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Research Paper

Incidence and Impact of Lymph Node Metastases in Advanced Ovarian Cancer: Implications for Surgical Treatment

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Abstract

Background: This study aimed to clarify the impact of node involvement (affected to resected nodes) in optimally cytoreduced (residual tumour ≤1cm) stage IIIC/IV ovarian cancer.

Methods: 108 consecutive patients with primary stage IIIC/IV ovarian cancer underwent stage-related surgery and got adjuvant platinum-based chemotherapy. Median follow-up: 53.5 months. All patients got systematic para-aortic and pelvic lymphadenectomy. Clinical parameters were retrospectively evaluated. Patients were stratified into 3 groups to evaluate node affection: 1) no (0%), 2) minor (>0%, ≤50%) >0 and 3) major (>50% of affected nodes). Kaplan-Meier survival curve was used to evaluate the prognostic value.

Results: On average, 21.3 pelvic and para-aortic nodes were removed per patient (range 1-60 nodes). Minor nodal involvement (node ratio >0-≤0.5: (59%) was most often detected. Increasing node ratio leads to significant decreased overall survival ($p<0.001$). Significant best overall survival was associated with minor node involvement (node ratio >0 to ≤0.5). Complete cytoreduction correlated with node affection shows significant best prognostic impact in minor node affection compared to incomplete resection (R>0-≤1cm) independent to nodal status (OS $p<0.001$).

Conclusion: Radical surgery is the main factor of improved overall and tumor free survival. Paraaortal and iliacal lymphadenectomy seems to play an important role for prognostic and therapeutic reasons: Prognostic in accurate staging and therapeutic in case of achieved optimal cytoreduction including lymph nodes with histology proven minor node involvement.

Key words: Advanced ovarian cancer; node ratio; lymphadenectomy; prognosis; residual tumour; node involvement.

Introduction

The 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 [3,4,5]. The increasing node involvement in advanced ovarian cancer is known with unidentified prognostic impact [6,7]. A rate of about 50% of node metastases has been observed [1,8] and accurate surgical staging, including lymphadenectomy, recognizes the true extent of disease by detection of occult node metastases. Many studies have reported a better prognosis for stage IIIC ovarian cancer patients with sole lymph node metastases (without peritoneal

carcinomatosis) compared to lymph node metastases and concomitant peritoneal carcinomatosis [9]. The new FIGO classification is considering this fact [10]. Our objective was to delineate the incidence and impact of pelvic and paraaortic node metastases in optimally cytoreduced (R≤1cm) stage IIIC/IV ovarian cancer patients.

Material/ Methods

A total of 108 consecutive patients with primary stage IIIc/IV (according to FIGO) optimally cytoreduced (R≤1cm) ovarian cancer were enrolled. Each patient underwent surgical staging followed by hysterectomy, bilateral adnexectomy omentectomy, pelvic and para- aortic lymphadenectomy or tumour debulking as clinically indicated. Pelvic and para-aortic lymphadenectomy was performed up to the level of the renal vessels in all patients with optimally cytoreduced ovarian cancer (R≤1cm) and in good state of health (Karnofsky- Index ≥ 80%); this procedure was performed in every case. All of the patients were treated with an adjuvant standard platinum- based chemotherapy.

Optimal cytoreduction is defined as a residual tumour mass ≤1cm and complete cytoreduction is defined as a residual tumour mass =0mm. Patients with suboptimal cytoreduction (R>1 cm) were excluded. All patients were evaluated with respect to age at diagnosis, stage, histology, histologic grade and residual tumour mass. Patients´ characteristics are given in table 1. On average, 21.3 pelvic and para-aortic lymph nodes were removed per patient (range 1 – 60 nodes). 108 patients met the inclusion criteria and were further evaluated. In median, the age of all patients was 60.2 years (range 25- 83 y). Every patient gave written informed consent for data acquisition prior to their inclusion in study. All surgical pathologic samples were examined by a gynecological pathologist. The histological diagnosis was classified according to FIGO- stages [11]. Residual tumor mass was subdivided in the following groups: R0 = complete cytoreduction (=0mm) and R>0mm- ≤10mm.

For the evaluation of the prognostic impact of lymph node metastases the patients were stratified into 3 groups depending on the extent of node involvement (node ratio=NR (affected to removed nodes) depending on no, minor and major nodal involvement: 1. no lymphnode metastases (NR = 0); 2. >0 and less than 50% of involved nodes (NR >0- ≤ 0.5); 3. more than 50% of involved nodes (NR: >0.5- ≤ 1).

Follow up

Follow up- data were collected when the patients presented in our department for follow up. The mean follow-up time was 53.5 months. Follow- up data of all 108 patients were evaluated.

For evaluation of the OS and PFS data on one patient were missing and this patient was not further evaluated in this subgroup. OS and PFS were evaluated of 107 patients.

Table 1. Patients´ characteristics. 108 patients in FIGO IIIC/ IV were analysed. Node involvement was analysed: for evaluation of lymph node ratio (affected to removed nodes) patients are stratified into 3 groups: 0; >0- ≤0.5 and >0.5-≤1 (see materials and methods).

Parameter	N(%)
FIGO IIIC/IV	108 (100)
Histologic grade	
G1/2	48 (44.44)
G3	60 (55.55)
Histology	
Serous	94 (87.04)
Non Serous	14 (12.96)
R- Status	
R=0mm	39 (36.45)
R>0mm- ≤1cm	68 (63.55)
N-Status	
N0	27 (25.0)
N+	81 (75.0)
Lymph Node ratio (affected to removed nodes)	
0	27 (25.0)
>0- ≤0.5	64 (59.26)
> 0.5- ≤1	17 (15.74)

Statistical analysis

Data were stored in a database and analyzed using PASW (Version 22 SPSS Inc., Chicago, IL., USA). Univariate analyses were performed 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 ratio and 95% CI for OS/ PFS. The log- rank test was used to test for significant differences between the groups. P-values <0.05 were considered statistically significant.

Results

Of the enrolled patients, all got optimal cytoreduction: 63.55% had >0mm and ≤10mm residual tumour mass and 36.45% had complete cytoreduction, respectively (table 1). The patients' characteristics are summarised in Table 1. Overall, most often node metastases (75.0%), histological grade 3 (55.55%) and serous histology (87.04%) were detected (table 1). A lymph node ratio between >0 to ≤0.5 mainly occurs, 59.26% of the patients had >0 and less than 50% of affected nodes (table 1). 25% of the

patients had no node metastases (node ratio =0; table 1); least frequently a node involvement of > 50% (node ratio >0.5-1) was seen in about 15.74% (table 1).

Concerning the impact of clinicopathologic parameters on node metastases the following was observed (table 2): most often a node ratio >0- ≤0.5 was associated with histologic grade 3, serous cancers and residual tumour mass >0mm- 1cm (table 2). Much rarer, a node ratio >0.5 regardless of histologic grade, histology and residual tumour mass was detected (table 2).

Table 2. Relations between lymph node involvement (node ratio) and the clinicopathological parameters (histologic grade, histological subtypes, R-status) in FIGO IIIc/IV; n=108.

	Node ratio n(%)		
Parameter	0	>0- ≤0.5	> 0.5- ≤1
Histologic grade			
G1/2	15 (13.88)	27 (25.0)	6 (5.55)
G3	12 (11.11)	37 (34.26)	11 (10.19)
Histology			
Serous	24 (22.22)	57 (52.77)	13 (12.04)
Non Serous	3 (2.77)	7 (6.48)	4 (3.7)
R- Status			
R= 0mm	11 (10.19)	23 (21.3)	5 (4.63)
R >0 - ≤1cm	16 (14.81)	41 (38.0)	12 (11.11)

The significant best prognostic impact on OS and PFS have patients with complete cytoreduction compared to R>0mm-≤1cm, respectively. Hereafter the prognostic impact of the lymph node involvement (node ratio) on OS and PFS in optimally cytoreduced patients was investigated (table 3): major nodal involvement (>50% affected lymph nodes) showed strong influence on OS and was associated with significant decreased survival (OS), respectively, (table 3). Thus, a significant prognostic advantage on OS was seen for patients with complete cytoreduction and moderate (minor) lymph node involvement (>0 to ≤0.5; p<0.001, table 3) compared to the other groups (table 3).

Subsequently, even PFS is significantly influenced by an increasing node affection (p<0.006; table 3). Patients with a moderate lymph node involvement showed longer PFS (>0 to ≤0.5; table 3) compared to the other 2 groups (table 3). Strong lymph node involvement (node ratio >0.5- ≤ 1) showed worst prognosis in optimally cytoreduced patients (OS/PFS; table 3). Subsequently, OS is significantly influenced by node affection (p<0.001; table 4) and a complete cytoreduction compared to residual tumour >0mm-10mm independent to nodal involvement. Patients with a moderate lymph node involvement and complete cytoreduction showed longer OS (>0 to ≤0.5; table 4) compared to the other 2 groups (table 4). Strong lymph node involvement (node ratio >0.5- ≤ 1) showed worst prognosis in optimally cytoreduced patients (OS/PFS; table 4). The prognostic impact on PFS is significant influenced by moderate lymph node involvement and complete cytoreduction (p=0.017; table 4).

Table 3: Prognostic impact of lymph node involvement on over-all survival and progression-free survival (OS/ PFS; months, 95% CI) in 107 stage IIIc/IV patients after optimal cytoreduction (R. ≤1cm).

Parameter	PFS (months; 95% CI)	p- value	OS (months; 95% CI)	p- value
Node ratio				
0 (n=26)	13.7 (11.7-15.8)		24.5 (20.58-28.36)	
>0- ≤0.5 (n=64)	14.9 (11.02-18.8)	0.006	30.5 (24.7-57.3)	P<0.001
>0.5 (n=17)	10.2 (9.2-11.2)		18.8 (9.7-27.9)	

Table 4: Prognostic impact of lymph node involvement on over-all survival and progression-free survival (OS/ PFS; months, 95% CI) in 107 in stage IIIc/IV patients depending on residual tumour mass (R=0mm and R>0-1cm).

Parameter	PFS (months; 95% CI)	p- value	OS (months; 95% CI)	p- value
R=0mm Node ratio				
0 (n=11)	17.5 (0-48.21)		36.3 (0-68.6)	
>0- ≤0.5 (n=23)	29.5 (18.5-40.4)		50.5 (41.5-58.1)	
>0.5 (n=5)	12.17 (1.8-22.5)		12.8 (0.7-24.9)	
R>0mm-1cm Node ratio		0.017		<0.001
0 (n=15)	12.6 (8.0-17.2)		24.5 (21.25-27.7)	
>0- ≤0.5 (n=41)	13.2 (11.7-14.7)		27.9 (22.6-33.1)	
>0.5 (n=12)	10.1 (9.2-11.04)		18.8 (11.2-26.4)	

Discussion

The optimal cytoreduction is the known significant most important prognostic factor in advanced ovarian cancer [8,9,12,13, 14]. Complete cytoreduction leads to significantly better prognosis than cytoreduction >0mm to 10mm [15]. Further known significant prognostic factors are FIGO stage, histology and histologic grade [15,16].

The prognostic relevance of a lymphadenectomy in the surgical management of ovarian cancer is still unclear [13,17,18] and is currently investigated in the prospective LION study (AGO-Ovar). Results of randomized controlled studies are still missing [19,20], but might probably answer the therapeutic

and prognostic impact of lymphadenectomy in initial management of ovarian cancer in a greater collective. In primary ovarian cancer, a pelvic and paraaortic lymphadenectomy after optimal cytoreduction is recommended with positive prognostic effect [19,21]. The randomized trial of Panici showed a positive impact of a systemic lymphadenectomy on PFS compared to resection of bulky nodes, but no impact on overall survival (OS) in optimally cytoreduced patients [3,4,22]. In contrast, Pereira showed a positive prognostic impact with a systematic lymphadenectomy with a significant longer survival in advanced ovarian cancer [4].

In advanced ovarian cancer node metastases are known in about 40%, even with affection of the pelvic and/ or para- aortic region [3,22]. In our collective node metastases were detected in 75.0% (table 1). Additionally, our data detected an association of node metastases most often with serous cancers, histologic grade 3 and residual tumour mass >0- 1cm (table 2); most often a moderate lymph node involvement was detected (>0-≤0.5; table 2). Most of these results are similar to previous reports, but to our knowledge, the extent of node involvement (node ratio (affected to removed)) was rarely included in other reports of risk factors for ovarian cancer before.

The prognostic relevance of node metastases in primary ovarian cancer is still unclear [4,23]. One study reported that the influence of lymph node metastases on prognosis decreases with the increase of residual tumor mass [6,9,24,25]. The authors also reported that node metastases seemed to be the second most important prognostic factor for advanced-stage ovarian cancer [6]. Although many risk factors of ovarian cancer are known, it is still questionable if lymphadenectomy in advanced ovarian cancer improves prognosis.

Unquestionable is that complete cytoreduction compared to R>0mm-≤1cm has significant best prognostic impact (PFS/ OS) [8,12,13,14]; even seen in our study (table 3). Out of our date the combination of radical surgery with lymphadeectomy seems additionally favourable (Table 4). The prognostic impact of clinicopathological factors associated with the node ratio has to be investigated in larger studies to improve the prognostic relevance of node metastases in FIGO IIIC. Mahdi [23] described that the impact of increasing node ratio was strongly related to OS, especially in patients with no macroscopic peritoneal disease [23]. Our study showed similar results; a node ratio (>0.5) was associated with significantly decreased survival, respectively ($p<0.001$; table 3). Patients with node positive ovarian cancer of less than 50% of removed nodes (ratio: >0 to ≤0.5) have an improved OS with significant positive prognostic impact (table 3). Significant best impact on OS was seen with decreasing node ratio, especially for patients with less than 50% of affected nodes ($p<0.001$; >0 to ≤0.5; table 3). Strong lymph node involvement (>0.5- ≤ 1) had worst prognosis (table 3), so affection of nodes seems to play a role in the prognosis in optimally cytoreduced patients.

Possibly in our study the group with a ratio >0 to ≤0.5 could contain patients with sole lymph node involvement without peritoneal lesions and are staged up to FIGO IIIC/IIIA1 [22,26,27]. These group of patients showed significant best OS in our study (table 4), as described in one report that ovarian serous carcinoma patients with sole extrapelvic peritoneal involvement have better survival than those with extrapelvic peritoneal involvement and lymph node metastases [11]. Additionally, an adequate staging is possible by performing a lymphadenectomy [5]. Considering the relatively favorable prognosis associated with lymphatic tumor spread compared with peritoneal tumor spread (stage IIIC), which was classified solely on the basis of lymph node metastasis, SU et al. suggests a modified FIGO classification with a down-staging of these patients [9]. Berek 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. One plausible explanation for the favorable prognosis of those patients might be the higher rate of optimal cytoreduction compared to the patients with stage IIIC disease showing intraperitoneal tumor implants >2 cm [9]. Our data support this hypothesis. Meanwhile there does exist a new classification for ovarian cancer in which this fact is considered [10]. Since ovarian cancer is known to spread simultaneously both intraperitoneally and retroperitoneally, the presence of tumor spreading mainly through lymphatic channels without intraperitoneal dissemination suggests that such tumors might be associated with a favorable biologic behavior [9].

Potentially these patients with minor node involvement could benefit from a systematic lymphadenectomy in FIGO IIIC compared to patients with strong node involvement (node ratio: >0.5-1). If the prognostic impact is caused by removing of positive nodes is still unclear, but maybe these results can help in treatment decisions.

Perhaps the stratification of this subpopulation of node positive EOC based on nodal burden provides a significant prognostic value that may be considered in future staging and aid in management decisions

[23]; our study supports this hypothesis: an increasing node involvement leads to worse prognosis.

In our study, interesting results were found and node ratio might be prognostically interesting. Based on our survey, node ratio may be used to 1) guide intraoperative decision making regarding lymphadenectomy in incomplete cytoreduction with possible abandonment of lymphadenectomy and 2) to estimate the prognosis (OS) in patients with advanced ovarian cancer after optimal cytoreduction. The outstanding results from the current prospective LION study (AGO-Ovar) will help to answer the validity of the lymphadenectomy on treatment strategies in optimally cytoreduced patients.

Conclusion

Main intention of primary surgery in advanced ovarian cancer is optimal cytoreduction with significant best prognostic impact. More extensive lymphadenectomy seems to play an important role in providing accurate staging and the node ratio might give prognostic information in optimally cytoreduced stage IIIc/IV ovarian cancer. The modification of the FIGO staging system, done in 2014, especially for stage IIIC ovarian cancer patients, has considered the prognostic differences depending on nodal involvement and complete cytoreduction. These changes are in the line with our results leading to downstaging (FIGO IIIC to FIGO IIIA1) of patients with exclusive nodal involvement with precisely best prognostic impact in our collective.

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Ethical standards

Our investigation of 108 patients has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All persons gave their informed consent prior to their inclusion in the study.

Competing Interests

The authors have declared that no competing interest exists.

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