

Role of Pelvic and Para-aortic Lymph Node Metastases in Optimally Cytoreduced Advanced Ovarian Cancer

CORNELIA BACHMANN¹, ROBERT BACHMANN³, SARA Y. BRUCKER¹, ANETTE STAEBLER²,
FALKO FEND², EVA-MARIA GRISCHKE¹ and DIETHELM WALLWIENER¹

Departments of ¹Gynecology, and ²Pathology, University of Tübingen, Tübingen, Germany;

³Department of General, Visceral and Transplant Surgery, University Hospital Tübingen, Tübingen, Germany

Abstract. *Aim: To delineate the role of pelvic and para-aortic node involvement in patients with optimally cytoreduced ($R \leq 1$ cm; R =residual tumor) stage IIIC ovarian cancer. Patients and Methods: Ninety-five consecutive optimally cytoreduced patients with primary stage IIIC ovarian cancer underwent stage-related surgery and adjuvant platinum-based chemotherapy, with a median follow-up of 53.5 months. All patients underwent systematic lymphadenectomy. On average, 24.7 pelvic and para-aortic lymph nodes were removed per patient (range=1-60 nodes); Patients were stratified into three groups to evaluate nodal involvement (ratio of affected to resected nodes): 0: no lymph node metastases; $>0-0.5$: >0 and fewer than 50% of involved nodes; $>0.5-1$: more than 50% of nodes involved. Clinical parameters were retrospectively evaluated. Results: Most often, serous histology, histological grade 3 and a node ratio $>0-0.5$ (61.1%) were detected. Complete cytoreduction ($R=0$ mm) had significant best prognostic impact compared to $R>0$ mm-1 cm (overall survival: $p=0.047$, progression-free survival: $p<0.001$). Nodal involvement was associated with serous histology and grade 3 tumor. Best overall survival was associated with a node ratio $>0-0.5$ ($p=0.011$). A solitary affection of the pelvic or rather para-aortic nodes was detected in 22.1% vs. 16%, respectively; a combined affection of pelvic and paraaortic nodes were detected in 34.8%. Conclusion: The goal is optimal cytoreduction in advanced ovarian cancer. More extensive pelvic and para-aortic lymphadenectomy seems to play an important role in providing accurate*

staging in optimally-cytoreduced advanced ovarian cancer and the node ratio might give prognostic information. Current prospective studies should investigate if these data have therapeutic implications and may be considered in future staging.

Initial management of primary ovarian cancer includes surgical staging, cytoreductive surgery, lymphadenectomy followed by a platinum- based chemotherapy, except for pT1aG1 cases (1, 2). However, the importance of systematic lymphadenectomy in primary advanced ovarian cancer and its prognostic relevance is still unclear (3-5). Nodal involvement increases in advanced ovarian cancer, with unknown prognostic impact (6, 7). A rate of about 50% of nodal metastases has been reported (1, 2) and accurate surgical staging including lymphadenectomy recognizes the true extent of disease by detection of occult nodal metastases.

Many studies have reported better prognosis for stage IIIC ovarian cancer with sole lymph node metastases (without peritoneal carcinomatosis) compared to lymph node metastases and concomitant peritoneal carcinomatosis (8). The objective was to delineate the role of pelvic and para-aortic node metastases in patients with optimally cytoreduced stage IIIC ovarian cancer.

Patients and Methods

Ninety-five consecutive patients with primary stage IIIC [according to the Fédération Internationale de Gynécologie Obstétrique (FIGO) (9)] optimally cytoreduced ($R \leq 1$ cm) ovarian cancer were enrolled. All gave their informed consent prior to their inclusion in the study. Our investigation of these 95 patients was approved by the appropriate Ethics Committee and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Every patient underwent surgical staging including hysterectomy, bilateral oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy and cytoreduction as clinically indicated and an adjuvant standard platinum-based chemotherapy.

Correspondence to: Cornelia Bachmann, MD, Department of Gynecology, University Tübingen, Calwer Str. 7, 72070 Tübingen, Germany. Tel: +49 70712982211, Fax: +49 7071294525, e-mail: cornelia.bachmann@med.uni-tuebingen.de

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Table I. Characteristics of 95 patients with stage IIIC ovarian cancer. Nodal involvement was analysed; for evaluation of the lymph nodal ratio (affected to removed nodes) the patients were stratified into three groups (see Patients and Methods).

Parameter	n (%)
FIGO IIIC	95 (100)
Histological grade	
G1/2	46 (48.4)
G3	49 (51.6)
Histology	
Serous	84 (88.4)
Non serous	11 (11.6)
R Status	
R=0-≤10 mm	95 (100)
N Status	
N0	25 (26.3)
N+	70 (73.7)
Lymph nodal ratio	
0	25 (26.3)
>0- ≤0.5	58 (61.1)
>0.5- ≤1	12 (12.6)

FIGO IIIC: Fédération Internationale de Gynécologie et d'Obstétrique.

In primary ovarian cancer, pelvic and para-aortic lymphadenectomy up to the level of renal vessels is part of primary surgical intervention after optimal cytoreduction and in good state of health (Karnofsky Index ≥80%); this procedure was performed in every case. Patients with suboptimal cytoreduction (R>1 cm) were excluded. All patients were evaluated with respect to age at diagnosis, stage, histology, histological grade and residual tumour mass. Patients' characteristics are given in Table I. On average, 24.7 pelvic and para-aortic lymph nodes were removed per patient (range=1-60 nodes). Ninety-five patients met the inclusion criteria and were further evaluated. The median age of patients was 60.7 years (range=25-83 years). All surgical pathological samples were examined by a gynaecological pathologist. The histological diagnosis was classified according to the FIGO stages (9) residual tumor mass was subdivided into the following groups: R0=complete cytoreduction (0 mm) and R>0-10 mm.

For evaluation of the prognostic impact of lymph node metastases, the patients were stratified into three groups depending on the extent of nodal involvement [*i.e.* nodal ratio (NR), the number of affected to removed nodes: NR=0 no lymph node metastases; NR >0-0.5: >0 and fewer than 50% of involved nodes; NR >0.5-1: more than 50% of nodes involved. The average number of pelvic and para-aortic nodes removed per patient in the subgroups was: 19.7 (range=5-40), 26.7 (range=1-60) and 26.7 (range=12-43), respectively. Additionally the node affection of the pelvic and/ or para-aortic region was evaluated to evaluate the distribution pattern of pelvic and para-aortic node metastases in FIGO IIIC patients.

Follow-up. Follow-up data were collected when the patients presented at our Department for follow-up. The mean follow-up time was 53.5 months. Follow-up data of all 95 patients were evaluated.

Table II. Relationship between lymph node involvement (nodal ratio) and clinicopathological parameters in patients with stage IIIC ovarian cancer (n=95).

Parameter	Nodal ratio, n (%)		
	0	0>0-≤.5	>0.5-≤1
Histological grade			
G1/2	15 (15.7)	25 (26.4)	6 (6.3)
G3	10 (10.5)	33 (34.8)	6 (6.3)
Histology			
Serous	22 (23.1)	52 (54.7)	10 (10.5)
Non serous	3 (3.2)	6 (6.3)	2 (2.1)
R Status			
R=0 mm	11 (11.6)	21 (22.1)	3 (3.2)
R >0-≤10 mm	14 (14.7)	37 (38.9)	9 (9.5)

Statistical analysis. Data were stored in a database and analysed using PASW (Version 22; SPSS Inc. Chicago, IL, USA). The results are expressed as means, standard deviations, minimums, maximums and percentages. Kaplan–Meier analyses were used to calculate hazard ratios and 95% Confidence interval (CI) for overall survival (OS) and progression-free survival (PFS). The log-rank test was used to test for significant differences between the groups. *p*-Values less than 0.05 were considered statistically significant.

Results

All patients underwent optimal cytoreduction: 63.2% had residual tumour mass >0-≤10 mm and 36.8% had complete cytoreduction (Table I). Most often, nodal metastases (73.7%), histological grade 3 (51.6%) and serous histology (88.4%) were detected (Table I). NR between >0 to ≤0.5 was mainly reported, in 61.1%; almost 26% of the patients had no nodal metastases (NR=0); NR >0.5-1 was seen least frequently, in about 12.6% (Table I).

Concerning the impact of clinicopathological parameters on nodal metastases, the following was observed (Table II): most often a NR >0-≤0.5 was associated with histological grade 3, serous cancer and residual tumor mass >0-10 mm. Much rarer, a NR >0.5 regardless of histological grade, histology and residual tumor mass was detected.

Concerning the relevance of the region affected by nodal metastases, the following was observed (Table III): 22.1% of the patients had sole positive pelvic nodes without metastases to para-aortic nodes; 34.8% had positive pelvic and para-aortic nodes, and 16.8% had solitary affected para-aortic nodes without pelvic nodes being affected.

The significant best prognostic impact on rates of OS and PFS was found for patients with complete cytoreduction compared to R>0-≤1 cm (Table IV; OS: *p*=0.047, PFS: *p*<0.001). Thus, a significant prognostic advantage in OS was seen for patients with a moderate lymph node

Table III. Distribution of nodal involvement in pelvic and para-aortic regions in patients with FIGO IIIC (Fédération Internationale de Gynécologie et d'Obstétrique) ovarian cancer.

Parameter	Pelvic+/para-aortic-, n (%)	Pelvic+/para-aortic+, n (%)	Pelvic-/para-aortic+, n (%)	Pelvic-/para-aortic-, n (%)
FIGO IIIC	21 (22.1)	33 (34.8)	16 (16.8)	25 (26.3)

+Positive nodes; -negative nodes.

Table IV. Prognostic impact of residual tumour mass ($R=0$ mm vs. $R >0-10$ mm) on overall survival (OS) and progression-free survival (PFS) in 95 patients with optimally cytoreduced stage IIIC ovarian cancer.

Resection status	OS (95% CI), months	<i>p</i> -Value	PFS (95% CI), months	<i>p</i> -Value
R 0 mm (n=35)	58.5 (42.5-70.7)	0.047	31.7 (27.95-35.6)	<0.001
R >0-<10 mm (n=60)	26.0 (23.5-28.5)		13.9 (12.3-15.5)	

CI: Confidence interval.

Table V Prognostic impact of lymph node involvement on overall survival (OS) and progression-free survival (PFS) in 95 patients with stage IIIC ovarian cancer after optimal cytoreduction ($R \leq 1$ cm).

Nodal ratio	OS (95% CI), months	<i>p</i> -Value	PFS (95% CI), months	<i>p</i> -Value
0 (n=25)	25.97 (22.4-29.5)	0.011	13.0 (9.2-18.6)	0.034
>0-≤0.5 (n=58)	31.4 (28.2-57.3)		15.2 (11.1-19.3)	
>0.5 (n=12)	18.8 (6.8-30.8)		10.2 (6.4-14.0)	

CI: Confidence interval.

involvement (NR >0 to ≤0.5; $p=0.011$) compared to the other groups (Table V).

Subsequently, PFS was found to be significantly influenced by an increasing NR ($p=0.034$; Table IV). Patients with moderate lymph node involvement (NR >0 to ≤0.5) had a longer PFS compared to those in the other two groups. Therefore, strong lymph node involvement (NR >0.5-≤1) conferred the worst prognosis in optimally cytoreduced patients (Table IV).

OS was also found to be significantly influenced by an increasing NR ($p=0.019$; Table V) in those patients with complete cytoreduction and in those without. Patients with a moderate lymph node involvement (NR >0 to ≤0.5) had longer OS compared to the other two groups (Table V). Strong lymph node involvement (NR >0.5-≤1) conferred the worst prognosis in optimally cytoreduced patients (Table V).

Discussion

Optimal cytoreduction is the most significant prognostic factor in advanced ovarian cancer (2,8,10-12), as shown even

in our study (OS: $p=0.047$; PFS: $p<0.001$; Table IV). Complete cytoreduction leads to significantly better prognosis than cytoreduction of >0 to 10 mm (12). Further known significant prognostic factors are FIGO stage, histology and histological grade (9, 13).

The prognostic relevance of lymphadenectomy in surgical management of ovarian cancer is still unclear (10,14,15) and is currently being investigated in the prospective Phase III LION study (AGO-Ovar;<https://clinicaltrials.gov/ct2/show/NCT00712218?term=LION+study&rank=20>). Results of randomized controlled studies are still lacking (16, 17). In primary ovarian cancer, pelvic and para-aortic lymphadenectomy after optimal cytoreduction are recommended with positive prognostic effect (16, 18). The randomized trial of Panici *et al.* (3) and others (5, 19) showed a positive impact of systemic lymphadenectomy on PFS compared to resection of bulky nodes, but no impact on OS in optimally cytoreduced patients. In contrast, Pereira *et al.* showed a positive prognostic impact of systematic lymphadenectomy, with a significantly longer survival in advanced ovarian cancer (4).

In advanced ovarian cancer, nodal metastases are found in about 40% of cases, even with affection of the pelvic or para-aortic regions (3,19). In our collective, nodal metastases were detected in 73.7% (Table I). Additionally, our data detected an association of nodal metastases most often with serous cancer, histological grade 3 and residual tumour mass >0.1 cm (Table II); most often moderate lymph node involvement was detected (>0.5 ; Table II). Most of these results are similar to previous reports, but to our knowledge, the extent of nodal involvement (*i.e.* the NR) was rarely included in other reports of risk factors for ovarian cancer before.

The prognostic relevance of nodal metastases in primary ovarian cancer is still unclear (4, 20). One study reported that the influence of lymph node metastases on prognosis decreases with increasing residual tumor mass (21). The authors also reported that nodal metastases seemed to be the second most important prognostic factor for advanced-stage ovarian cancer (6). Given the many risk factors of ovarian cancer, it is still questionable if lymphadenectomy in advanced ovarian cancer improves prognosis. In FIGO IIIC metastases of the pelvic lymph nodes were detected in about 56.9% and the para-aortic nodes were affected in 51.6% (Table III). Even a solitary affection of the pelvic or para-aortic region was detected in 22.1% vs. 16.8% in FIGO IIIC optimally cytoreduced patients (Table III). If an extent of lymphadenectomy (pelvic and para-aortic) improves prognosis is still questionable.

Unquestionably, complete cytoreduction compared to residual tumour of up to 1 cm has significant prognostic impact (2, 9-11), even in our study (Table IV). The prognostic impact of clinicopathological factors associated with the NR needs to be investigated in larger studies to improve the prognostic relevance of nodal metastases in FIGO IIIC. Mahdi *et al.* described that the impact of increasing NR was strongly related to OS, especially in patients with no macroscopic peritoneal disease (21). Our study showed similar results: an increasing NR was associated with significantly decreased survival ($p=0.011$; Table V). Patients with node-positive ovarian cancer with fewer than 50% removed nodes affected (NR >0 to ≤ 0.5) have significantly improved overall survival (Table V). Significant best impact on OS was seen with decreasing NR, especially for patients with fewer than 50% affected nodes ($p=0.011$; Table V). Strong lymph node involvement (>0.5 - ≤ 1) had the worst prognosis (Table II), hence nodal involvement seems to play a role in the prognosis of optimally cytoreduced patients.

Possibly in our study, the group with NR >0 to ≤ 0.5 could contain a few patients with solitary lymph node involvement without peritoneal lesions staged up to FIGO IIIC (19, 22, 23). These patients had the best OS in our study (Table V). Similarly, as described in one report, patients with serous

ovarian carcinoma with solitary extrapelvic peritoneal involvement have better survival than those with extrapelvic peritoneal involvement and lymph node metastases (4). Additionally, an adequate staging is possible by performing a lymphadenectomy (9). Considering the relatively favourable prognosis associated with lymphatic tumour spread compared with peritoneal tumor spread (stage IIIC), which was classified solely on the basis of lymph node metastasis, Suh *et al.* suggests a modified FIGO classification with down-staging of these patients (8). Hoskins *et al.* argued that FIGO should consider modifying the ovarian cancer staging by further stratifying stage III disease on the basis of the better OS in patients with retroperitoneal node metastasis without peritoneal carcinomatosis than in patients with macroscopic peritoneal carcinomatosis (13). One plausible explanation for the favourable prognosis of those patients might be the higher optimal cytoreduction rate compared to patients with stage IIIC disease with intraperitoneal tumor implants >2 cm (8). Our data support this hypothesis. Meanwhile there is a new classification for ovarian cancer in which this is considered (24). Since ovarian cancer is known to spread simultaneously intraperitoneally and retroperitoneally, the presence of tumour spreading mainly through lymphatic channels without intraperitoneal dissemination suggests that such tumours might be associated with a favourable biological behaviour (8).

Potentially patients with partial nodal involvement could benefit from systematic lymphadenectomy in FIGO IIIC compared to patients with strong nodal involvement (NR >0.5 -1). Whether the prognostic impact is due to removal of positive nodes is still unclear, but these results may help in treatment decisions.

Perhaps the stratification of this sub-population of node-positive ovarian cancer based on nodal burden provides significant prognostic value that may be considered in future staging and aid in management decisions (20); our study supports this hypothesis: an increasing nodal involvement leads to worse prognosis.

From our study, the NR may be used to estimate the prognosis (OS) in patients with advanced ovarian cancer after optimal cytoreduction. Patients with NR <0.5 had significantly better OS than patients with a high NR (>0.5), but prospective studies should examine the prognostic impact of the NR in ovarian cancer. The outstanding results from the current prospective LION study (AGO-Ovar) will help answer the validity of lymphadenectomy in treatment strategies in optimally cytoreduced patients. Further studies are needed in order to gather sufficient information. The main intention of primary surgery in advanced ovarian cancer is optimal cytoreduction with significant best prognostic impact. More extensive lymphadenectomy (pelvic and even para-aortic) seems to play an important

role in providing accurate staging and the NR might provide prognostic information in optimally cytoreduced stage IIIC ovarian cancer. Prospective studies should investigate if these data have therapeutic implications and may be considered in future staging. The modification of the FIGO staging system, especially for patients with stage IIIC ovarian cancer, should be considered regarding the prognostic differences depending on nodal involvement and complete cytoreduction.

Conflicts of Interest

The Authors declare that there are no conflicts of interest with regard to this study.

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