Relevance of Pelvic and Para-aortic Node Metastases in Early-stage Ovarian Cancer

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Abstract. Aim: To delineate the relevance of pelvic and para-aortic node involvement in early-stage ovarian cancer. Patients and Methods: Data on 75 consecutive patients with primary stage T1 and 2 ovarian cancer treated at the Department of Gynecology, University Tübingen, Germany were retrospectively analyzed. All patients underwent stage-related surgery with pelvic and para-aortic lymphadenectomy and adjuvant platinum-based chemotherapy (except pT1aG1). Median follow up was 53.5 months. Clinico-pathological parameters and the distribution pattern of node metastases were evaluated. Statistical analyses were performed using PASW. Results: Lymph node metastases were detectable in T1 and T2 in 6 (8%) of 75 patients. Three patients (4%) had lymph node metastases in the pelvic nodes only, 2 patients (2.7%) in the para-aortic nodes only; 1 patient (1.3%) both in the pelvic and para-aortic nodes. On multivariate analysis, histological grade 1/2 and 3 tumors, serous and endometrioid histology were independent predictors for node metastases, respectively. The risk of relapse was significantly higher with detection of node metastases (p=0.004). Conclusion: A systematic lymphadenectomy in early-stage ovarian cancer leads to an upstaging in a few patients after detection of node metastases even in pelvic or para-aortic nodes, especially in patients with grade 3 tumours and serous cancers. Pelvic and para-aortic lymphadenectomy may detect node involvement in early-stage ovarian cancer and might be helpful in correct staging.

Initial management of primary ovarian cancer includes surgical staging, hysterectomy, salpingo-oophorectomy, lymphadenectomy and adjuvant platinum-based chemotherapy, except for pT1aG1 cases (1). However, the importance of systematic lymphadenectomy in initial management of primary early ovarian cancer and its prognostic relevance is still unclear. A rate of 30% of node metastases in stage 1/2 ovarian tumours has been observed (1) and accurate surgical staging including lymphadenectomy detects for the true extent of disease by detection of occult node metastases. Our objective was to delineate the relevance of pelvic and para-aortic node metastases in early-stage ovarian cancer.

Patients and Methods

Seventy-five consecutive patients with primary T1/T2 epithelial ovarian cancer treated at the Department of Gynecology, University Tübingen, Germany were retrospectively analyzed. Every patient underwent surgical staging including hysterectomy, bilateral adnexectomy, supracolic omentectomy and pelvic and para-aortic lymphadenectomy up to the renal vessels. In our hospital, lymphadenectomy (pelvic/para-aortic) is part of primary surgical intervention in primary ovarian cancer patients with a good state of health (Karnofsky-Index ≥80%). This procedure was performed over the whole examined time period. All patients were treated with an adjuvant standard platinum-based chemotherapy, except patients with pT1aG1 ovarian cancer (according to guidelines by AGO-Ovar/Arbeitsgemeinschaft Gynäkologische Onkologie). All 75 patients met the inclusion criteria and were enrolled. On average, 21.71 pelvic and para-aortic lymph nodes were removed per patient (range 1-54 nodes). Removal of less than 10 lymph nodes was carried out in 5 patients; in all other patients more than 10 lymph nodes were removed. The affected region of node metastases in the pelvic or para-aortic region and even the risk factors that lead to node metastases were identified (table 1). All patients gave informed consent for data acquisition prior to their inclusion in the study. Univariate survival analyses were performed to investigate variables associated with outcome. Based on the small number of patients with node metastases, the statement on prognostic impact is limited.

Histology. All surgical tissues were examined by a pathologist and final pathology reports were obtained. All surgical pathological samples were examined by a gynecologic pathologist and each diagnosis was reviewed and classified as benign or malignant. The histological diagnosis was classified according to T-stages (4).

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Key Words: Node metastases, early ovarian cancer, prognosis, lymphadenectomy, histology.
Follow-up. Follow-up data were collected at presentation in our outpatient department. The mean follow-up time was 53.5 months.

Statistical analysis. Statistical analyses, multivariate checking, were performed with PASW (version 22 PASW Inc., Chicago, IL, USA). For testing significant differences between the examined groups we used student t-test and Mann Whitney-Test. Significance level was defined as p<0.05.

Results

Out of the enrolled patients 61.3% (n=46) were classified to T1, 38.7% (n=29) to T2 (Table I). Patients’ characteristics are shown in Table I. The median age was 60.7 years (range=25-85 years). Overall, most frequently, histological grade 1/2 (69.3%) and serous histology (58.6%) were found (Table I).

The second most common histology was an endometrioid ovarian cancer (22.7%) (Table I). Overall, lymph node metastases were detectable in 83 (6 patients; Table I).

Considering the affected lymph node regions, the following pattern is shown (Table I): 3 patients (4%) had lymph node metastases in the pelvic nodes only, 2 patients (2.7%) in the para-aortic nodes only, while 1 patient (1.3%) had metastases both in the pelvic and para-aortic nodes.

On multivariate analysis, histological grade 1/2 and 3, serous and endometrioid histology were independent predictors for node metastases, respectively (Table II). Most often serous histology leads to node metastases; but even patients with mucinous and endometrioid histology had node metastases in early-stage ovarian cancer (Table III).

Patients with endometrioid histology had lymph node metastases in the pelvic nodes only and even in the para-aortic nodes only (Table III). Serous cancers showed next to lymph node metastases in the pelvic nodes only and even in the para-aortic nodes only (Table III). Mucinous cancers affected the pelvic and para-aortic lymph nodes, as well as node metastases in early-stage ovarian cancer (Table I). The T classification of the patients with node metastases was: one patient was T1b; two patients were T2a, and three patients T2c. These patients were up-staged to FIGO IIIa (new classification IIIA1). The risk of relapse was significantly higher upon detection of node metastases in early-stage ovarian cancer’s (p=0.004) (Table IV).

Discussion

The impact of node involvement in primary early-stage ovarian cancer is still unclear (3, 4). There are currently no data of prospective studies evaluating the impact of lymphadenectomy in early-stage ovarian cancer. Di Re et al. found that the incidence of metastatic lymph nodes significantly increased with advanced stages, serous histology and greater amount of residual tumor (4-6). Possibly the prognostic influence of node involvement plays a greater role in the early stages than in advanced stages, in which the residual tumor mass has greater prognostic impact (5, 6). Nevertheless, the probability of having node metastases is lower in early stages than in advanced stages (7, 8). Even in our collective 8% of patients had node metastases in early ovarian cancer (Table I). Risk factors for node metastases were serous cancers and histologic grade 3 (18) (Table II). On multivariate analysis, grade 3 tumors, serous and endometrioid histology were independent predictors for lymph node metastases in T2 ovarian cancers, respectively (Table II).

Several studies describe that both node metastases in the pelvic and para-aortic lymph nodes, as well as node metastases in the pelvic or para-aortic region can only be found in early ovarian cancer in about 20% of cases (10-12), as seen in our study (Table I). Our collective involved nodes in the pelvic and para-aortic region in T1 and T2 (Tables II and III); even one patient had para-aortic lymph node metastases only, without any involvement of the pelvic region (Table III). Our collective showed the following pattern: 4 patients had affected pelvic nodes, out of which one patient had even additionally affected para-aortic nodes (Table III). These results are comparable to the work of Chang et al., with detection of lymph node metastases in T1 and 2 ovarian cancer patients (9).

In our collective, serous cancers showed a distribution pattern of node involvement with combined or isolated affection of the pelvic and/or para-aortic region (Table III);
Mucinous cancers showed affection of the pelvic nodes without affection of the para-aortic nodes; additionally one patient with endometrioid cancer presented an isolated affection of the para-aortic nodes (Table III). None of the patients with non-serous cancers showed both an affection of pelvic and para-aortic nodes (Table III).

Overall, studies showed a rate of about 45% to 59.1% of node involvement in advanced ovarian cancer patients (13). The prognostic impact of systematic lymphadenectomy in the initial surgical management in primary advanced ovarian cancer is still unclear (11). The randomized trial of Panici et al. described that systematic lymphadenectomy improves PFS, but not survival in women with optimally debulked advanced ovarian cancer compared to resection of bulky nodes (11, 13).

Abe et al. did not notice an advantage for OS and PFS for patients after lymphadenectomy in the early stages compared to the renunciation of the lymphadenectomy (14). Possibly the positive impact of lymphadenectomy in early FIGO stages is caused by removing the positive nodes and patients without lymphadenectomy in early stages could have clinically-inapparent positive nodes and were staged to FIGO I/II (10). Studies showed that patients that were upgraded to FIGO IIIC due to detection of positive nodes had similar OS compared to FIGO I patients (11). According to the current FIGO classification, published in January 2014, patients with positive retroperitoneal lymph nodes and T1/T2 N1 M0 are staged up to FIGO IIIA1 (15, 16).

This fact supports the hypothesis that adequate staging can be achieved with lymphadenectomy and possibly a positive prognostic impact can be reached in early-stage ovarian cancer. The removal of positive lymph nodes in the pelvic or para-aortic region could explain the positive prognostic influence of the performed lymphadenectomy in early stages (4, 17). Possibly this impact is caused by involved nodes in the para-aortic region that are not removed by isolated pelvic lymphadenectomy alone. Chang et al. described affection of para-aortic nodes and recommended a para-aortic lymphadenectomy up to the renal vessels that may detect occult metastases and can help tailor appropriate adjuvant treatment, as well as offer useful prognostic information (9).

Most often serous cancers lead to node involvement in pelvic and para-aortic nodes, but even non-serous cancers like endometrioid and mucinous cancers lead to node metastases in pelvic and para-aortic nodes. Node positivity is uncommon for patients with early-stage ovarian clear cell carcinoma (18); in our study no patient of this subgroup showed node metastases. Node involvement in this sub-group leads to worse prognosis (18), therefore lymphadenectomy seems to have a prognostic impact and leads to an adequate staging with detection of occult node metastases.

It is still unclear if lymphadenectomy in the early stages is reasonable in all patients and if a systematic pelvic and para-aortic or a pelvic lymphadenectomy should be performed. Prospective studies need to investigate the prognostic impact of lymphadenectomy in early-stage ovarian cancer, perhaps depending on histology and distribution pattern of node metastases. If a supplementary preoperative PET examination is useful to optimize the staging and to detect patients who might benefit from lymphadenectomy is still unclear. One study showed that 18F-FDG PET/CT is an accurate tool for the detection of nodal metastases in early ovarian cancer (2).

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**Table II. Description of node involvement depending on clinicopathological parameters (histology; histological grade) in 75 T1/2 ovarian cancer patients.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N0 (n (%))</th>
<th>N+ (n (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/2</td>
<td>49 (65.3)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>3</td>
<td>20 (26.7)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>41 (54.6)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Non-Serous mucinous</td>
<td>6 (8)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Clear cell</td>
<td>5 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>15 (20)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>2 (2.7)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**Table III. Description of node involvement and of affected pelvic and/or para-aortic region depending on histology in 75 T1/2 ovarian cancer patients.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pelvic +/ paraaortic (−n)</th>
<th>Pelvic +/ paraaortic (+n)</th>
<th>Pelvic −/ paraaortic (+n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-Serous mucinous</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clear cell</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>

(+ = positive nodes; − = negative nodes).
Our findings suggest the possibility, that pelvic and paraaortic lymphadenectomy in early ovarian cancer leads to an adequate staging and might detect occult node metastases (Table II). Prospective studies may benefit from investigating the clinical implications of our results. Consequently, the efficacy of systematic lymphadenectomy on prognosis in early ovarian cancer is still unknown due to the lack of prospective randomized controlled studies.

Conclusion

Node involvement is detectable in early ovarian cancer (stage T1/2) in pelvic and even para-aortic nodes. More extensive lymphadenectomy plays an important role in providing accurate staging by detection of occult metastases, and subsequently patients were staged up to FIGO IIIA1 (new classification) (16). We emphasize on the need to investigate the risk factors and metastatic patterns of such patients in a multi-center analysis.

Conflicts of Interest

Every Author declares that there is no conflict of interest.

References


