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Surgical treatment of ovarian cancer in different hospital categories – A prospective nation-wide study in Finland

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ABSTRACT

This prospective nation-wide study was performed to evaluate the effect of hospital category and subspeciality training on surgical treatment of ovarian cancer. Data were obtained from a questionnaire filled in by the operating unit, and from the surgical and histopathology reports. The survey included 307 patients. Half of them were operated in the university hospitals where gynaecologic oncologists performed 72% of the operations. This was the case in only 4% and 19% in the central and district hospitals, respectively. In university hospitals, pelvic lymphadenectomy was performed in 88%, and para-aortic lymphadenectomy in 73%, of the patients with stage I disease. The corresponding figures ranged from 11% to 21% in central and district hospitals. For stage III patients operated by gynaecologic oncologists, the estimated odds ratio for no macroscopic tumour was 3.0 times higher (95% CI 1.2–7.5) than for those operated by general gynaecologists. These results favour centralisation of surgical treatment of ovarian cancer.

1. Introduction

The standard treatment of ovarian cancer is surgery followed by combination chemotherapy. It has been suggested that the initial operation provides the most important opportunity to affect survival [1–3]. Primary surgery is important for accurate staging of the disease, and for optimal removal of the tumour. The rate of lymph node involvement in early stage ovarian cancer has been reported to range from 4% to 25% [4–7]. Therefore, for the staging of patients with early stage disease, a comprehensive examination of the abdominal cavity, as well as pelvic and para-aortic lymph nodes is mandatory. According to the most recent FIGO guidelines, adequate surgical staging includes: careful evaluation and washings of peri-

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toneal surfaces, infracolic omentectomy, lymphadenectomy of the pelvic and para-aortic lymphnodes, random and focused biopsies, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and appendicectomy for mucinous tumours [8].

The rate of positive lymph nodes in advanced ovarian cancer has been reported to range from 55% to 77% [5,6,9–12]. The rationale of cytoreductive surgery is based on strong indirect evidence of clinical benefit in patients who are left with minimal residual disease. Retrospective studies have shown that optimally debulked patients have better survival than suboptimally debulked patients [1,3,13–16]. According to a prospective study by Eisenkop and co-workers [17], cytoreduction to macroscopically disease-free status has a more significant influence on survival than the extent of metastatic disease before surgery.

This nation-wide prospective study was carried out to obtain accurate and detailed information about the quality and extent of primary surgical treatment of ovarian cancer in different hospital categories, ranging from university hospitals to district hospitals. The quality of surgical treatment refers to FIGO guidelines [8]. In addition, primary operations performed by general gynaecologists and gynaecologic oncologists were compared. Practically all patients who underwent laparotomy for ovarian cancer in Finland in 1999 were included in this study.

2. Patients and methods

In Finland, five university hospitals are tertiary referral centres for the total population of 5.2 million people. In addition, there are 16 central hospitals, which do not necessarily have all the specialist services, e.g., radiotherapy units, and may have the services of gynaecologic oncologists only occasionally. The third hospital category consists of smaller city and district hospitals and other miscellaneous units. Some of the central hospitals serve as primary referral units for these smaller hospitals. Surgical treatment of ovarian cancer is not centralised in Finland. The site of the primary operation of ovarian tumour patients is based on the referral policy of individual hospitals. The costs are covered by the state, municipalities, and patients. Patients' travelling expenses are covered by the national social security. The service is complemented by the private section health care. This survey was performed in all hospital categories in Finland in 1999. The study was approved by the local ethical committees of individual hospitals, as well as by the Ministry of Social Affairs and Health. Informed consent was obtained from all patients.

Detailed data on the clinical characteristics of the patients, as well as on surgical treatment, were collected using a specific questionnaire, and checked from operative and histopathologic reports. The questionnaire was sent to 54 hospitals or units where ovarian carcinoma patients were operated according to our previous survey carried out in 1983–1994 [18]. Since then, the number of these hospitals has decreased by 13. All five university hospitals, 15 out of 16 central hospitals and 19 out of 21 district hospitals participated in the study. A small central hospital on the Åland Islands referring ovarian cancer patients either to Finland or to Sweden for treatment, as well as two district hospitals, did not participate in the study.

In addition to the questionnaire filled in by the operating physicians or other physicians in the unit, copies of the surgical reports, as well as histopathology and cytology reports, were collected. Thus, the size of the primary tumour, the extent of the operation, the International Federation of Gynaecologists and Obstetricians (FIGO) stage, histology and residual tumour could be confirmed from two sources. Since there is no accurate method of calculating the volume of residual disease, only the maximum diameter of the largest residual tumour was recorded. All the data were then checked and recorded into a database, and missing or more accurate information was requested by a second questionnaire.

Questionnaires were returned on 401 ovarian cancer patients, including those with borderline tumours. After checking the data, 29 patients were excluded for one of the following reasons; primary origin of the tumour was uncertain, recurrent ovarian cancer, or synchronous second primary tumour. The final study population consisted of 307 patients with invasive ovarian cancer, and 65 patients with borderline tumour. Only patients with invasive cancer were included in the current study. Sixteen of the patients were operated twice within three months due to an unsatisfactory primary operation. Six patients were re-operated in a university hospital after primary operation in a district hospital. One patient was first operated in a district hospital and then re-operated in a central hospital. Six patients were operated twice in the same university hospital, and three patients were operated twice in the same central hospital. These patients appear in Tables 1 and 3 and in Figs. 1 and 2 according to the site of the final staging operation, whereas the extent of the surgery reflects both procedures (Table 2).

The coverage of the present study was checked from the population-based, nation-wide Finnish Cancer Registry that collects data on all cancer cases diagnosed in Finland. The coverage of this registry is 99% for solid tumours [19]. In 1999, the number of invasive ovarian cancers reported to the Finnish Cancer Registry was 397. This figure also includes 34 patients who had never been operated, 11 patients with ovarian cancer diagnosed at autopsy, and 5 patients who had not been operated in 1999. After manually checking the data on missing patients, there were 40 patients who had been operated for invasive ovarian cancer but had not been reported to the current study. Thus the current survey covered 88% (307/347) of the patients who had undergone surgical treatment for invasive ovarian cancer in Finland in 1999. The percentages of unreported patients were 8%, 13% and 19% in university, central, and district hospital categories, respectively.

Data analysis were mainly performed using Microsoft Excel. The difference in proportions of patients with no postoperative macroscopic tumour between operations performed by gynaecologic oncologists and general gynaecologists was analysed using Fisher's exact test. The patients with no preoperative macroscopic tumour were classified as not improving by cytoreductive surgery.

Differences between preoperative and postoperative findings were evaluated using McNemar's test. It was assumed that patients with no macroscopic preoperative tumour were

Table 1 – Characteristics of the patients in different hospital categories

	University	Central	District	All
Patients				
Number of patients	156 (51%)	109 (36%)	42 (13%)	307 (100%)
Mean age, years	57 (16–93)	63 (29–91)	66 (32–87)	60 (16–93)
Mean BMI	25 (17–44)	25 (18–38)	25 (16–37)	25 (16–44)
Mean CA 12–5 U/l	1326 (3–40 100)	814 (8–7908)	657 (5–4914)	1052 (3–40 100)
CA 12–5 $\leqslant$ 35 kU/l	23 (15%)	21 (19%)	9 (21%)	53 (17%)
CA 12–5 missing	4 (3%)	10 (9%)	6 (14%)	20 (7%)
Mean ascites, ml	2026 (8–13 000)	1767 (5–12 000)	1372 (5–6500)	1853 (5–13 000)
No ascites	43 (28%)	22 (20%)	14 (33%)	79 (26%)
FIGO stage				
I	48 (31%)	28 (26%)	9 (21%)	85 (28%)
II	18 (12%)	12 (11%)	8 (19%)	38 (12%)
III	65 (42%)	59 (54%)	21 (50%)	145 (47%)
IV	25 (16%)	10 (9%)	4 (10%)	39 (13%)

*16 patients were operated twice due to unsatisfactory primary surgery and appear in the table according to the site of the final staging operation as explained in Section 2.
BMI, body mass index. The numbers are given as median and range. CA 12–5 values were taken preoperatively.

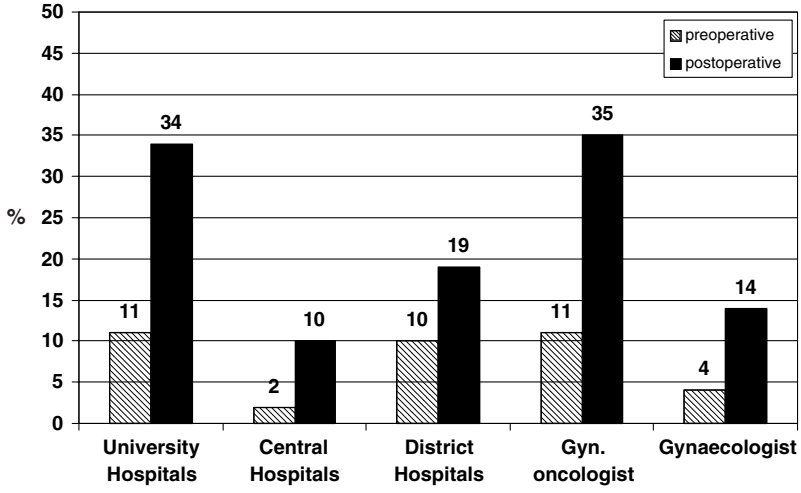

Fig. 1 – The percentage of stage III patients with no macroscopic tumour before and after cytoreductive surgery in different hospital categories, and when operated on by gynaecologic oncologists and general gynaecologists. * The category gynaecologist includes six patients operated on by a general surgeon.

included among those without postoperative macroscopic tumour.

3. Results

The results based on 307 ovarian cancer patients operated in 39 hospitals showed that 51% of the patients were operated in 5 university hospitals, 36% in 15 central hospitals, and 13% in 19 district or city hospitals. The demographic characteristics of the patients in different hospital categories are presented in Table 1. In the whole study population, 29% of the patients were $\geqslant$70 years of age. The patients operated in university hospitals were younger than those operated in central or district hospitals. On the other hand they had higher mean CA-12–5 value and more ascites. Of the patients under 40 years of age, 21 were operated in university hospitals, five in central, and one in a district hospital.

Of 307 primary operations, 291 (95%) were elective and 16 (5%) were performed for acute reasons. Only three of the sixteen emergency operations were performed in the university hospitals. Open laparotomy was done in 289 (94%) and an endoscopic operation in 5 (2%) cases. In 13 (4%) cases, the operation was converted from diagnostic laparoscopy to open surgery. The number of surgical procedures performed in different hospital categories is presented in Tables 2 and 3. Age-specific variation in the surgical treatment is shown in Table 4. Among women $\geqslant$70 years of age, less stage I patients and less staging procedures were reported than among the younger patients. The number of lymphadenectomies and staging biopsies was higher in university hospitals than in other hospitals in both age groups (Table 5).

Re-operations performed on 16 patients due to an unsatisfactory primary operation included 13 pelvic lymphadenectomies, 11 para-aortic lymphadenectomies, 7 unilateral

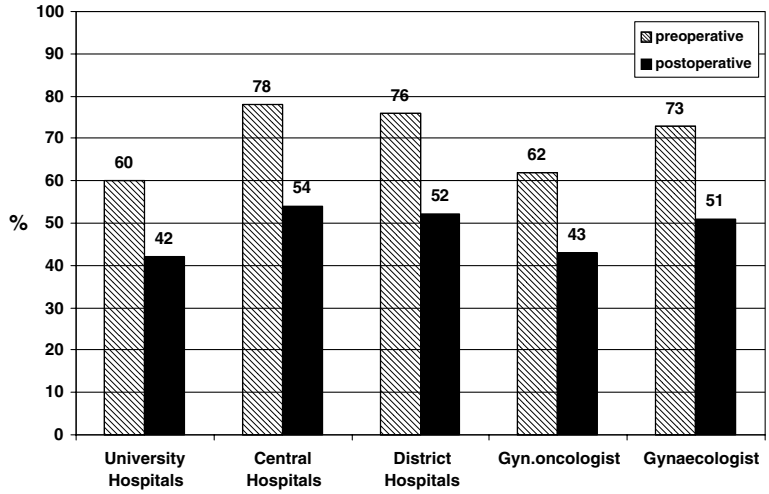

Fig. 2 – The percentage of stage III patients with >2 cm tumour nodules before and after cytoreductive surgery in different hospital categories and when operated on by gynaecologic oncologists and general gynaecologists. * The category gynaecologist includes six patients operated on by a general surgeon.

Table 2 – Previous operations and the number of different surgical procedures performed in patients with primary ovarian cancer in different hospital categories

	University	Central	District	All
Previous operations				
USO	13 (8%)	2 (2%)	1 (2%)	16 (5%)
Hysterectomy	19 (12%)	14 (13%)	6 (14%)	39 (13%)
Current operations				
Only biopsies	11 (7%)	15 (14%)	6 (14%)	32 (10%)
Uni/bilat. oophorectomy	136 + 5 (90%)	93 + 2 (87%)	36 (86%)	272 (89%)
Hysterectomy	114 + 5 (76%)	69 + 3 (66%)	24 (57%)	215 (70%)
Omentectomy	121 + 10 (84%)	72 + 3 (69%)	26 (62%)	232 (76%)
Staging biopsies	65 + 6 (46%)	23 + 2 (23%)	5 (12%)	101 (33%)
Appendicectomy	45 + 4 (31%)	12 + 2 (13%)	7 (17%)	70 (23%)
Lymphadenectomy-pelvic				
Unilateral	4 (3%)	1 (1%)	0 (0%)	5 (2%)
Bilateral	77 + 11 (56%)	9 + 2 (10%)	4 (10%)	103 (34%)
-Para-aortic	70 + 9 (51%)	3 + 2 (5%)	3 (7%)	87 (28%)
Bowel resection	2 + 1 (2%)	13 (12%)	0 (0%)	16 (5%)

USO, Unilateral salpingo-oophorectomy.
+, The number of procedures performed at the second operation on the 16 reoperated patients.

oophorectomies, 8 hysterectomies, 13 omentectomies and 6 appendicectomies. According to the pathology report, twelve of these 16 patients had FIGO stage I carcinoma, two had stage II, and two had stage III ovarian cancer. One clinical stage IA tumour was upstaged to operative stage III C due to lymph node metastases.

The extent of the operation in each hospital category is presented in Table 2. Salpingo-oophorectomy was performed bilaterally in 249 patients and unilaterally in 23 patients. Hysterectomy was carried out in 215 patients (70%), including 31 patients with a subtotal hysterectomy. The number of previous operations is presented in Table 2. Previous hysterectomy had been performed in 13%, and unilateral salpingo-oophorectomy in 5% of the patients. These procedures are presented separately in Table 2, and they decrease the number of surgical procedures reported in the current study.

In university hospitals, 72% of the operations were performed by gynaecologic oncologists, compared with only 4% in central and 19% in district hospitals. In university hospitals, the demographic characteristics of the patients operated by gynaecologic oncologists and general gynaecologists were similar. The percentages of different FIGO stages operated by general gynaecologists were: stage I, 31%; stage II, 22%; stage III, 28%; and stage IV, 24%. Thus general gynaecologists working in university hospitals operated an equal share of patients with early and advanced stage ovarian cancers. Also the mean age (57 years vs. 57 years) and mean CA 12–5 values (1375 kU/l vs. 1177 kU/l) were similar among

Table 3 – Pelvic and para-aortic lymphadenectomy or lymph node sampling according to reported FIGO stage, hospital category and operating physician

	University	Central	District	Gyn.oncologist	Gynaecologist
Stage I (n = 85)					
Pelvic	42 (88%)	6 (21%)	1 (11%)	30 (86%)	19 (38%)
Para-aortic	35 (73%)	3 (11%)	1 (11%)	23 (66%)	16 (32%)
Stage II (n = 38)					
Pelvic	11 (61%)	3 (25%)	1 (13%)	10 (63%)	5 (23%)
Para-aortic	10 (56%)	1 (8%)	0 (0%)	8 (50%)	3 (14%)
Stage III (n = 145)					
Pelvic	34 (52%)	4 (7%)	2 (10%)	26 (50%)	14 (15%)
Para-aortic	29 (45%)	2 (3%)	2 (10%)	24 (46%)	9 (10%)
Stage IV (n = 39)					
Pelvic	5 (20%)	0 (0%)	0 (0%)	4 (21%)	1 (5%)
Para-aortic	5 (20%)	0 (0%)	0 (0%)	5 (26%)	0 (0%)
All (n = 307)					
Pelvic	92 (59%)	13 (12%)	4 (10%)	70 (57%)	39 (21%)
Para-aortic	79 (51%)	6 (6%)	3 (7%)	60 (49%)	28 (15%)

* 16 patients were operated twice due to unsatisfactory primary surgery and appear in the table according to the site of the second, definitive surgery as explained in Section 2.
** The category gynaecologist includes six patients operated by a general surgeon.

Table 4 – Stage distribution and surgical staging of ovarian cancer patients according to age

Characteristic	<70 years (n = 218)	⩾70 years (n = 89)
FIGO stage		
I	69 (32%)	16 (18%)
II	22 (10%)	16 (18%)
III	101 (46%)	44 (49%)
IV	26 (12%)	13 (15%)
Surgery		
Omentectomy	179 (82%)	53 (60%)
Pelvic lymph.	91 (42%)	17 (19%)
Para-aortic lymph.	74 (34%)	13 (15%)
Staging biopsies	79 (36%)	22 (25%)

Table 5 – Surgical staging of ovarian cancer in different hospital categories according to age

Characteristics	<70 years	⩾70 years
University hospitals	(n = 123)	(n = 33)
Omentectomy	108 (88%)	23 (70%)
Pelvic lymph.	78 (63%)	14 (42%)
Para-aortic lymph.	67 (54%)	12 (36%)
Staging biopsies	57 (46%)	14 (42%)
Other hospitals	(n = 95)	(n = 56)
Omentectomy	71 (75%)	30 (54%)
Pelvic lymph.	13 (14%)	3 (5%)
Para-aortic lymph.	7 (7%)	1 (2%)
Staging biopsies	22 (23%)	8 (14%)

patients operated by gynaecologic oncologists and general gynaecologists. Outside university hospitals, gynaecologic oncologists carried out altogether eight operations in four district hospitals and four operations in one central hospital. Six patients were operated by a general surgeon. Four of these six laparotomies were performed because of an acute abdomen, and ovarian cancer was an unexpected finding. In the data analysis, these six cases were combined with the patients operated by general gynaecologists (Table 3 and Figs. 1 and 2).

In the whole patient population, 111 (36%) patients had macroscopic stage I disease and 190 (62%) had advanced disease with macroscopic tumour outside the ovaries. In 6 (2%) cases, the extent of the carcinoma was not defined. The final percentage of operative stage I patients was 28% , since 26 patients had microscopic disease outside the ovaries according to pathologic reports. Three patients with macroscopic stage I tumour were upstaged on the basis of lymph node metastases only. Two of these patients underwent lymphadenectomy in the primary operation, while one of the thirteen re-operated patients with clinical stage I tumour had para-aortic lymph node metastasis. In the university hospitals, 41% patients had clinical, whereas only 31% had surgical stage I disease. The corresponding figures were 30% and 26% in the central, and 33% and 21% in the district hospitals, respectively. It should be noted that the number of stage I patients operated outside the university hospitals is low.

No macroscopic residual tumour was left in 47% of the patients. In two cases, residual tumour was not defined. The number of patients with no macroscopic disease increased because of primary surgery by 14%, 8%, and 5% in university, central and district hospitals, respectively. The percentage of stage III patients with no macroscopic tumour was highest in the university hospitals and when operated by gynaecologic oncologists (Fig. 1). For stage III patients operated by gynaecologic oncologists, the estimated odds ratio for no postoperative macroscopic tumour in Fisher's exact test was 3.0 times higher (95% CI 1.2–7.5) than for those operated by general gynaecologists. The percentage of stage III patients with >2 cm tumour nodules before and after cytoreduction is shown in Fig. 2. No clear differences were seen between the three hospital categories.

4. Discussion

Surgical treatment of ovarian cancer has been evaluated in only a few prospective studies on a national level [17,20–22], while national statistics on the number and extent of ovarian cancer operations from different countries are not available. Most of the earlier reports evaluating the extent and result of surgical treatment of ovarian cancer are retrospective studies performed in one institution or health care region [13,16,23–28]. However, a comprehensive prospective survey or a national registry is the cornerstone for improving the treatment of ovarian cancer. In the current nation-wide, prospective study, detailed data on surgical treatment of ovarian cancer were obtained directly from the operating physicians, and checked from surgical and histopathologic reports. This allowed the collection of more detailed data than is possible on the basis of hospital records alone. The current survey forms a representative cohort on the surgical treatment of ovarian cancer covering a 12-month period in one country.

The patients operated in the university hospitals had higher mean CA 12–5 values, more ascites, and more often stage IV disease than patients operated in the other hospital categories. On the other hand, more stage I patients and young patients with stage I disease were operated in university hospitals. These differences in patient characteristics may indicate the referral of patients with obviously malignant tumours, as well as young women with possibly malignant tumours, to university hospitals. Only 3 out of 16 emergency operations were performed in the university hospitals. This may reflect better possibilities for diagnostics facilities in larger units.

FIGO staging of ovarian cancer has been operative since 1988. However, a national survey performed in the USA revealed that only 11–25% of the patients had adequate peritoneal, diaphragmatic, and lymph node biopsies to allow accurate surgical staging [29]. According to the current survey, pelvic lymphadenectomy was performed in 58%, and para-aortic lymphadenectomy in 46% of the patients with macroscopic tumour confined to ovaries. According to pathology reports, 26 patients had a tumour outside the ovaries and were upstaged. Furthermore, one of the 13 reoperated patients with macroscopic tumour confined to ovaries was upstaged to stage IIIC. The results are in agreement with earlier studies [4–7], and indicate that lymph node assessment is especially important in the staging of early ovarian cancer. The lack of lymphadenectomy and peritoneal biopsies means suboptimal staging operation and potentially suboptimal treatment. In all stages, the number of lymphadenectomies was higher in university hospitals than in the other hospitals. Therefore, outside university hospitals, adequate surgical staging was performed only in a minority of the patients.

It is to be noted, that the patients operated in the university hospitals were younger than the patients operated in the other hospitals. Higher incidence of co-morbidity associated with older age may partly explain the differences in the extent of staging procedures. Recent studies have shown that older women are likely to be treated surgically more conservatively than younger women [30–32]. Maas and co-workers evaluated the influence of age, stage, co-morbidity and hospital on the treatment of ovarian cancer patients. The study population consisted of 1116 patients operated in 15 non-academic hospitals including two gynaecologic oncology centers. Patients aged 70 or older were treated with surgery and adjuvant chemotherapy less often and with chemotherapy or no treatment more often [31]. The database obtained from hospital records did not provide detailed information on surgical treatment. All patients included in the current survey were operated and in both age groups the number of lymphadenectomies and staging biopsies was higher in the university hospitals. This is in line with the data obtained from a gynaecologic oncology unit indicating that age is not a limiting factor in achieving optimal debulking in those patients who have been chosen for surgical treatment [30].

In the whole study population, the majority of the lymphadenectomies were performed by a gynaecologic oncologist. This indicates that most general gynaecologists are not trained to perform comprehensive staging of ovarian cancer. Surprisingly, in 1999, every fourth patient undergoing surgical treatment for ovarian cancer at a university hospital was operated by a general gynaecologist. Since then, the number of gynaecologic oncologists has increased in Finland and, currently, only a small minority of patients with gynaecologic cancer treated at university hospitals are operated by general gynaecologists.

The percentage of patients with optimally cytoreduced advanced ovarian cancer has been reported to vary from 17% to 87%, with a mean of 35% [2]. It is likely that the great

variability in the figures reflects both the differences in the quality of surgical treatment and the difficulty in estimating the amount of residual tumour. The percentage of patients with no macroscopic tumour may be a more accurate parameter to describe the extent of optimal cytoreduction. In the present study, the percentage of patients with no macroscopic tumour increased most in university hospitals, and when operated by a gynaecologic oncologist. Several studies indicate that the specialisation of gynaecologists in cancer treatment including surgery improves the treatment results of ovarian cancer [23,27,33,34].

The 5-year survival data of the present study is not yet available. The survival data obtained from the Finnish Cancer Registry gives a general view of the standard of cancer treatment in Finland. In 1999, there were 397 patients with malignant ovarian neoplasm registered to the Finnish Cancer Registry. Their overall 5-year cumulative relative survival rate (RSR) was 50.5% (95% CI 44.3–56.2%). According to the cancer registry data, 314 patients were operated on and their 5-year RSR was 58.8%. 269 patients were less than 70-years-old and their 5-year RSR was 56.5%. The 5-year RSR for patients 70-years-old or older ($n = 128$) was 33.2%. Patients with localised tumours had very high 5-year RSR (96.1% for patients less than 70, and those older than that had RSR over 100%). Patients less than 70-years-old with non-localised disease had the 5-year RSR of 42.5% ($n = 190$), but for patients older than 70 years the RSR was only 19.1% ($n = 96$). In international comparisons, the survival rates of Finnish ovarian cancer patients were very high. They were higher than those reported in Europe in 1990–1994 [35] and similar to those reported in late 1999s in the USA [36]. Our results indicate that this nationwide survey can be used in international comparisons of operative treatment of ovarian cancer in other countries.

The results of the present study demonstrate differences in surgical treatment of ovarian cancer in different hospital categories in favour of university hospitals. Operative treatment of ovarian cancer can be improved with systematic training and with centralisation of primary surgery to hospitals where the number of treated patients is sufficient to guarantee the training and maintenance of surgical skills. This means centralisation to the five existing university hospitals in Finland, to which the highly specialised health care has been centralised for all specialities. Centralisation can be achieved with a good collaboration and referral policy, and accurate preoperative evaluation of pelvic tumours, e.g. by using the risk of malignancy index [37,38]. Women suspected of having ovarian carcinoma should be given the opportunity to have surgical treatment performed in a multidisciplinary unit with physicians specialised in ovarian cancer surgery and chemotherapy.

Conflict of interest statement

None declared.

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