The prognostic relevance of node metastases in optimally cytoreduced advanced ovarian cancer

Cornelia Bachmann · Sara Y. Brucker · Bernhard Kraemer · Ralf Rothmund · Anette Staebler · Falko Fend · Diethelm Wallwiener · Eva-Maria Grischke

Abstract
Purpose To delineate the relevance of pelvic and para-aortic node involvement in optimally cytoreduced (residual tumour <1 cm) stage IIIC ovarian cancer patients.
Methods Ninety-five consecutive optimally cytoreduced (R ≤ 1 cm) patients with primary stage IIIc ovarian cancer underwent stage-related surgery and got adjuvant platinum-based chemotherapy. Median follow-up: 53.5 months. All patients got 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 node involvement (ratio: affected to resected nodes): (1) (=0); (2) (>0–≤0.5) >0 and ≤50 % of affected nodes; (3) (>0.5–≤1) >50 % of affected nodes. Clinical parameters were retrospectively evaluated. Kaplan–Meier survival curve was used to evaluate the prognostic value.
Results Most often serous histology, histologic grade 3 and a node ratio >0–≤0.5 (61.1 %) were detected. Complete cytoreduction (R = 0 mm) has significant best prognostic impact compared to R > 0 mm–1 cm (OS: p = 0.047, PFS: p = 0.00). Node involvement was associated with serous histology and grade 3. Increasing node ratio leads to significant decreased OS (p = 0.019) and significant best OS was associated with node ratio >0–≤0.5.

Conclusions The goal is optimal cytoreduction in advanced ovarian cancer. More extensive lymphadenectomy seems to play an important role in providing an accurate staging, and the node ratio might give prognostic information. Current prospective studies like the LION study (AGO-Ovar) had to investigate if these data have therapeutic implications and may be considered in future staging.

Keywords Advanced ovarian cancer · Node ratio · Lymphadenectomy · Prognosis · Residual · Tumour · Node metastases

Introduction
Initial management of primary ovarian cancer includes surgical staging, cytoreductive surgery, lymphadenectomy followed by a platinum-based chemotherapy, except for pT1aG1 cases (Du Bois et al. 2009; Bristow et al. 2002). However, the importance of systematic lymphadenectomy in primary advanced ovarian cancer and its prognostic relevance is still unclear (Panici et al. 2005; Pereira et al. 2012; Scarabelli et al. 1997). Known is the increasing node involvement in advanced ovarian cancer with unknown prognostic impact (Bachmann et al. 2012; Harter et al. 2007). A rate of about 50 % of node metastases has been observed (Du Bois et al. 2009; Wimberger et al. 2007), and accurate surgical staging including lymphadenectomy recognizes the true extent of disease by detection of occult node 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 (Suh et al. 2013). Our objective was to delineate the relevance of
pelvic and para-aortic node metastases in optimally cytoreduced (R ≤ 1 cm) stage IIIC ovarian cancer patients.

Materials/methods

Ninety-five consecutive patients with primary stage IIIc (according to FIGO) optimally cytoreduced (R ≤ 1 cm) ovarian cancer were enrolled. Every patient underwent surgical staging including hysterectomy, bilateral oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy or tumour debulking as clinically indicated and an adjuvant standard platinum-based chemotherapy. 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 (R ≤ 1 cm) 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, histologic grade and residual tumour mass. Patients’ characteristics are given in Table 1. 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. In median, the age of all patients was 60.7 years (range 25–83 years). Every patient gave written informed consent for data acquisition prior to their inclusion in study. All surgical pathologic samples were examined by a gynaecological pathologist. The histologic diagnosis was classified according to the FIGO stages (Bakkar et al. 2014). Residual tumour mass was subdivided in 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 node involvement (node ratio = NR (affected to removed nodes): (1) no lymph node metastases (NR = 0); (2) >0 and ≤50 % of involved nodes (NR: >0–≤0.5); and (3) more than 50 % of involved nodes (NR: >0.5–≤1). The number of removed nodes in the subgroups was: group 1 with node ratio =0: on average, 19.7 pelvic and para-aortic nodes were removed per patient (range 5–40 nodes); group 2 (node ratio >0–≤0.5): on average, 26.7 pelvic and para-aortic nodes were removed per patient (range 1–60 nodes); group 3 (node ratio >0.5): on average, 26.7 pelvic and para-aortic nodes were removed per patient (range 12–43 nodes). Even in every subgroup, median and range of affected to removed nodes were evaluated.

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 95 patients were evaluated.

Statistical analysis

Data were stored in a database and analysed 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

All patients got optimal cytoreduction: 63.2 % had >0 and ≤10 mm residual tumour mass and 36.8 % had complete cytoreduction, respectively (Table 1). Most often node metastases (73.7 %), histologic grade 3 (51.6 %) and serous histology (88.4 %) were detected (Table 1). A lymph node ratio between >0 and ≤0.5 mainly occurs, and 61.1 % of the patients had >0 and <50 % of affected nodes (Table 1). Almost 26 % of the patients had no node metastases (node ratio = 0; Table 1); least frequently, a node

Table 1 Patients’ characteristics. Ninety-five patients with stage IIIC ovarian cancer were analysed

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIGO IIIC</td>
<td>95 (100)</td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
</tr>
<tr>
<td>G1/2</td>
<td>46 (48.4)</td>
</tr>
<tr>
<td>G3</td>
<td>49 (51.6)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>84 (88.4)</td>
</tr>
<tr>
<td>Non-serous</td>
<td>11 (11.6)</td>
</tr>
<tr>
<td>R-status</td>
<td></td>
</tr>
<tr>
<td>R = 0 mm–≤1 cm</td>
<td>95 (100)</td>
</tr>
<tr>
<td>N-status</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>25 (26.3)</td>
</tr>
<tr>
<td>N+</td>
<td>70 (73.7)</td>
</tr>
<tr>
<td>Lymph node ratio (affected to removed nodes)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>25 (26.3)</td>
</tr>
<tr>
<td>&gt;0–≤0.5</td>
<td>58 (61.1)</td>
</tr>
<tr>
<td>&gt;0.5–≤1</td>
<td>12 (12.6)</td>
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</tbody>
</table>

Node involvement was analysed: for evaluation of the lymph node ratio (affected to removed nodes), the patients were stratified into three groups: 0; >0–≤0.5 and >0.5–≤1 (‘Materials and methods’).
involvement >50% (node ratio >0.5–1) was seen in about 12.6% (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 >0 mm–1 cm (Table 2). Much rarer, a node ratio >0.5 regardless of histologic grade, histology and residual tumour mass was detected (Table 2).

Significant best prognostic impact on OS and PFS has patients with complete cytoreduction compared to \( R > 0 \) mm–≤1 cm, respectively (Table 3; OS: \( p = 0.047 \); PFS: \( p = 0.00 \)). Hereafter, the prognostic impact of the lymph node involvement (node ratio) on OS and PFS in optimally cytoreduced patients was investigated (Table 4): an increasing node ratio (0 \( \rightarrow \) >0 to ≤0.5 \( \rightarrow \) >0.5–1) showed strong influence on OS and was associated with significant decreased survival (OS), respectively, (Table 4). Thus, a significant prognostic advantage on OS was seen for patients with a moderate lymph node involvement (>0 to ≤0.5; \( p = 0.011 \), Table 4) compared to the other groups (Table 4).

Subsequently, even PFS is significantly influenced by an increasing node ratio (\( p = 0.034 \); Table 4). Patients with a moderate lymph node involvement showed longer PFS (>0–≤0.5; Table 4) compared to the other two groups (Table 4). Therefore, strong lymph node involvement (node ratio >0.5–≤1) showed worst prognosis in optimally cytoreduced patients (OS/PFS; Table 5). There is no significant difference between node involvement and residual tumour (\( p = 0.069 \); Table 5).

### Discussion

Optimal cytoreduction is the known significant most important prognostic factor in advanced ovarian cancer (Wimberger et al. 2007; Suh et al. 2013; Abe et al. 2010; Nomura et al. 2011; Chekerov et al. 2013), as even shown in our study (OS: \( p = 0.047 \); PFS: \( p = 0.00 \); Table 3). Complete cytoreduction leads to significantly better prognosis than cytoreduction >0–10 mm (Hoskins et al. 1994). Further known significant prognostic factors are FIGO stage, histology and histologic grade (Ulker et al. 2014; Hoskins et al. 1994).

The prognostic relevance of lymphadenectomy in surgical management of ovarian cancer is still unclear (Nomura et al. 2011; di Re et al. 1996; Aletti et al. 2006) and is currently investigated in the prospective LION study (AGO-Ovar). Results of randomized controlled studies are still missing (Carnino et al. 1997; Kim et al. 2010). In primary ovarian cancer, a pelvic and para-aortic lymphadenectomy after optimal cytoreduction is recommended with positive prognostic effect (Carnino et al. 1997; Onda et al. 1998).

The randomized trial of Panici showed a positive prognostic impact of a systemic lymphadenectomy on PFS compared to resection of bulky nodes, but no impact on overall survival (OS) in optimally cytoreduced patients (Panici et al. 2005; Pereira et al. 2012; Takeshima et al. 2005). In contrast, Pereira showed a positive prognostic impact with a systematic lymphadenectomy with a significant longer survival in advanced ovarian cancer (Pereira et al. 2012).

In advanced ovarian cancer, node metastases are known in about 40%, even with affection of the pelvic and/or para-aortic region (Panici et al. 2005; Takeshima et al. 2005). In our collective node, metastases were detected in 73.7% (Table 1). Additionally, our data detected an association of node metastases most often with serous cancers, histologic grade 3 and residual tumour mass >0–1 cm (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, extent of node involvement (node ratio (affected to remove)) 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 (Pereira et al. 2012; Mahdi et al. 2011). One study reported that the influence of lymph node metastases on prognosis decreases with the increase of residual tumour mass (Bachmann et al. 2012; Suh et al.

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### Table 2 Relations between lymph node involvement (node ratio) and the clinicopathological parameters (histologic grade, histologic subtypes and R-status) in stage IIIc; \( n = 95 \)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Node ratio ( n ) (%)</th>
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<tbody>
<tr>
<td>( R = 0 ) mm</td>
<td>11 (11.6) 21 (22.1) 3 (3.2)</td>
</tr>
<tr>
<td>( R &gt; 0–1 ) cm</td>
<td>14 (14.7) 37 (38.9) 9 (9.5)</td>
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<thead>
<tr>
<th>Histologic grade</th>
<th>Node ratio ( n ) (%)</th>
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<tbody>
<tr>
<td>G1/2</td>
<td>15 (15.7) 25 (26.4) 6 (6.3)</td>
</tr>
<tr>
<td>G3</td>
<td>10 (10.5) 33 (34.8) 6 (6.3)</td>
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<table>
<thead>
<tr>
<th>Histology</th>
<th>Node ratio ( n ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>22 (23.1) 52 (54.7) 10 (10.5)</td>
</tr>
<tr>
<td>Non-serous</td>
<td>3 (3.2) 6 (6.3) 2 (2.1)</td>
</tr>
</tbody>
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<thead>
<tr>
<th>R-status</th>
<th>Node ratio ( n ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R = 0 ) mm</td>
<td>11 (11.6) 21 (22.1) 3 (3.2)</td>
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<td>14 (14.7) 37 (38.9) 9 (9.5)</td>
</tr>
</tbody>
</table>
The authors also reported that node metastases seemed to be the second most important prognostic factor for advanced-stage ovarian cancer (Bachmann et al. 2012). Knowing many risk factors for ovarian cancer, it is still questionable if lymphadenectomy in advanced ovarian cancer improves prognosis.

Unquestionable is that complete cytoreduction compared to \( R > 0 \text{ mm}–\leq 1 \text{ cm} \) has significant best prognostic impact (PFS/OS) (Wimberger et al. 2007; Abe et al. 2010; Nomura et al. 2011; Chekerov et al. 2013); even seen in our study (Table 3). 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 (Mahdi et al. 2011) described that the impact of increasing node ratio was strongly related to OS, especially in patients with no macroscopic peritoneal disease (Mahdi et al. 2011). Our study showed similar results; an increasing node ratio (0 \( \rightarrow >0 \text{ to} \leq 0.5 \rightarrow >0.5 \)) was associated with significantly decreased survival, respectively (\( p = 0.011 \); Table 4).

Patients with node-positive ovarian cancer of <50 % of removed nodes (ratio: >0 to \( \leq 0.5 \)) have an improved OS with significant positive prognostic impact (Table 4). Significant best impact on OS was seen with decreasing node ratio, especially for patients with <50 % of affected nodes (\( p = 0.011 \); >0 to \( \leq 0.5 \); Table 4). Strong lymph node involvement (>0.5–\( \leq 1 \)) had worst prognosis (Table 2), 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 \( \leq 0.5 \) could contain a few patients with sole lymph node involvement without peritoneal lesions and are staged up to FIGO IIIC (Takeshima et al. 2005; Chan et al. 2007; Denny et al. 2012). These 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 (Bakkar et al. 2014). Additionally, an adequate staging is possible by performing a lymphadenectomy.
the prognostic impact of node ratio in ovarian cancer. In node ratio (>0.5), but prospective studies had to examine showed significant better OS than patients with a strong after optimal cytoreduction. Patients with node ratio <0.5 ment leads to worse prognosis. Our data support this hypothesis: an increasing node involve-
ment may be used to estimate the prognosis (OS) in patients with advanced ovarian cancer after optimal cytoreduction. Patients with node ratio <0.5 showed significant better OS than patients with a strong node ratio (>0.5), but prospective studies had to examine the prognostic impact of node ratio in ovarian cancer. In our study, interesting results were found, and node ratio might be prognostically interesting. 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. Further studies are needed in order to achieve sufficient information.

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 opti-

mally cytoreduced stage IIIc ovarian cancer. The not N0 group (N > 0–≤0.5 (Table 5)) has significantly best OS compared to N0 and N > 0.5. There was no significant impact on PFS for patients with N > 0–≤0.5 (Table 5).

Prospective studies had to investigate if these data have therapeutic implications and may be considered in future staging. The modification of the FIGO staging system, especially for stage IIIc ovarian cancer patients, should be considered regarding the prognostic differences depending on node involvement and complete cytoreduction with best prognostic impact in our collective.

References


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Bachmann C, Bachmann S, Fehm T, Staehler A, Becker S, Roth-


Ethical standards Our investigation of 95 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.

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Conflict of interest The authors declare that there are no conflict of interests.
Onda T, Yoshikawa H, Yasugi T et al (1998) Patients with ovarian carcinoma upstaged to stage III after systematic lymphadenectomy have similar survival to Stage II patients and superior survival to other Stage III patients. Cancer 83(8):1555–1560