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Ovarian Cancer Surgery – A Population-based Registry Study

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Abstract. *Background/Aim: To evaluate ovarian cancer surgery in tertiary centers (TC) and regional hospitals (RH). Patients and Methods: Data from the GynOp registry on patients undergoing surgery for ovarian cancer or borderline tumor from 2013 to 2015 were analyzed. Results: Four TC and 21 RH reported 1,108 cases of surgery with curative intent, 770 cases (69.5%) in TC and 338 cases (30.5%) in RH. Out of 458 patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC-IV disease 396 (86.5%) had surgery in TC. We found differences in selection for primary debulking surgery (PDS) (45% to 93%, p<0.001) and PDS achieving no residual tumor (36% to 70%, p<0.001) between the four TC. Major complications, re-admissions and re-operation rates did not differ between TC and RH. Conclusion: Tertiary centers perform more extensive surgery compared to regional hospitals without increased frequency of major complications. Tertiary centers display significant differences among patient selection for PDS, as well as achieving no residual tumor.*

In 2014, 700 Swedish women were diagnosed with ovarian cancer (1). The majority of patients are diagnosed with advanced stages of the disease, reflecting poor outcome. The relative 5-year survival rate in Sweden from 2010 to 2014 was 48% (2).

The standard-of-care for ovarian cancer is primary debulking surgery (PDS). In advanced stages, International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or IV, an alternative is neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) after 3 to 4 cycles (NACT-IDS). The difficult question is which patients should be selected for PDS and who should benefit more from NACT-IDS (3). The possible benefits of PDS must be weighed against a considerable postoperative morbidity and mortality (4). In advanced stages, the strongest factor for survival is no macroscopic residual tumor after PDS, as well as IDS (5). This calls for a high level of surgical competence as the surgical procedures needed to achieve complete cytoreduction may include bowel resection, splenectomy, cholecystectomy, lymphadenectomy, peritoneal stripping and/or resection of the ureter or urinary bladder. Patients operated on by surgeons with gynecological oncology sub-specialization have superior outcome regarding no residual tumor and survival (6). Concentrating ovarian cancer treatment to tertiary hospitals with high patient volumes significantly improves survival (5).

In 2012, national recommendations proposed a concentration of ovarian cancer treatment to tertiary referral centers (all University Hospitals) in Sweden (7). The National guideline advocates that all adnexal lesions with suspicion of malignancy or patients with risk of malignancy index (RMI) above 200 should be referred to a tertiary center. This has led to an increasing number of patients having surgery by experienced ovarian cancer surgeons (from 49% in 2008 to 67% in 2013) (8), but existing guidelines are not mandatory and patients are not always referred to tertiary centers as recommended.

The purpose of this study was to evaluate the current surgical treatment and postoperative outcomes in patients with ovarian cancer reporting to the Quality Registry of Gynecological Surgery, GynOp.

Patients and Methods

The GynOp registry started to collect data from patients undergoing gynecological surgery in 1997. Since 2004, GynOp includes all major gynecological surgery. The registry is not mandatory and some regions by tradition report to another surgical quality registry. Gynecological clinics in four out of six regions in Sweden, covering 5.03 million people or 52% of the Swedish population, report to GynOp.

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Key Words: Ovarian, cancer, population, registry, surgery, complication.

Sweden has a publically financed health care system. A patient attending a regional hospital (RH) or primary care facility with suspected malignancy should be referred to the tertiary center (TC) in the region; very few patients are referred outside of their region as GynOp is considered to have full population coverage in the regions reporting to the register.

All cases of surgery with curative intent for ovarian, tubal or peritoneal malignancy, including borderline tumor, registered in GynOp from 2013 to 2015 were included in the study.

GynOp collects data from patient questionnaires and doctors' forms. Patients are identified with their personal number in the register. The patient is included in the registry when surgery is scheduled by the operation planner of the clinic and patient's reported data are collected in a preoperative questionnaire online or on paper. The doctor reports data to the registry at admission, surgery and discharge and when the histopathology results arrive. A postoperative patient questionnaire is sent to the patient eight weeks after surgery. The questionnaire includes questions on activities of daily living (ADL) as follows: "How many days after surgery did it take until you were able to perform normal daily activities and get along without more help than before surgery (for example personal hygiene, cook food for yourself, make your bed, walk a short distance)?". Postoperative complications are reported by the patient in the questionnaire and subsequently assessed by the surgeon who will grade the reported complication as major or minor according to the definitions listed below. Surgeons will even report complications to the registry at time of surgery, discharge or in the event of re-admission or re-operation. Major complications include the following: injury to bowel, urinary tract, nerves or vessels that caused re-operation or prolonged hospital stay more than 7 days or persistent physical handicap or death; Bleeding more than 3,000 ml or bleeding that caused re-operation; infection that led to re-admission; deep vein thrombosis or pulmonary embolism; any other major complication, *i.e.* aspiration, allergic shock, myocardial infarct or cerebral complication. Minor complications are defined as: organ injury with less than 7 days prolonged hospital stay; infection leading to antibiotic treatment without re-admission; bleeding less than 3,000 ml with blood transfusion but no re-operation; pain or urinary tract problems with less than 7 days prolonged hospital stay.

Approval for this study was obtained by the Regional Ethics Board, University of Umeå Dnr 2013-155-32M (Supplement to 08-120M) Umeå 2013.

Statistical analyses were performed using R (v3.2.3, 2015; R core team, Vienna, Austria).

The Mann–Whitney *U*-test was used for testing differences in distributions between TCs and RHs. Equalities of proportions were tested using Pearson's chi squared test. Comparisons between tertiary hospitals were made using ANOVA, chi squared test or Fisher's exact test. Logistic regression models were constructed to test potential risk factors for complications.

All tests were two-sided and a 5% level of significance was used.

Results

From January 2013 through December 2015, 1,108 cases of surgery with curative intent for ovarian, tubal or peritoneal malignancy, including borderline tumors, were registered in Gy-nOp. Four TCs (Linköping, Lund, Umeå and Uppsala University Hospitals) reported a total of 770 (69.5%) cases and 21 RH reported 338 (30.5%) cases (Figure 1). We decided to include Örebro University Hospital serving a small region with a population of 292,000 in the RH group. RHs are ranked according to case volume; the names of individual hospitals have been omitted for integrity. All TCs had a case volume above 25 per year, while no RH reached above 20 cases per year. Patients' characteristics did not differ regarding age, body mass index (BMI), smoking habits, American Society of Anesthesiologists (ASA) classification or comorbidity between the TC and RH. More patients were staged with advanced disease, FIGO IIIC-IV, in the TC group, 396 (51.4%) *vs.* 62 patients (18.3%) in RH; ($p<0.001$). Pre-operative RMI, an algorithm incorporating menopause status, ultrasound findings and CA-125 level (9), was registered for 471 (61.2%) of TC patients and 243 (71.9%) of RH patients ($p<0.001$). The proportion of patients with RMI higher than 200, indicating a high risk of epithelial ovarian cancer was higher in TC, 83% compared with 67% in RH ($p<0.001$) (Table I). Table II shows the distribution of FIGO stages in the two groups, with borderline tumors being excluded. Complete information on FIGO stage was available in 88.3% of TC patients and 54.7% of RH patients ($p<0.001$).

Only patients with advanced disease (FIGO stage IIIC-IV) were included in the following analyses on surgical outcome. Out of 458 patients with advanced disease (FIGO stage IIIC-IV), 396 (86.5%) had surgery in TC and 62 (13.5%) in RH. PDS was performed in a higher proportion of patients in RH than in TC (80.9% *vs.* 66.9%, $p<0.05$). The proportion of patients with no residual tumor after PDS did not differ significantly between TH and RH (54% *vs.* 48%) (Table III). Significant differences were found between the four TCs with PDS performed in 45% to 93% of patients and no residual tumor achieved in 36% to 70% of PDS patients ($p<0.001$) (Table IV). For IDS patients, no residual tumor was achieved in 53% at TC and 25% at RH. Between the four TCs, residual tumor rates in IDS ranged from 37% to 68%. None of these differences were significant (Table IV).

More TC patients had non-gynecological additional cytoreductive surgery with 44.9% *vs.* 21% of RH patients ($p<0.001$) undergoing one or more of the procedures listed in Table V. Colon resection was the most common procedure performed in 33.8% of TC patients *vs.* 17.7% of RH patients ($p<0.05$) (Table V).

The median operation time for PDS was longer in TC; 261.5 min *vs.* 148.5 min in RH ($p<0.001$) (Figure 2, Table VI). The median length of stay in hospital after PDS was 8 days in TC *vs.* 4 days in RH ($p<0.001$) (Figure 3, Table VI). Median time to normal ADL was 12.5 days in TC *vs.* 7 days in RH ($p<0.001$). No significant differences were found in perioperative bleeding (Table VI).

Within eight weeks after surgery, there were 2.7% readmissions in TC *vs.* 1.5% in RH and 1.4% re-operations

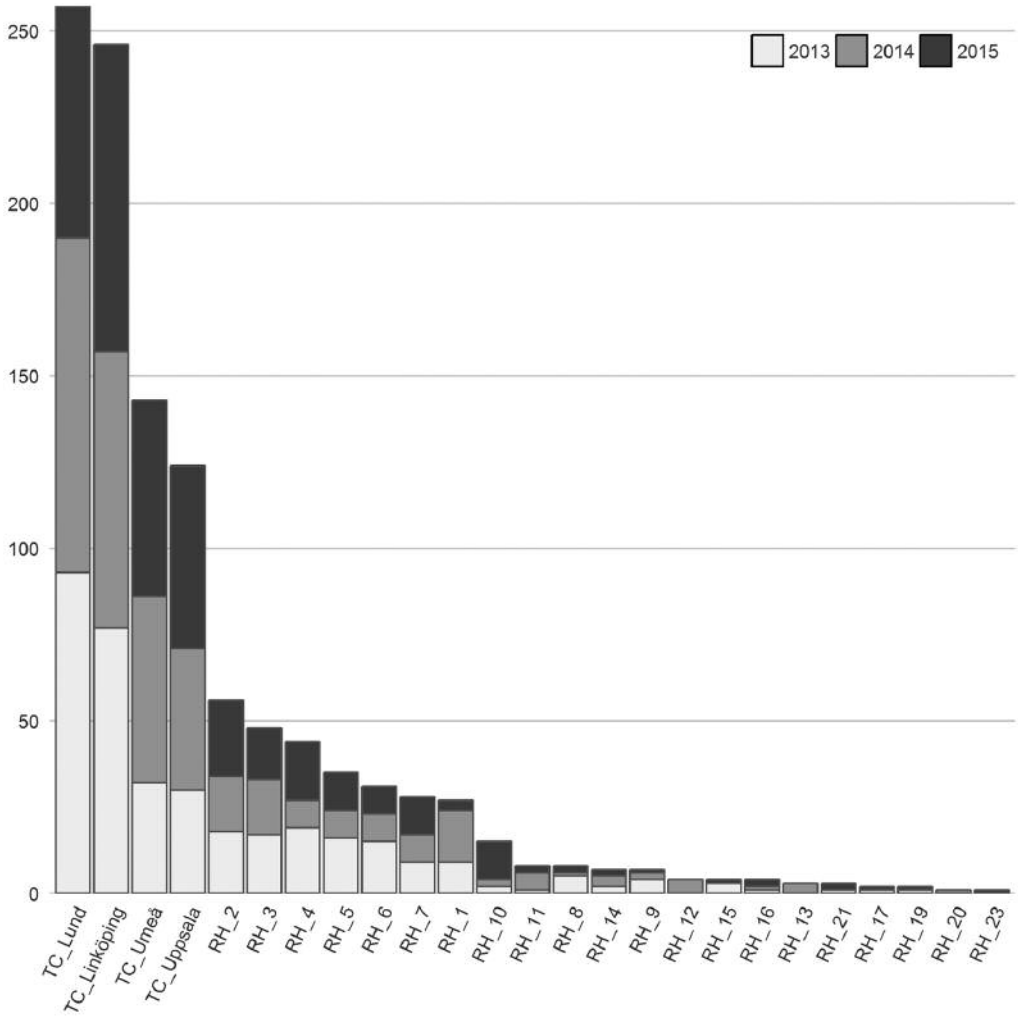

Figure 1. *Total number of surgical procedures with curative intent for ovarian/tubal/peritoneal malignancy, including borderline tumors, registered in GynOp from 2013 to 2015.*

in TC *vs*. 1.2% in RH with no significant differences between the two groups (Table VII). The overall patient response rate on the 8-week questionnaire was 85%.

Overall complication rates after surgery were higher in TC; 25.5% *vs*. 13.3% in RH ($p<0.001$). The most common complication within eight weeks after surgery was infection, affecting twice as many patients in TC as in RH (21.7% *vs*. 10.7% of RH patients ($p<0.001$)). Major complications were registered in 5.2% of TC patients *vs*. 2.7% of RH patients (n.s.) (Table VII).

Table VIII lists specified major complications within 8 weeks after surgery. There were no significant differences among the specific major complications between TC and RH.

A logistic regression model was constructed to evaluate potential risk factors for severe postoperative complications including age, ASA classification, BMI, smoking, care level (TC *vs*. RH), comorbidity, FIGO stage (IIIC-IV yes/no) and surgical treatment (PDS *vs*. IDS). In the whole patient population, FIGO stage IIIC-IV was the only factor associated with increased risk of severe complication, odds ratio (OR)=2.38 (1.11-5.45), $p<0.05$. Limiting the logistic regression to the FIGO IIIC-IV population with the same variables as above revealed no significant risk factors.

The median waiting time for histopathological diagnosis after surgery was 22 days (interquartile range (IQR)=17-35) for TC and 24 days (IQR=15-35) for RH (n.s.).

Discussion

This population-based survey shows that 70% of surgery for ovarian malignancy, including borderline tumors, was performed in tertiary referral centers from 2013 through

Table I. *Patients' characteristics.*

	Tertiary Centers n=770 median	IQR	Regional Hospitals n=338 median	IQR	*p*-Value
Age	64	55-71	66	57-73	n.s.
BMI	25.2	22-29	25.3	23-29	n.s.
	%	n*	%	n*	
Active smoking	10%	63/632	12.6%	28/223	n.s.
ASA 3-4	10.3%	77/745	10.3%	33/320	n.s.
FIGO stage IIIC-IV	51.4%	396/770	18.3%	62/338	<0.001
RMI >200	83%	392/471	67%	163/243	<0.001
Comorbidities:					
Heart disease	10.8%	69/639	13.2%	31/234	n.s.
Lung disease	15.4%	97/631	20.5%	47/229	n.s.
Diabetes	7.8%	50/642	7.7%	18/235	n.s.
Hypertension	35.5%	228/642	36.6%	86/235	n.s.

IQR, Interquartile range; n.s., non-significant; BMI, body mass index; ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; RMI, risk of malignancy index; *missing values are excluded from calculations.

Table II. *FIGO stage in patients with invasive ovarian/tubal/peritoneal cancer.*

	Tertiary Centers		Regional Hospitals		
FIGO stage*	n	%	n	%	*p*-Value
I	104	16%	45	19.2%	n.s.
II	27	4.1%	8	3.4%	n.s.
IIIA+B	49	7.5%	13	5.6%	n.s.
IIIC	319	48.9%	48	20.5%	<0.001
IV	77	11.8%	14	6%	<0.05
X**	76	11.7%	106	45.3%	<0.001
Total	652	100%	234	100%	

*Borderline tumor excluded (n=219). Missing information on histopathology (n=3). **Stage X: Incomplete information on stage. FIGO, International Federation of Gynecology and Obstetrics; n.s., non-significant.

Table III. *Surgery in FIGO stage IIIC-IV.*

Surgery in stage IIIC-IV	Tertiary Centers		Regional Hospitals		*p*-Value
	n	%	n	%	
PDS	265	66.9%	50	80.6%	*p*<0.05
No residual tumor after PDS	144/265	54%	24/50	48%	n.s.
IDS	131	33.1%	12	19.4%	*p*<0.05.
No residual tumor after IDS	69/131	53%	3/12	25%	n.s.
Total	396	100%	62	100%	

FIGO, International Federation of Gynecology and Obstetrics; PDS, primary debulking surgery; IDS, interval debulking surgery; n.s., non-significant.

Table IV. *Surgery in FIGO stage IIIC-IV in tertiary centers only.*

Surgery stage IIIC-IV		PDS			IDS		
	Total	Total	No residual tumor		Total	No residual tumor	
	n	n	%	n	%	n	%	n	%
Linköping	136	73	54%	26/73	36%	63	46%	32/63	51%
Lund	134	124	93%	77/124	62%	10	8%	6/10	60%
Uppsala	77	46	60%	32/46	70%	31	40%	21/31	68%
Umeå	49	22	45%	9/22	41%	27	55%	10/27	37%
Total	396	265	70%	144/265	54%	131	33%	69/131	53%

Logistic regression analysis shows a significant difference between University Hospitals in patients with no residual tumor after PDS ($p<0.001$) but not after IDS. FIGO, International Federation of Gynecology and Obstetrics; PDS, primary debulking surgery; IDS, interval debulking surgery.

2015 in the regions of Sweden reporting to GynOp. No regional hospital had a case load above 20 ovarian cancer patients per year. In the RH group there will be some surgical procedures included with an unexpected finding of early stage malignancy, which may explain very few cases reported in several of RH. In stage IIIC-IV disease, 86% of the patients had their surgery in TC. RH reported 62 cases of stage IIIC-IV surgery. This number may be higher though as complete information on stage was not available in 2 out of 5 RH patients and this group may include a considerable number of patients with advanced disease.

RMI (9) is a widely used algorithm for the preoperative assessment of pelvic masses and has been demonstrated to distinguish advanced ovarian cancer from benign ovarian masses with a sensitivity of 92% and a specificity of 82% (cut-off=200) (10, 11). The Swedish Ovarian Cancer Treatment Guidelines (7) advocate that patients with RMI above 200 or suspicion of malignancy, according to ultrasound examination, are referred to a TC with surgeons specialized in gynecological oncology. In this study, RMI above 200 was more common among TC patients (83% *vs.* 67%). Still, many patients with preoperative RMI above 200 had their primary surgery in RH. New and improved

Table V. *Additional cytoreductive procedures in FIGO stage IIIC-IV surgery.*

Cytoreductive procedure	Tertiary Centers n=396 patients		Regional Hospitals n=62 patients		
	n	%	n	%	*p*-Value
Resection of colon/rectum	134	33.8%	11	17.7%	<0.05
Splenectomy	62	15.7%	1	1.6%	<0.01
Small bowel resection	33	8.3%	6	9.7%	n.s.
Resection of diaphragm	29	7.3%	0	0%	n.s.
Cholecystectomy	24	6.1%	0	0%	n.s.
Liver resection	21	5.3%	1	1.6%	n.s.
Resection of stomach	4	1%	0	0%	n.s.
Resection of bladder	3	0.8%	0	0%	n.s.
Urinary tract deviation	1	0.3%	0	0%	n.s.
Total number of patients with one or more procedures	178	44.9%	13	21%	<0.001

FIGO, International Federation of Gynecology and Obstetrics; n.s., non-significant.

Table VI. *Outcome of PDS in FIGO stage IIIC-IV.*

	Tertiary Centers		Regional Hospitals		
	median	range	median	range	*p*-Value
Operation time (min)	261.5	152.3-385.3	148.5	104.5-193.5	<0.001
Estimated blood loss (ml)	600	300-1200	450	200-800	n.s
Length of hospital stay (days)	8	4-11	4	3-8	<0.001
Time to normal ADL(days)	12.5	7-20	7	4-14	<0.05

FIGO, International Federation of Gynecology and Obstetrics; PDS, primary debulking surgery; ADL, activity of daily living; n.s., non-significant.

diagnostic tools are implemented in clinical practice in recent years, *i.e.* risk of ovarian malignancy algorithm (ROMA) (12) and the ultrasound-based Simple Rules (13). However, if gynecologists at RH do not follow the guidelines and do not refer the patient to a TC when ovarian malignancy is suspected, there is little use for these algorithms and the patients are at risk of not receiving optimal treatment.

Improved survival at high volume hospitals (>20 cases per year) with high-volume physicians (>10 cases per year) has been shown by Bristow *et al*. (14) and is in consistence with a nation-wide Finnish study by Kumpulainen *et al*. (15) that shows better surgical outcome (as measured in amount of residual tumor) in high-volume hospitals. The Danish and Norwegian centralization of treatment to TCs has significantly improved outcome in advanced ovarian cancer (16, 17). A recent Swedish article showed that centralized primary care of advanced ovarian and fallopian tube cancers increased complete cytoreduction, decreased time interval from PDS to chemotherapy, as well as improved relative survival (18). Rosen *et al*. state that every surgeon should perform at least 30 procedures per year and that the team in the hospital should have at least 100 procedures per year in order to establish and maintain high quality in a specific surgical procedure (19). The published articles and this study indicate a need for further concentration of the treatment for

Table VII. *Complications <8 weeks after surgery, all stages, borderline tumor patients included.*

	Tertiary Centers n=770		Regional Hospitals n=338		
	n	%	n	%	*p*-Value
Re-operation	21	2.7%	5	1.5%	n.s.
Re-admission	11	1.4%	4	1.2%	n.s.
Major complications*	40	5.2%	9	2.7%	n.s.

*see Table VIII for specific major complications. n.s., non-significant.

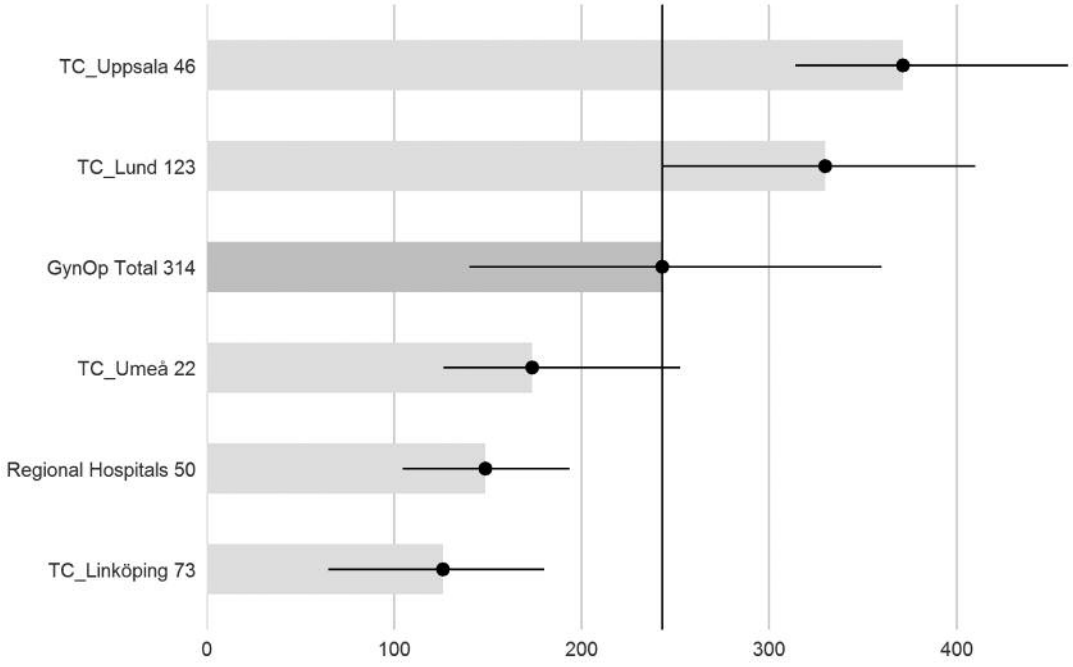

Figure 2. *Operation time in the International Federation of Gynecology and Obstetrics (FIGO) stage IIIC-IV primary surgery.*

Table VIII. *Specified major complications <8 weeks after surgery, all stages, borderline tumor patients included.*

Complication	Tertiary Centers n=770	%	Regional Hospitals n=338	%	*p*-Value
Urinary bladder	1	0.1%	0	0%	n.s
Ureter	2	0.3%	1	0.3%	n.s
Fascia rupture	2	0.3%	1	0.3%	n.s
Bleeding/Hematoma/anemia	10	1.3%	1	0.3%	n.s
Sepsis	3	0.4%	1	0.3%	n.s.
Bowel complication*	12	1.6%	2	0.6%	n.s.
Ileus	13	1.7%	4	1.2%	n.s.
Respiratory problem or aspiration	1	0.1%	1	0.3%	n.s.
Deep vein thrombosis	5	0.6%	3	0.9%	n.s.
Major not specified complication	9	1.2%	3	0.9%	n.s.
Total number of patients with one or more major complications	40	5.2%	9	2.7%	n.s.

*Bowel complication: perforation, anastomotic leak, abscess. n.s., non-significant.

ovarian cancer in Sweden. Optimally, all patients with suspected ovarian cancer should be referred to a tertiary high-volume center.

Opponents of aggressive surgery claim that tumor biology determines the surgical outcome and that aggressive surgery is associated with high morbidity. Contradictory, several studies have reported that aggressive surgery can make up for tumor biology (20). No residual tumor surgery is the goal in surgery for advanced ovarian cancer (5). Analysis of risk factors, such as age, performance status, nutrition and obesity, may allow the surgical team to triage patients at highest risk of serious morbidity to alternative primary treatment in multidisciplinary setting. Complete cytoreduction is achievable in up to 60% of patients with FIGO stage IIIC-IV ovarian cancer, although highly dependent on center expertise (20-22). Survival analysis has shown increased median survival after increasing surgical aggressiveness was instituted in a large center (21). In this

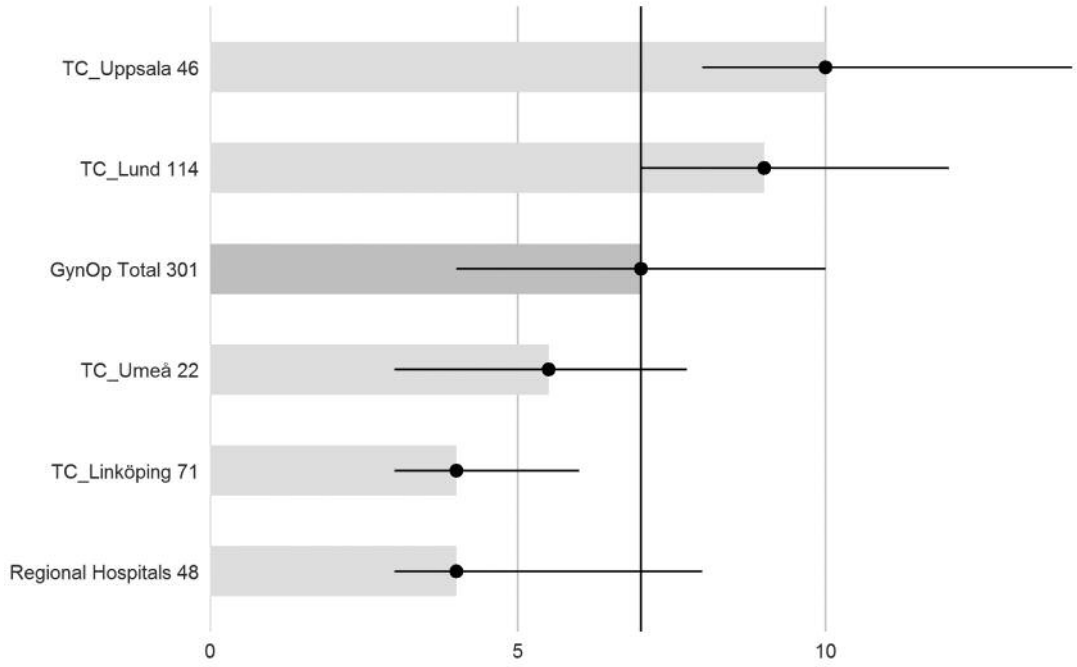

Figure 3. *Postoperative days in hospital after International Federation of Gynecology and Obstetrics (FIGO) stage IIIC-IV primary surgery.*

paper, the complete cytoreduction rate in TC patients was 54% in upfront PDS in advanced disease. A slightly lower rate of 48% was seen in RH patients, although the difference was non-significant, probably reflecting a low patient volume. We found considerable differences in selection for PDS *versus* IDS, as well as in debulking rates in the four TC. These differences cannot be due to patient selection in referral patterns. The national guidelines advocate neoadjuvant chemotherapy should be offered to patients with stage IIIC-IV with tumor extent in surgically inaccessible areas, old age or significant co-morbidity after discussion at multi-disciplinary conference. According to recommendations from the Society of Gynecologic Oncology and American Society of Clinical Oncology in 2016, "primary cytoreductive surgery is preferred if there is a high likelihood of achieving cytoreduction to <1 cm (ideally to no visible disease) with acceptable morbidity" (23). The differences in patient selection for PDS and even in achieving complete debulking must be due to different strategies and policies at the different TCs that should be further analyzed and discussed in order to provide optimal and more equal preoperative assessment and treatment to patients throughout the country.

The operating time, as well as postoperative hospital stay and time to normal ADL, were longer for advanced stages PDS in TC and correlates well with the more frequent use of additional cytoreductive surgical procedures in TC. The importance of an aggressive surgical approach to improve survival in FIGO IIIC-IV disease, including extensive upper abdominal procedures to achieve complete debulking, is well-stablished (5, 24, 25) and this is more often accomplished when the surgeon has gynecological oncological subspecialty training (26). The increased number of additional surgical procedures in TC in this study is likely to reflect more aggressive surgical efforts by surgeons with a higher degree of subspecialty training, including colorectal surgical competence. The most common additional debulking procedure is colon resection, as this is, in many cases, required for the optimal removal of the pelvic tumor, often performed as *en bloc* recto-sigmoid resection with a sigmoid-rectal anastomosis or with a colostomy. When performed in TC by surgeons with gynecological oncology training, the complication rates are shown to be acceptably low with anastomotic leak in 3-6% (27-29). Ideally, surgery for advanced disease should always involve at least one surgeon with gynecological oncological subspecialty training. In Sweden, there is an established 3-year subspecialty training program for gynecological oncological surgery since 1999.

The only significant risk factor for major complications after surgery was advanced stage disease (FIGO IIIC-IV) (OR=2.38) in our study. An increasing number of cytoreductive procedures is correlated to a higher rate of

complications in the literature (30, 4, 31) reporting higher complication rates in high-volume hospitals compared to hospitals with low- and intermediate-volume, but lower mortality rates for patients treated at high-volume hospitals, explained by higher ability to rescue patients with complications in high-volume hospitals. In accordance with these findings, we found more postoperative complications in TC patients, although major complications were uncommon and did non-significantly differ between TC and RH.

Waiting for definitive histopathological findings, diagnosis was long and did not differ for the two hospital groups. Several studies point to the importance of early initiation of chemotherapy after surgery. The paper by Mahner *et al*. (32) revealed that earlier recurrence and decreased overall survival were observed when chemotherapy was initiated more than 19 days after primary surgery. Hospitals with long time to histopathological diagnosis after surgery need to improve the logistics both to reduce the patient's time in uncertainty and to improve survival.

This study comprises of prospectively collected data covering all patients in the areas served by the hospitals reporting to the GynOp Registry, thus reducing the risk of selection bias. The patients' reported response rate was high (85%) in the postoperative questionnaires that have been shown to provide more complete and thorough postoperative information than follow-up visits (33). There are limitations in the study. The number of referrals from the RH to TC could not be analyzed due to lack of information in the registry. Patients who never had any surgery were not included and, due to short follow-up, progression-free or overall survival could not be evaluated.

TCs perform more extensive surgery without increased frequency of major complications compared with RHs. Despite national and international recommendations, patients with suspicion of ovarian cancer still have primary surgery at RH. Four TCs performed more than 25 procedures per year with significant differences in patient selection for PDS, as well as achieving no residual tumor at surgical debulking. These differences need to be further analyzed and discussed. Published international papers and our data highlight the need for better preoperative assessment of patients with suspicion of ovarian cancer and concentration of the surgical treatment for ovarian cancer to TCs.

Conflicts of Interest

No conflicts of interest have been declared from any of the Authors.

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