoted explanation for varying treatment results is the existence of subspecialty training programs in gynecological oncology. Several reports showed superior outcome for patients treated by specialists both in Northern America[3–6] and in Europe[7,8]. However, these reports also showed the large variety of treatment results still existing in countries with established programs. The existence of an established subspeciality did not seem not to be directly predictive for outcome in Europe[2].

Other factors reported to be associated with better outcome in oncology were hospital volume[9,10] and participation in clinical studies[11,12]. The validity of the latter has been questioned due to several methodologic pitfalls including selection bias resulting in noncomparability of patients treated within study protocols and those treated outside trials[13].

The Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Organkommission OVAR, a subcommittee of the German Cancer Society, has started a program aiming at the improvement of outcome in ovarian cancer in 1999. Parts of this program are biannual editing of the German Guidelines for Diagnostics and Treatment of Ovarian Tumours[1], educational programs, and surveys of the pattern of care of ovarian cancer in Germany. The last was first performed for patients diagnosed in 2000[12,14] and was repeated for patients diagnosed in the third quarter of 2001 (Q III 2001), which is the subject of this report.

Materials and methods

In phase I, all 1 123 German gynecology departments were contacted and asked to report the numbers of newly diagnosed patients with ovarian cancer treated in 2001 and whether they were members of one of the two German cooperative study groups, ie, the AGO Ovarian Cancer Study Group with 312 associated centers and the Northeastern Society of Gynaecologic Oncology with 99 associated centers. Phase II was initiated approximately 1 year after diagnosis. All responding hospitals were asked to document all patients diagnosed in Q III 2001 and to send surgical and pathology reports. Only patients with newly diagnosed and histologically proven epithelial invasive ovarian cancer were accepted. Trained data managers cross-checked report forms with surgical and pathologic reports and queries were cleared by mail. Follow-up questionnaires were sent, and survival data up to 2 years after diagnosis were collected.

The main outcome endpoint was survival calculated from the day of diagnosis to the date of last contact or death. Secondary endpoints were adherence to treatment guidelines. Standard care for early ovarian cancer stages FIGO I–IIA was defined as complete surgical staging including eight items: (1) vertical laparotomy, (2) total abdominal hysterectomy, (3) bilateral salpingo-oophorectomy with (4) removal of all tumor tissue, (5) omentectomy, (6) peritoneal sampling, (7) cytology, and (8) pelvic and para-aortic lymph node staging. However, total abdominal hysterectomy and bilateral salpingo-oophorectomy were not deemed mandatory in patients with highly differentiated FIGO IA tumors and an option for fertility sparing surgery. Adjuvant platinum-based chemotherapy was regarded as standard of care for all patients with early ovarian cancer except those with FIGO IA and highly differentiated tumors. Standard care for more advanced disease stages FIGO IIB–IV contained surgery aiming at maximal debulking and administration of chemotherapy containing platinum and paclitaxel, the latter according to the German guidelines.

Patient variables included were age (<65 vs ≥ 65 years), performance status according to Eastern Cooperative Oncology Group (ECOG), comorbidity defined as concurrent illness influencing choice or performance of therapy, and history of second malignancies. Disease variables were stage, tumor grade, histologic subtype, presence of ascites of >500 mL. Characteristics of treating institutions were hospital volume defined as treating 1–15 versus 16+ newly diagnosed ovarian cancer patients per year and participation in clinical studies of one of the two German cooperative study groups. The study secretaries of both study groups checked all hospital declarations. Some of the hospitals participated only in selected studies, some participated in both study groups. However, the effect of participation in cooperative study groups was deemed to cover much more than only recruiting some patients. Therefore, study participation was also counted if no patient was recruited within the observation period but if patients had been recruited before Q III 2001.

Data management and statistical analysis were performed in SPSS version 11.0 (SPSS Inc., Chicago, IL). Continuous data were summarized using descriptive statistics and categoric data using frequency counts and percentages. Between-group comparisons were assessed with the two-tailed *t*-test (for continuous variables) and Pearson chi-square test (for categoric variables). Survival curves were prepared with the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards model was used to assess the relationship between survival and some variables. Firstly, patient characteristics, disease

variables, and characteristics of treating institutions were evaluated separately using univariate models. Secondly, all variables were entered simultaneously into a multivariate model. The second approach failed to identify additional significant factors. Therefore, a final model using only the significant variables from the univariate analysis and the two treatment variables (hospital volume and participation in clinical studies) was fitted. In all analyses, *P* values greater than 0.05 (two-tailed) were considered not significant.

Results

In phase I, 481 of 1123 gynecological departments responded (42.8%). Thirty-eight hospitals indicated that they did not treat ovarian cancer patients at all. The remaining 443 hospitals indicated that they had treated 5272 ovarian cancer patients in 2001. The self-estimated numbers would account for approximately 90% of all invasive ovarian cancers diagnosed annually in Germany. In 1998, 7437 ovarian malignancies were diagnosed in Germany[15] including approximately 5853 cases of invasive epithelial ovarian cancer[16]. A larger number of hospitals with higher patient volumes participated in phase II. The 165 hospitals that took part reported that they had treated 2682 patients, which accounted for 48% of all patients treated annually. These hospitals documented 517 patients from Q III 2001. Twenty-eight patients had to be excluded because first diagnosis was dated before July 1, 2001, and a further 13 patients were found ineligible because of wrong histology. The analysis was based on the remaining 476 who represented 34% of 1413 patients diagnosed quarterly in Germany.

Overall, only 59 patients were enrolled in prospectively randomized studies, but 80 of the 165 hospitals (48.5%) were participating in cooperative study groups. These 165 study hospitals documented 57.8% of patients in phase II studies. A cutoff of 16 patients per year was chosen for analysis of hospital volume because it represented the median split of the patient population: 238 patients (50.0%) were treated in hospitals with an annual caseload of 16+ patients. The latter category accounted for 55 of 165 hospitals (33.3%).

The mean age of the study population was 63 years (range, 20–97). Second malignancies were reported in 14.3% of patients. Among these, the most common were breast (39.7%), uterine (35.3%), and colon cancer (11.8%). The majority of patients were diagnosed with advanced ovarian cancer. Two hundred sixty-seven patients (56.1%) suffered from FIGO III disease. Of these, 82.0% had FIGO stage IIIC. Fifty-four patients (11.3%) were diagnosed stage IV. Patients in study clinics had higher FIGO stages and more frequently poorer differentiated tumors (Table 1).

Early ovarian cancer FIGO stages I–IIA

One hundred twenty-four patients were diagnosed with FIGO I–IIA ovarian cancer; among these seven patients were younger than 50 years and had FIGO IA G1 tumors. Standard surgical staging was defined

Table 1. Patient characteristics (bold figure indicates $P < 0.05$, χ^2 test)

	All	Hospitals participating in studies	Hospitals without study participation	*P* value[a]	High-volume hospitals (16+ per year)	Low-volume hospitals (1–15 per year)	*P* value[a]
Hospitals (*n*)	165	80	85		55	110	
Patients (*n*)	476	275	201		238	238	
Mean age (years)	63	63	63	0.829	63	62	0.377
65+ years (%)	46	45	46	0.945	45	46	0.782
PS ECOG[b] 0/1 (%)	79	79	79	0.987	79	79	1.000
Comorbidity (%)	24	24	25	0.663	21	27	0.135
Second cancer (%)	14	12	17	0.161	15	13	0.600
% FIGO							
I	24	18	32		21	28	
II	8	8	9		8	8	
III	56	60	50		60	52	
IV	11	13	9	**0.004**	11	12	0.268
Grading G3/4 (%)	45	50	39	**0.017**	49	42	0.117
Serous histology (%)	69	71	66	0.234	68	70	0.766
Ascites >500 mL (%)	40	40	40	0.989	45	36	**0.040**

[a] χ^2 test.
[b] PS ECOG: performance status according to Eastern Cooperative Oncology Group criteria.

according to the German guidelines and contained eight items as pointed out above. Overall, only 15 of 124 patients (12.1%) with early ovarian cancer in 2001 received complete surgical staging. Fifty-three patients (42.7%) had surgical staging with none or only one item missing. Patients in study hospitals had a higher chance of receiving more complete staging than those treated in hospitals not participating in trials (Fig. 1). This held true if 0–1 versus more missing items were analyzed (OR = 2.59, 95% CI: 1.25–5.39; $P = 0.010$). No such association was found for hospital volume (OR = 1.94, 95% CI: 0.94–4.00; $P = 0.072$). Two of the three items most frequently omitted neither need special surgical skills nor are associated with remarkable burden for the patient: peritoneal biopsies and cytology were missed in 68.5% and 35.5% of patients, respectively. No lymph node staging was performed in almost half (46.8%) of the patients (Table 2).

Twenty patients had highly differentiated tumors FIGO IA and therefore should not have received adjuvant chemotherapy. However, two of these patients received chemotherapy. One hundred four patients fulfilled the criteria for adjuvant chemotherapy, but only 66 (63.5%) received any adjuvant platinum. Combining surgical staging with none or only one item missing and adjuvant platinum therapy revealed that only 44 of 124 patients (35.5%) with early ovarian cancer received the recommended treatment. Patients treated in study centers had a more than three-fold chance of receiving standard treatment compared to patients not attending a study center (50.0% vs 23.5%; OR = 3.25, 95% CI: 1.51–7.00; $P = 0.002$). In contrast, hospital volume showed no significant impact on quality of care for early ovarian cancer (40.7% vs 31.4%; OR = 1.50, 95% CI: 0.71–3.15; $P = 0.283$).

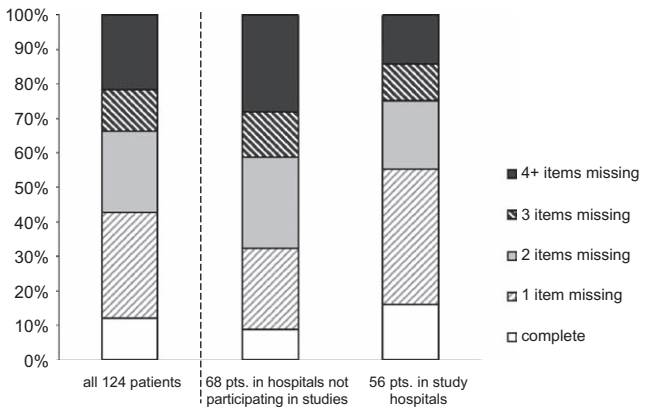

Figure 1. Completeness of surgical staging in early ovarian cancer according to treatment in centers with or without participation in cooperative study groups (0/1 item missing: OR = 2.59, 95% CI, 1.25–5.39; $P = 0.010$).

Advanced ovarian cancer FIGO stages IIB–IV

Three hundred fifty-two patients had advanced ovarian cancer FIGO IIB–IV. Of these, 219 (62.2%) and 171 (48.6%) were treated in study hospitals and high-volume centers, respectively. So-called optimal debulking with postoperative residual tumor of maximum diameters of up to 1 cm was achieved in 216 patients (61.4%). Operation in high-volume hospitals had no significant impact on postoperative tumor residuals (OR = 1.34, 95% CI: 0.87–2.06; $P = 0.182$). In contrast, operation at study hospitals resulted in significantly higher proportions of patients ending up with optimal debulking (OR = 1.63, 95% CI: 1.05–2.53; $P = 0.030$; Fig. 2).

German guidelines for chemotherapy in advanced ovarian cancer recommend combination therapy containing carboplatin and paclitaxel. For this analysis, each regimen containing any platinum analogue and any taxane was regarded as equivalent. No chemotherapy was recorded for 53 of 352 patients (15.1%). Nine patients had refused chemotherapy, one patient had died before the start of chemotherapy, and two further patients had moved. Forty-one patients had no documented chemotherapy, but hospitals could not provide additional details. Due to this uncertainty, the analysis regarding chemotherapy was limited to the 299 patients for whom details about chemotherapy were available. One hundred eighty-eight (62.9%) and 143 (47.8%) of these patients were treated in study hospitals and high-volume centers, respectively.

A total of 93.3% received at least platinum as part of their first-line therapy. A platinum–taxane combination was administered to 77.6% of the 299 patients. Patients treated in study hospitals had a higher chance of receiving standard chemotherapy compared to patients treated in hospitals not participating in cooperative clinical studies (OR = 1.77, 95% CI: 1.02–3.07; $P = 0.041$; Fig. 3). Again, the case volume did not have any significant impact on the probability of receiving standard treatment (OR = 1.29, 95% CI: 0.75–2.22; $P = 0.362$).

Overall survival

So far, 147 deaths have been observed after a median follow-up time of 24 months for patients who remained alive. Only 11 patients with early-stage ovarian cancer had died. In contrast, 136 deaths occurred in advanced stages, and median survival in FIGO IIB–IV was 27.4 months. The size of postoperative tumor residuals showed a significant impact on survival probabilities in FIGO IIB–IV ovarian cancer. Only 18

Table 2. Missing items in surgical staging of early ovarian cancer FIGO I–IIA (bold figures indicate $P < 0.05$, χ^2 test)

	All	Hospitals participating in studies	Hospitals without study participation	High-volume hospitals (16+ per year)	Low-volume hospitals (1–15 per year)
Patients (*n*)	124	56	68	54	70
Peritoneal biopsy (%)	68.5	**58.9**	**76.5**	**57.4**	**77.1**
Lymph node staging[a] (%)	46.8	41.1	51.5	42.6	50.0
Cytology/washings (%)	35.5	**23.2**	**45.6**	31.5	38.6
Omental biopsy (%)	26.6	26.8	26.5	24.1	28.6
Vertical incision (%)	17.7	16.1	19.1	**7.4**	**25.7**
Hysterectomy[b] (%)	12.1	12.5	11.8	9.3	14.3
Bilateral salpingo-oophorectomy[c] (%)	8.1	7.1	8.8	9.3	7.1
Complete resection of all tumor tissue (%)	6.5	1.8	10.3	7.4	5.7

[a]Pelvic and/or para-aortic lymph node biopsy.
[b]Excluding patients with prior hysterectomy.
[c]Excluding patients with prior oophorectomy.

of 117 patients with no macroscopic residuals, 34 of 99 patients with 1- to 10-mm tumor residuals, and 84 of 136 patients with tumor residuals exceeding 1 cm had already died ($P < 0.0001$).

Univariate analysis of prognostic factors showed that FIGO stages IIB–IV, performance status higher than ECOG 1, age over 65 years, presence of comorbidity, presence of ascites >500 mL, poor tumor grade, and serous histologic subtype were significantly associated with worse survival (Table 3). Hospital volume did not show a significant impact on survival. Treatment in a hospital that did not participate in cooperative studies resulted in a 30% elevated risk but was not statistically significant in the univariate analysis (HR = 1.29, 95% CI: 0.93–1.78; $P = 0.123$). However, as shown above, population in study hospitals differed markedly from population in nonstudy hospitals, especially with respect to FIGO stage. Consequently, we explored a Cox regression model with both factors. In this model including FIGO stage (I–IIA, IIB–IV) and treating hospital (study hospital, nonstudy hospital), both factors were statistically significant. Patients treated in nonstudy hospitals had a 1.6-fold higher risk of death compared with those treated in study hospitals, even after adjustment for FIGO stage (95% CI: 1.14–2.19; $P = 0.006$). There was no interaction between FIGO stage and treating hospital. A univariate analysis carried out in FIGO IIB–IV patients revealed a highly significant survival advantage for patients treated in hospitals that participate in cooperative studies (Fig. 4). Within the observation period, 72 patients

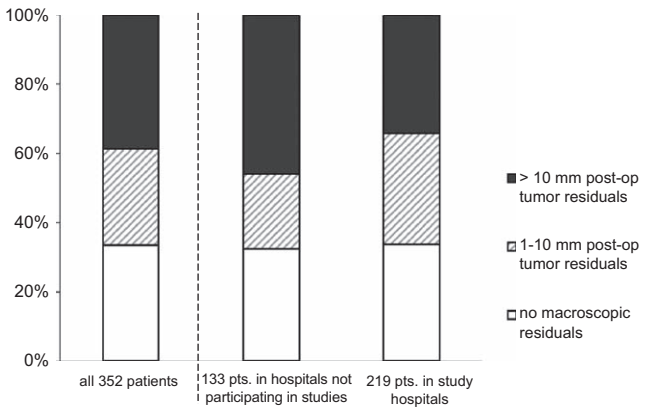

Figure 2. Postoperative residual tumor in ovarian cancer FIGO IIB–IV according to treatment in centers with or without participation in cooperative study groups (residuals ≤1 cm: OR = 1.63, 95% CI, 1.05–2.53; $P = 0.030$).

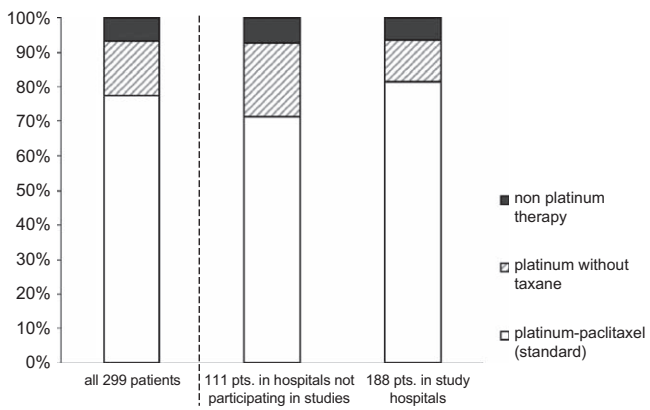

Figure 3. Selection of chemotherapy regimens in advanced ovarian cancer according to treatment in centers with or without participation in cooperative study groups (OR = 1.77, 95% CI, 1.02–3.07; $P = 0.041$).

Table 3. Univariate analysis of prognostic factors for overall survival in invasive epithelial ovarian cancer in Germany 2001

Prognostic factors		Hazard ratio	95% Confidence interval	*P* value[a]
Stage	FIGO IA–IIA	1		
	FIGO IIB–IV	5.38	2.91–9.94	<0.0001
PS	ECOG 0/1	1		
	ECOG >1	4.67	3.36–6.47	<0.0001
Age	<65 years	1		
	≥65 years	3.26	2.30–4.62	<0.0001
Comorbidity	None	1		
	Present	3.19	2.30–4.43	<0.0001
Ascites	≤500 mL	1		
	>500 mL	2.63	1.89–3.66	<0.0001
Grading	G1/2/unknown	1		
	G3/4	1.61	1.16–2.23	0.004
Histology	Others	1		
	Serous	1.56	1.06–2.29	0.018
Second malignancy	None	1		
	Present	1.42	0.94–2.16	0.111
Hospital volume	High (16+ per year)	1		
	Low (1–15 per year)	1.08	0.78–1.49	0.657
Study participation	Yes	1		
	No	1.29	0.93–1.78	0.123

[a]Likelihood ratio test.

(32.9%) in study hospitals and 64 patients (48.1%) in nonstudy hospitals died.

Finally, a model using the two treatment characteristics (hospital volume and participation in clinical studies) and variables that were significant in the univariate analysis was fitted. Advanced FIGO stage, poorer performance status, presence of ascites >500 mL, comorbidity, and higher age were confirmed as independent prognostic factors (Table 4). Variables such as histologic type and grade did not reach statistical significance. In this final analysis, treatment in a nonstudy hospital was associated with an 82% elevated risk of death ($P = 0.001$). No such association was found for hospital volume (Table 4).

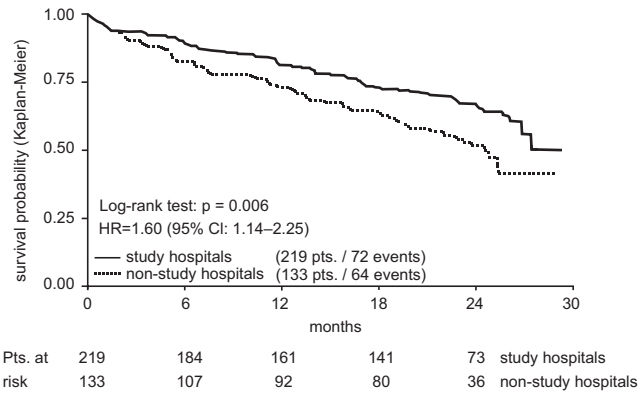

Figure 4. Kaplan–Meier survival curves in ovarian cancer FIGO IIB–IV according to treatment in centers with or without participation in cooperative study groups.

Discussion

This second National survey on quality and pattern of care for ovarian cancer included more than one third of all patients diagnosed within the observation period in Germany. Patients were reported from only 15% of all German hospitals. This could reflect centralization, but a bias toward participation of higher volume hospitals and those centers being more interested in quality assurance cannot be ruled out. A further bias can be assumed regarding study participation. Fifty percent of participating hospitals were members of cooperative study groups, while only about 25% of all German hospitals fulfill this criterion. The latter could indicate that results of treatment pattern could even be worse if one could examine all the German hospitals. However, national cancer registries are not established in Germany, and this report is the most representative data collection available. It showed considerable deficits in the treatment pattern of ovarian cancer and allows identification areas for improvement.

Staging in early ovarian cancer has already been reported in the late 1980s to be a critical area where standards are not transferred to clinical routine[17]. More recently, the impact of adequate surgical staging on survival has been reconfirmed[18]. In Germany, less than half of the patients received adequate staging. In addition, adjuvant chemotherapy was given to about 60% of eligible patients only. Comparable analyses for the United States showed an increase in the use of adjuvant chemotherapy from 36% in 1991[19] to 72% in

Table 4. Multivariate analysis (Cox model) of prognostic factors for overall survival in invasive epithelial ovarian cancer in Germany 2001 (bold figures indicate $P < 0.05$, χ^2 test)

Variable		Hazard ratio	95% Confidence interval	*P* value[a]
Stage	FIGO IA–IIA	1		
	FIGO IIB–IV	4.01	2.11–7.62	**<0.0001**
PS	ECOG 0/1	1		
	ECOG >1	3.00	2.03–4.44	**<0.0001**
Ascites	≤500 mL	1		
	>500 mL	1.91	1.35–2.71	**0.0002**
Study participation	Yes	1		
	No	1.82	1.27–2.61	**0.001**
Comorbidity	None	1		
	Present	1.77	1.23–2.54	**0.002**
Age	<65 years	1		
	≥65 years	1.76	1.18–2.64	**0.006**
Histology	Others	1		
	Serous	1.22	0.82–1.82	0.311
Grading	G1/2/unknown	1		
	G3/4	1.15	0.83–1.61	0.398
Hospital volume	16+ OP/y	1		
	1–15 OP/y	1.05	0.74–1.51	0.774

[a]Likelihood ratio test.

1996[20]. Consequently, the rate of patients with early ovarian cancer receiving standard treatment in Germany was 35.5% and lower compared to the United States[21]. Treatment guidelines were available for both early and advanced ovarian cancer. However, the even more obvious deficits in the treatment of early ovarian cancer might be related to the fact that until late 2002 no large clinical study in this field had ever been active in Germany. The hypothesis that study activity contributes to better standard treatment is supported by the observation that quality of care in advanced ovarian cancer, an area with vital study activities in Germany, was much more comparable to international standards. More than 90% of patients with advanced ovarian cancer received platinum-containing chemotherapy and more than 75% received additional paclitaxel. These rates compare well to data reported for the United States in 1996[21] or a survey in the UK in 1998–2001[22]. Surgical results showed a 61.3% rate of optimal debulking almost approaching the estimated 70% rate reported from a survey among United States gynecological oncologists[23]. However, we observed a considerable variety among individual centers even after adjustment for confounding factors.

Hospital or surgeon volume had been associated with better outcome for a variety of diagnoses in oncology, but evidence in ovarian cancer had remained weak. A Finnish study reported only marginally significant improvements when highest volume hospitals were compared with lower volume centers by quartiles[24]. A Canadian study reported a significant relation between hospital case volume (>15 operation per year [OP/year]) and survival but failed to show the same relation when individual surgeon's caseload was analyzed[4]. Another study failed to show an impact with a lower cutoff of 5 OP/year and surgeon[25]. Our data did not reveal a significant impact of hospital volume on survival in ovarian cancer in a multivariate analysis adjusting for relevant prognostic factors. In contrast, treatment in a hospital that participated in cooperative clinical studies was identified as an independent and significant prognostic factor even after adjusting for prognostic factors and hospital volume. Study centers more frequently adhered to treatment guidelines in early ovarian cancer and both achieved optimal debulking in more patients and selected more appropriate chemotherapy regimens for advanced ovarian cancer. Benefits for patients enrolled in study protocols in oncology have been reported earlier, but several pitfalls interpreting these effects have been identified[13]. The simplest explanation could be that the respective experimental treatment arm shows superiority. Probably, this did not explain our observations. The active German protocol for ovarian cancer in 2001 (AGO-OVAR-7) did not show short-term superiority for the experimental arm[26]. Superior outcome of study patients could be attributed to confounding factors and bias with respect to inclusion and exclusion procedures[27,28]. Caution to this pitfall should especially be paid when trial and nontrial patients within the same institutions are compared[29,30]. However, survival advantages observed in this survey cannot be attributed to patients enrolled in study protocols. We did not compare trial versus nontrial

patients but evaluated a "natural experiment"[13] by comparing all patients treated in institutions participating in trials versus all patients treated in institutions that do not participate. A third explanation which probably applies to our observation has been called "participation effect." Study centers do not only recruit patients but tend to have special infrastructures associated with study participation. They have team members interested in ovarian cancer and motivated to perform studies; these institutions are subject to regular auditing and they participate in study group quality assurance programs, and team members attend the regular educational and scientific meetings. Probably, patients treated in these institutions but who are not enrolled in trials receive quality of care above average as well. This hypothesis is supported by our data indicating that the observed benefit could not be limited to patients enrolled in active protocols. Only 21% of patients treated in study centers had actually been enrolled in trials, and positive effects were also observed in early ovarian cancer where no protocol had been active.

Pattern of care for ovarian cancer showed a considerable range of quality in Germany 2001. Many items of standard care not commonly provided to patients could obviously be implicated in routine practice rather easily. For individual patients, selecting an institution that participates in cooperative studies might be an option for seizing a chance for higher quality of care even when exclusion criteria might hamper study enrollment[31].

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