Lymph node sampling is of prognostic value in early stage epithelial ovarian carcinoma

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Summary

Purpose: The importance of lymph node involvement as a prognostic factor is still under debate. In the present study, the impact of surgical staging for prognosis in early stages of epithelial ovarian cancer was evaluated in a series of 113 patients.

Material and Methods: A retrospective study was carried out at the Department of Gynecological Oncology, Örebro University Hospital, during the period 1994-1998. In a subgroup of 20 out of 113 patients, pelvic lymph node sampling or pelvic lymphadenectomy was included in the standard surgical procedure. In cases of positive lymph nodes, the tumors were upstaged to FIGO Stage III. Pearson's chi-square, the t-test, the log-rank test and Cox multivariate analysis were used in the statistical analyses.

Results: The 20 patients with lymph node sampling or lymphadenectomy were compared with the remaining 93 patients without a comprehensive surgical staging procedure. A survival analysis demonstrated a significant (p = 0.005) difference in disease-free survival rates between the two subgroups, where there was a survival benefit in the subgroup of patients who had undergone comprehensive surgical staging. In a Cox proportional hazard regression analysis with disease-free survival as the endpoint, high tumor grade (HR = 3.14) and comprehensive surgical staging with at least a node sampling (HR = 0.09) were significant and independent prognostic factors.

Conclusion: The benefit in survival after the procedure of lymph node sampling in early stages of epithelial ovarian carcinoma could probably be explained by the fact that the surgical procedure detects otherwise unrecognized Stage III disease.

Key words: Early-stage ovarian cancer; Prognostic factors; Lymph node sampling.

Introduction

The stage of ovarian cancer is defined as the extent of disease at the time of diagnosis [1].

The spread of this frequently lethal disease occurs at two levels; in the abdominal cavity and in the retroperitoneal space [2]. As described by Plentl and Friedman [2, 3], there are three main departure routes from the lymphatic subovarian plexus. The first accompanies the ovarian vessels to the vena cava and aorta, the second leads via the broad ligament to the pelvic and para-aortic lymph nodes, and the third follows the round ligament to the inguinal lymph nodes, although clinically this way is less significant. In the FIGO staging criteria for ovarian carcinoma from 1985, patients with positive lymph nodes in presumed Stage I or II are staged as IIIC regardless of peritoneal findings [4, 5]. According to the new criteria, lymphadenectomy has been introduced for epithelial ovarian cancer and the presence of pelvic and paraaortic lymph node metastases is suggested to be an important prognostic factor [5]. The pathologic status of lymph nodes cannot be predicted on the basis of clinical appearance, since in more than 60% of the cases with node metastases, the lymph nodes are not clinically suspected to be malignant [2, 6]. Therefore, Petru *et al.* [7] did not recommend that lymphadenectomy should be limited to any specific subgroup of patients with tumors in Stage I since clinico-morphological factors at surgery could not predict the status of the lymph nodes in 40 of 100 patients in a study of comprehensive surgical staging. Di Re *et al.* [8] defined a lymphadenectomy as yielding at least 20 nodes, and lymph node sampling yielding between five and 20 nodes. Lymph node sampling is inferior to radical lymphadenectomy in predicting the incidence of lymph node involvement, especially in the early stages [9]. However, no difference in the time to relapse or overall survival rate was found between two groups of patients in a randomized multicenter trial [10], where 99 patients underwent lymph node sampling with positive nodes detected in 10%, and 103 patients were treated with systematic lymph node dissection leading to detection of 19% positive lymph nodes.

In the present study the impact of surgical staging for prognosis in early stages of epithelial ovarian cancer was evaluated in a series 113 patients, where a subgroup of 20 patients underwent systematic staging, including lymph node sampling at the primary surgery.

Material and Methods

A retrospective study was carried out on all patients with early stage (FIGO Stages IA-IIC) ovarian cancer referred to the Department of Gynecological Oncology, Örebro University Hospital, during the 5-year period 1 January 1994 to 31 December 1998.

The surgical records were reviewed and the clinco-pathological data for each patient were retrieved and stored in a computerized database for subsequent analysis.

The primary surgery was performed at five different departments of gynecology and obstetrics in the Örebro medical region, and the patients were then referred to the Department of Gynecological Oncology for final staging, classification, and treatment planning. The staging procedure was done in all cases

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Table 1. — *Type of lymph node surgery performed.*

	Pelvic lymph node sampling			Pelvic and paraaortic lymph node sampling		
	Case	Nodes (no.)	FIGO Stage	Case	Nodes (no.)	FIGO Stage
Bilat	1	11	IIC	8 *	5	IA
	2	13	IA	9 *	10	IC
	3	10	IC	10 *	14	IIA
	4	5	IIC	11	14	IC
	5	7	IA	12 *	22	IA
	6	2	IA			
	7	3	IA			
Ipsilat	13	4	IC	17	8	IC
	14	3	IC	18	8	IC
	15	4	IA	19	6	IC
	16	4	IIA	20 *	19	IC

* Lymphadenectomy (LA) was performed in all these cases.
Mean number of lymph nodes removed was 9 (range 2-22).

at the time of primary surgery and the standard surgical procedure included abdominal exposure through a midline incision, pelvic and abdominal washings, manual exploration of all serosal surfaces with multiple peritoneal biopsies, total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy and appendectomy. At one of the referring departments (Karlstad), pelvic lymph node sampling or lymphadenectomy, ipsilateral or bilateral, with or without paraaortic node dissection was included in the standard surgical procedures (Table 1). In one case (no. 10), lymphadenectomy was performed at a secondary, separate surgical procedure. The final staging was undertaken postsurgically at the Department of Gynecological Oncology four to six weeks later. In cases of positive lymph nodes, the patients were upstaged to FIGO stage III and were excluded from the present study. The staging procedure was not adequate in 18 patients out of the complete series of 113 patients. In most of these cases the carcinoma diagnosis was not clinically suspected at primary surgery. At primary surgery, total abdominal hysterectomy and bilateral salpingo-oophorectomy were done in 102 cases, bilateral salpingo-oophorectomy alone in seven cases, and unilateral salpingo-oophorectomy alone in four cases. For the staging quality, infracolic omentectomy was performed in 86 cases, pelvic node sampling in 20 cases, appendectomy in 48 cases, and blind biopsies of pelvic peritoneum or adhesions close to the primary tumor in 48 cases. At primary surgery, ascites were found in 43 cases. The ascitic fluid was negative for tumor cells in 36 cases and positive in seven cases at the cytological analysis. For the 70 cases without ascites at primary surgery, cytological analysis of peritoneal washings demonstrated tumor cells in four cases. Rupture of the capsule of the tumor was recorded in 51 out of 113 cases (45%). The rupture was spontaneous in seven cases (6%) and secondary to the surgical procedure in 44 cases (39%).

Tissue samples of the ovarian cancers were obtained at the primary surgery. The histopathology specimens were primarily evaluated at three departments of pathology (Örebro, Karlstad, and Eskilstuna). All specimens were then reviewed and classified according to the WHO criteria for classification of ovarian tumors [11] at the Department of Pathology in Örebro. The degree of differentiation was determined according to Henson [12]. In the complete series of 113 patients, 103 were treated according to a standardized adjuvant chemotherapy protocol (cisplatin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 as a combination in four courses given every four weeks). The remaining ten patients were treated with other combinations of adjuvant chemotherapy. The follow-up data were obtained from clinical registers; the median follow-up time was 67 months and the range was between 36 and 97 months. The follow-up interval was defined as the interval from initial surgery to the date of the last follow-up or the date of death. The patients were followed-up at the Department of Gynecological Oncology or at the referring departments every three to four months during the first three years, every six months up to five years, and then once a year up to ten years. No patients were lost to follow-up. In most cases of tumor recurrences, the patients were treated with chemotherapy containing a combination of a platinum and a taxoid agent.

Pearson's chi-square test, the t-test, the log-rank test, and Cox's proportional hazard regression analysis were used in the statistical analyses. The statistical packages from StatSoft (Statistica 6.0) and from SPSS (version 11.0) were used for the analyses.

Results

After the final staging, 113 patients were found to have tumor confined to the pelvic cavity. The mean age at presentation was 61 years (range 23-88 years).

The distribution of histology showed serous tumors in 36 patients (32%), mucinous tumors in 29 patients (26%), endometrioid tumors in 31 patients (27%), clear cell tumors in 13 patients (12%) and anaplastic tumors in four patients (4%). The tumor grade distribution showed 26% grade 1 tumors, 36% grade 2 tumors, and 33% grade 3 tumors. In 5% of the cases (clear cell tumors) the tumors could not be graded.

Table 2. — *FIGO stages versus clinicopathological features in the complete series (n = 113).*

FIGO stages	IA No. (%) 37 (33)	IB No. (%) 6 (5)	IC No. (%) 45 (40)	IIA No. (%) 5 (4)	IIB No. (%) 4 (4)	IIC No. (%) 16 (14)
Histopathology						
Serous	8 (22)	4 (67)	16 (36)	1 (20)	1 (25)	6 (38)
Mucinous	17 (46)	0	8 (18)	1 (20)	2 (50)	1 (6)
Endometrioid	7 (19)	1 (17)	13 (29)	3 (60)	1 (25)	6 (38)
Clear cell	4 (11)	0	7 (16)	0	0	2 (13)
Anaplastic	1 (3)	1 (17)	1 (2)	0	0	1 (6)
						p = 0.163 (χ^2)
Tumor grade						
G1	14 (38)	4 (67)	8 (18)	0	0	3 (19)
G2	16 (44)	1 (17)	17 (38)	0	2 (50)	5 (31)
G3	7 (19)	1 (17)	15 (33)	5 (100)	2 (50)	7 (44)
Not graded	0	0	5 (11)	0	0	1 (6)
						p = 0.015 (χ^2)
Six tumors were not graded (all clear cell carcinomas)						
Disease-free survival						
Disease-free	33 (89)	4 (67)	29 (64)	3 (60)	1 (25)	7 (44)
Dead of disease or alive with disease	4 (11)	2 (33)	16 (36)	2 (40)	3 (75)	9 (56)
						p = 0.005 (χ^2)

Table 2 outlines the clinco-pathologic characteristics per FIGO substage of the complete series of 113 patients. Tumor grade was statistically significantly (p = 0.015) associated with the FIGO stage and it was shown that the grade 3 tumors were most frequent in FIGO Stage IC and Stages IIA-IIC. The disease-free survival rate was also significantly associated with the FIGO stage as well as with tumor grade (Figure 1). In the complete series, the 5-year disease-free survival rate was 68.1% and the overall survival rate 71.0%.

Twenty patients (18%) had a comprehensive surgical

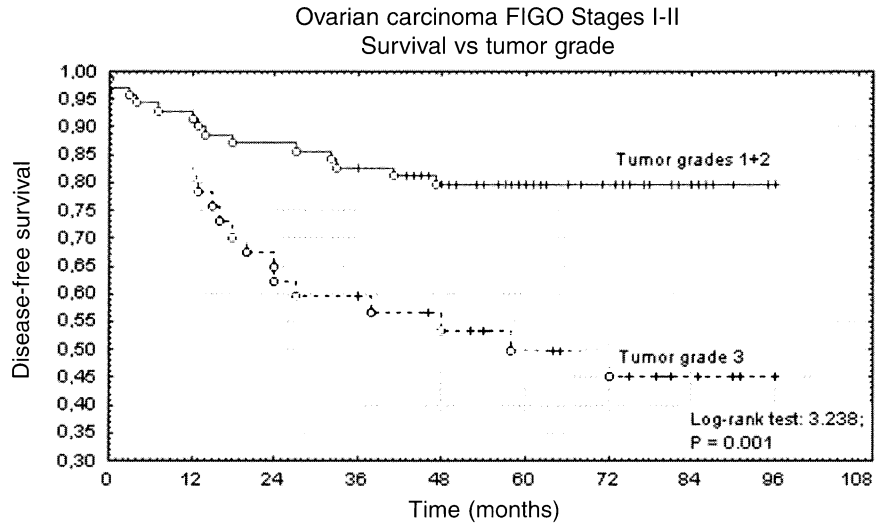

Figure 1. — Disease-free survival vs tumor grade of the complete series (n = 107). In six cases no grading was performed.

staging procedure with lymph node sampling or lymphadenectomy performed (Table 1). In Table 3, this subgroup of patients is compared with the 93 remaining patients (82%) without a comprehensive surgical staging procedure with lymph node sampling or lymphadenectomy. The two groups were comparable with regard to age, FIGO stage, the histopathological subtype and tumor grade. However, there was a significant (p = 0.004) survival benefit in patients who had undergone comprehensive surgical staging and lymph node sampling. A survival analysis (Figure 2) demonstrated a significant (p = 0.005) difference in the disease-free survival rates between the two subgroups. The difference in survival between the two subgroups of patients could not be explained by capsule rupture (p = 0.989), type of capsule rupture (p = 0.187), presence of ascites (p = 0.843), type of adjuvant treatment (p = 0.508), or residual tumor (p = 0.555) at the time of the surgical procedure.

Among the 113 patients, eight did not achieve primary cure and seven of those died due to their disease. The total number of recurrences in the complete series was 30 out of 113 (26.6%) and 19 of these patients (63.3%) died due to their disease.

In a Cox proportional hazard regression analysis, FIGO stage, histopathology, tumor grade, and the surgical status of the tumors were analyzed with disease-free survival as the endpoint (Table 4). Tumor grade and the surgical staging procedure with regard to the lymph nodes were the only statistically significant and independent prognostic factors. It was shown that the surgical procedure with lymph node sampling reduced the risk of tumor recurrences by 90% in the group with complete surgical staging compared with cases undergoing incomplete staging and no evaluation of the lymph nodes.

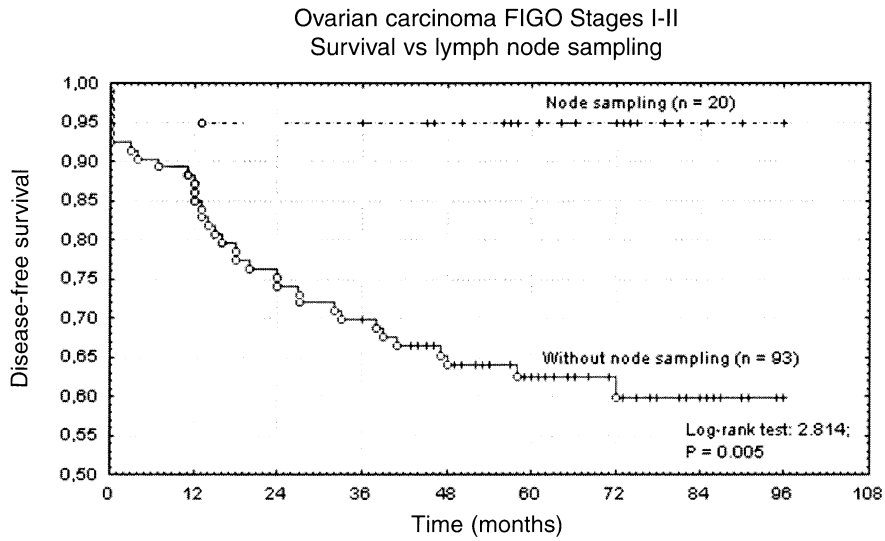

Figure 2. — Disease-free survival vs type of surgery. Comprehensive surgical staging with at least node sampling (n = 20) vs less extensive surgery with no lymph node sampling (n = 93).

Table 3. — *Clinicopathologic characteristics versus surgical status in the complete series (n = 113).*

Features	Patients with node sampling (n = 20)		Patients without sampling (n = 93)		p value
Age (mean) years	63.5		60.5		0.391 (t-test)
FIGO stage	N	%	N	%	
IA-IB	7	35.0	36	39.0	
IC	9	45.0	36	39.0	
IIA-IIB	2	10.0	7	7.0	
IIC	2	10.0	14	15.0	0.499 (χ^2)
Histopathologic subtype					
Serous	7	35.0	29	31.2	
Mucinous	4	20.0	25	26.9	
Endometrioid	6	30.0	25	26.9	
Clear cell	2	10.0	11	11.8	
Anaplastic	1	5.0	3	3.2	0.959 (χ^2)
Tumor grade					
G1	4	20.0	25	26.9	
G2	7	35.0	34	36.6	
G3	7	35.0	30	32.2	
Not graded *	2	10.0	4	4.3	0.715 (χ^2)
* all clear cell carcinomas					
Disease-free survival					
Disease-free	19	95.0	58	62.4	
Dead of disease or alive with disease	1	5.0	35	37.6	0.004 (χ^2)

Table 4. — *Cox proportional hazard regression analysis with disease-free survival as endpoint.*

Factor	Coefficient	S.E.	Odds ratio	95% C.I.	p value*
FIGO stage					
IC, IIC vs IA-B, IIA-B	0.649	0.388	1.913	0.894-4.093	0.095
Histopathology					
Other types vs serous	–0.338	0.369	0.713	0.346-1.470	0.360
Tumor grade					
Grade 3 vs 1-2	1.144	0.357	3.139	1.559-6.320	0.001
Lymph node sampling					
Sampling vs no sampling	–2.391	1.016	0.092	0.013-0.670	0.019

* Wald statistics

Discussion

In the therapy of ovarian carcinoma, the importance of surgical management is universally recognized, but the importance of lymph node involvement as a prognostic factor is not yet clear. Lymph node sampling does not give such precise information on the incidence of lymph node metastases as radical lymphadenectomy. The lymph node involvement is also lower in early stages. At the present time, the therapeutic significance of lymphadenectomy is also debated [9]. In the literature, the average rate of lymph node involvement in clinical Stage I ovarian cancer is 16% whereas in clinical Stage II it is 29% [13]. Benedetti-Panici *et al.* suggested that ipsilateral lymphadenectomy (pelvic and para-aortic) is feasible for clinical Stage IA disease at primary surgery. This conclusion was based on results from six patients in a study including 156 patients with the purpose of determining how lymphadenectomy should be performed. They found that the ipsilateral procedure reduced the complication rate and maintained diagnostic accuracy [14]. However, Cass *et al.* found that ipsilateral node sampling could result in understaging of the tumors since isolated contralateral lymph node metastases were found in three patients out of ten with lymph node metastases in a study on 96 patients with disease confined to one ovary at primary surgery [15]. These findings are in agreement with other reported retrospective studies, e.g., Petru *et al.* [7], Wu *et al.* [16], Onda *et al.* [17], and Walter *et al.* [18]. In addition, Wu *et al.* noted a high incidence of contralateral-only nodal involvement in Stages II-IV disease, when the primary tumor site was the right ovary [15, 16]. Therefore, it is concluded that bilateral lymph node evaluation is required in apparent early-stage disease, which is consistent with the FIGO-staging guidelines, where it is specifically recommended to perform bilateral pelvic and para-aortic lymph node sampling in all patients with invasive ovarian adenocarcinoma suspected of being confined to one or both ovaries [4, 18]. In the present study, an ipsilateral lymphadenectomy was performed in one case with Stage IIA disease at the final staging. Therefore, it may be concluded that ipsilateral lymphadenectomy (pelvic and/or para-aortic) in clinical Stage IA (when the tumor is clinically confined to one ovary) disease at primary surgery does have some limitations for diagnostic accuracy, since occult adenocarcinoma may be found in the uterus (IIA) or in the opposite ovary (Stage IB) at the histopathological evaluation of the surgical specimen.

Tumor grade and disease-free survival were associated with the FIGO substage in univariate analyses, but the FIGO stage was not a prognostic factor in multivariate analyses. In multivariate analyses, tumor grade (grade 3 vs grades 1-2) was the single most important variable predicting relapse. A survival analysis (Figure 1) also demonstrated an unfavorable outcome for patients whose tumors were poorly differentiated. Rubin *et al.* [19] observed in a study on 62 patients with high-risk Stage I ovarian cancer that grade 3 tumors were associated with an increased risk of relapse compared with grade 1-2 tumors. Some authors advocate that tumor grade [20], the most powerful prognostic indicator in Stage I ovarian cancer, should be used more frequently in the therapy setting and should also be included in the FIGO staging system. The problem with the reproducibility of the tumor grade may affect the prognostic value of this factor, however.

In the present study, the extent of surgical staging (lymph node sampling) was a statistically significant (p = 0.019) and independent prognostic factor in multivariate analysis. In survival analysis, one (5%) relapse was recorded in the 20 patients with surgically proven early-stage disease (FIGO Stage IA-IIC), but among the remaining 93 patients with incomplete surgical staging 29 (31%) relapses were found. All patients received adjuvant cisplatin-based chemotherapy after the primary surgery. In a study conducted in Canada [21], including 60 patients with surgically proven FIGO Stage I disease, six (10%) patients with no adjuvant therapy recurred, whereas seven (28%) of 25 patients with incomplete surgical staging and no adjuvant therapy recurred (p = 0.036). Logistic regression analysis showed that age, grade of tumor and lack of a proper staging surgery were important predictors of recurrence. The prognostic value of lymph node assessment in early ovarian cancer is

obvious, since the presence of node metastases upstages the tumors to FIGO Stage III [2].

With regard to the therapeutic role of systematic lymphadenectomy, few data in the literature are available and, what is most important, they are not derived from experimental studies [9]. In a series of 100 evaluable patients in FIGO Stage I, Petru *et al.* [7] could not find any difference in 5-year survival between 40 patients undergoing radical lymphadenectomy (82%) compared with 60 patients with no lymphadenectomy performed (87%). This is also in agreement with the results from another study [22], where the survival for 14 out of 67 patients who had tumors limited to the pelvis but with positive lymph nodes were compared with a group of 53 patients, also with tumors in clinical FIGO Stages I-II, but with negative lymph nodes. No significant differences were noted (84% vs 96%; $p = 0.107$). However, according to Kanazawa *et al.* [23], survival was significantly ($p = 0.017$) worse in a node-positive group compared with a node-negative group with tumors in clinical Stages I and II. They also concluded that for further evaluation of the prognostic significance of lymph node involvement survivals should be compared among patients with de novo node disease, with node disease removed, and otherwise similar patients without node disease in a prospective, randomized study, including a large number of patients.

Some of the prognostic factors analyzed for early stage ovarian carcinoma are intrinsic or biological, e.g. tumor grade, and others are extrinsic, e.g. completeness of surgical staging or type of adjuvant treatment [24]. In agreement with Zanetta *et al.* [24], we found that tumor grade, one of the most important intrinsic prognostic factors, remains the most powerful indicator of survival. It was also found in the present work that the thoroughness of the surgical staging procedure, with regard to lymph node sampling, was most important among the extrinsic prognostic factors. The difference in survival between the two groups of patients according to the accuracy of the surgical staging procedure could probably be explained by the fact that the procedure of lymph node sampling detects otherwise unrecognized Stage III tumors that are excluded from the early FIGO stages.

Further prospective and randomized studies, including a large number of patients, are needed in the future to assess the prognostic impact and the therapeutic role of systemic lymph node dissection of the pelvic and paraaortic lymph nodes in patients with clinically early stages of epithelial ovarian carcinoma.

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