Review

The Involvement of Retroperitoneal Lymph Nodes in Primary Serous-papillary Peritoneal Carcinoma. A Systematic Review of the Literature

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Abstract. Background: Primary serous-papillary peritoneal carcinoma is able to spread to the retroperitoneal lymph nodes, but there is no evidence of the pattern of lymphatic metastasis. Because of the fact that this tumor entity is indistinguishable histologically from primary serous-papillary ovarian carcinoma, its taxonomic position has thus far remained unclear. Materials and Methods: The Medline database was used to identify studies about lymphatic spread pattern and to compare those studies. Results: Four out of the fifteen studies were selected. Each based their analysis on a different classification of the pelvic and para-aortal lymph nodes: 63.9% of the women with primary serous-papillary peritoneal carcinoma had retroperitoneal lymph node involvement. Conclusion: Metastasis of primary serous-papillary peritoneal carcinoma to retroperitoneal lymph nodes is not an infrequent occurrence, but there is no evidence of a distinct pattern of spread.

Primary serous-papillary peritoneal carcinoma (PPC) was first described in 1959 by Swerdlow and represents a relatively new diagnostic tumor entity (1). It is an adenocarcinoma that develops from the peritoneum (2). PPC is rare and occurs almost exclusively in women (2), although there are reports of occurrences of PPC in men as well (3, 4). Because of the same histological presentation, nearly 10% of primary serous-papillary ovarian carcinomas (PSOC) diagnosed were reclassified as PPC (6-8). Compared to PSOC, the survival of patients with PPC appears to be nearly two to six months lower (9), although this was not verified in a younger study group (8). Risk factors are age, female sex and mutation in breast cancer 1 early onset gene (BRCA1) (2, 10).

Because of the similarity in histological presentation, several theories on the origin of PPC have been discussed in the literature. Female adenocarcinomas originate from the coelom epithelium (11-13), the inner surface of the tuba uterina (14-17), or the secondary Müllerian system. The secondary Müllerian system develops from the mesothelium or the subserous connective tissue (18, 19).

The pathological dissemination of malignant cells of PPC through the lymphatic vessels and lymph nodes is ill-defined and presents new challenges to the integration of systematic lymphadenectomy (LNE) in the treatment algorithm of PPC (20). Until now the lymphatic metastasis of PPC was thought to be similar to the lymphatic metastasis of PSOC due to existence of the same embryological ancestor (21, 22).

The preoperative diagnosis of PPC is often difficult because the existence of another primary tumor has to be excluded and the ovaries should be uninvolved or only minimally involved (20), which can only be confirmed postoperatively in a pathological examination. The diagnostic criteria of the Gynecologic Oncology Group (GOG) are needed to distinguish PPC from PSOC. To diagnose PPC, the following criteria have to be met: (i) the ovaries are either absent, normal in size or slightly enlarged; (ii) the involvement of extragranular sites should be greater than that on the ovarian surface of either ovary; (iii) if ovarian involvement is noted, it should be either surface involvement or cortical implants less than 5×5 mm in maximal dimensions; and (iv) the histological and cytological characteristics of the tumor should be of serous type (23).

Superficial invasive tumor growth, lymphatic (24) or hematogenous spread have been discussed (2). A systematic pelvic and para-aortal LNE allows correct tumor staging (25) and a pathological examination of the resected lymph nodes sheds light on the pattern of lymphatic spread.
The abdominal cavity is covered with the visceral and parietal peritoneum, so that it is divided into an intraperitoneal and extraperitoneal space. The extraperitoneal space can be further differentiated into the retroperitoneal and subperitoneal space. The retroperitoneal space consists of the aorta abdominalis, vena cava inferior and fatty tissue with embedded lymph vessels and lymph nodes. When a systematic pelvic and para-aortal LNE is performed, the lymph nodes in the following regions and the fatty tissue are resected (26): a) supramesenterial/infrarenal region: along the lateral aorta abdominalis, columna spinalis, vena renalis sinistra, inferior arteria mesenterica and kidney; b) inframesenterial region: along the lateral aorta abdominalis, inferior arteria mesenterica, bifurcatio aortae, columna spinalis and musculus psoas; c) interaortocaval region: space medial of the midline of the inferior vena cava and the midline of the aorta abdominalis between vena renalis sinistra, bifurcactio aortae and columna spinalis; d) paracaval region: lateral of the midline of the inferior vena cava, vena renalis dextra, bifurcatio aortae, fatty tissue of the kidney and musculus psoas; e) region of the arteria iliaca communis: along the bifurcatio aortae, musculi psosas, bifurcatio arteriae iliacae and os sacrum; f) region of the arteria iliaca externa: along the arteria iliaca externa, vena iliaca externa, musculus psosas, lacuna vasorum and os sacrum; g) in the fossa obturatoria region: along the arteria iliaca externa and interna and the pelvic wall; h) region of the arteria iliaca interna: lymph nodes medial of or near to the arteria iliaca interna.

The aim here was to shed light on lymphatic metastasis into the retroperitoneal space in PPC. The central questions addressed were: Which studies describe the pathological lymphatic spread pattern of PPC? How many patients with PPC show lymph node metastasis? Could a systematic review identify a typical spread pattern? Is there any prognostic value for systematic pelvic and para-aortic lymphadenectomy? Which tasks are required in further studies?

**Materials and Methods**

Only those studies which discussed the retroperitoneal lymph node involvement met the inclusion criteria. Because of the difficulty of PPC diagnosis, studies which used the Gynecologic Oncology Group (GOG) algorithm (23) were included; other studies which did not use the GOG criteria were further examined in regard to the possibility that they confused PPC with PSOC. Only studies with a control group (PSOC) and a study group (PPC) were included, so that possibility of confusion was reduced. Studies which used the following older terms for PPC were included: extraperitoneal serous peritoneal carcinoma, multiple focal extraperitoneal serous carcinoma, serous surface papillary carcinoma, papillary tumor of the peritoneum, extraperitoneal tumor of the surface papillary carcinoma, extraperitoneal pelvic serous tumor (27). Only the following two terms although used did not meet selection criteria because they represent a distinct tumor entity whereby their names had been used to describe PPC (2): mesodermoma and mesothelioma.

In order to discover a spread pattern and to describe the percentage distribution, only studies with a systematic pelvic and para-aortal LNE were selected, whereas studies with a sampling or selective lymph node resection of bulky nodes were excluded (27, 28, 33). Studies which concentrated on other malignancies of the peritoneum or other metastatic lymph nodes (28, 29) were also excluded.

PubMed, a service of the U.S. National Library of Medicine and of the National Institute of Health, was used to identify studies in the MEDLINE database. A systematic search was carried out from August 1st until August 4th 2010 and from September 1st until September 4th 2010. Without regard to the linguistic and temporal constraints, every article was considered to be useful for this review. MeSH (Medical Subject Headings) terms were used. The following MeSH terms were used: ‘ovarian neoplasms’, ‘peritoneal neoplasms’, ‘lymph nodes’, ‘lymph node excision’ and ‘lymphatic metastasis’. The following words were not represented in the MeSH database but were added to the search box as key words: ‘primary peritoneal carcinoma’, ‘primary peritoneal cancer’, ‘extraperitoneal serous peritoneal carcinoma’, ‘multiple focal extraperitoneal serous carcinoma’, ‘serous surface papillary carcinoma’, ‘papillary tumor of the peritoneum’, ‘extraperitoneal pelvic serous tumor’ and ‘extraperitoneal tumor of the surface papillary carcinoma’.


Table I. Search steps 1-18 and references found.

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Table II. Characteristics of the studies.

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<tr>
<th>Author</th>
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<th>n</th>
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<th>age</th>
<th>LNE</th>
<th>LN region</th>
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<td>Eltabbakh and Mount (20) 2002</td>
<td>11</td>
<td>27</td>
<td>72.72</td>
<td>63.2</td>
<td><strong>S</strong></td>
<td>Pelvic, para-aortal</td>
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<tr>
<td>Dubernard et al. (31) 2005</td>
<td>19</td>
<td>-</td>
<td>63.15</td>
<td>-</td>
<td><strong>60</strong></td>
<td>Pelvic, para-aortal, interaortocaval, paracaval</td>
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<tr>
<td>Ayhan et al. (30) 2006</td>
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<td>Aletti et al. (21) 2009</td>
<td>48</td>
<td>144</td>
<td>54.17</td>
<td>-</td>
<td>64</td>
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*Systematic lymphadenectomy performed. ** Median.

Table I summarizes the results of these search steps. Study characteristics are given in Table II and tumor characteristics in Table III. The number of resected lymph nodes of each lymph node region is shown in Table IV. In Table V the number of positive lymph nodes is shown. In order to make it clear that lymph node involvement is not an infrequent occurrence in PPC, the retroperitoneal space has been drawn and the percentage of lymph node metastasis was added. The quality of studies has often been investigated. The following three criteria: objectivity, reliability and validity were used to describe the quality of any given paper. The studies described which procedure was included in systematic pelvic and para-aortal LNE. Therefore the borders of pelvic and para-aortal lymph node basins were described. The systematic pelvic and para-aortal LNE was based on an optimal residual disease (RD) after surgical procedure, and was defined as RD<1 cm. If RD<1 cm was achieved, pelvic and para-aortal lymph node basins were extirpated. The FIGO-classification (Fédération Internationale de Gynécologie et d'Obstétrique) allows staging of gynecological malignancies. Its grading system allows the precise description of a tumor.

**Results**

Ayhan et al. (30) were the only ones who used blinding to prevent any selection bias, and in addition, they mentioned how many patients were lost during follow-up. Furthermore, Dubernard et al. (31) also mentioned how many patients died during follow-up.

In order to compare the case group with the control group, several tests were used. Aletti et al. (21) used the chi-squared test, Fischer’s exact test and t-test. Dubernard et al. (31) did not mention the use of any tests. Eltabbakh and Mount (20) used the chi-squared and t-test. Ayhan et al. (30) used the Chi-squared, t-, and Mann-Whitney U tests. A p-value was used in all studies in order to describe statistical significance and p<0.05 was set as being statistically significant. Eltabbakh and Mount (20), Ayhan et al. (30) and Aletti et al. (21) had a control group of women who suffered from PSOC, and analyzed their retroperitoneal lymph nodes.

Often patients were excluded in order to reduce bias. Eltabbakh and Mount (20) excluded women with peritoneal mesothelioma or borderline tumor or invasive ovarian tumor. Dubernard et al. (31) excluded women which suffered from epithelial or non-epithelial ovarian or tubal carcinoma and ovarian or tubal borderline tumor. Ayhan et al. (30) and Aletti et al. (21) did not mention any exclusion criteria.
**Table V. Lymph node metastasis in PPC and PSOC.**

<table>
<thead>
<tr>
<th>Lymph node basin</th>
<th>Eltabbakh and Mount (20)</th>
<th>Dubernard et al. (31)</th>
<th>Ayhan et al. (30)</th>
<th>Aletti et al. (21)</th>
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<td>p-Value</td>
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<td>7</td>
<td>63.3</td>
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<tr>
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<td>72.7</td>
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<tr>
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<tr>
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<td>72.7</td>
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*8/11 Patients had lymph node metastasis, especially above the inferior arteria mesenterica.*
Table I summarizes the results of the eighteen search steps. Every step explains which studies were included or why they had been excluded. Articles which had been found in previous steps, articles without an abstract or free text were characterized or indicated. For the latter two variants, the articles were ordered and collected from the journal library of the Charité University Hospital Berlin. In total, 15 studies were identified. Eleven studies were rejected because other lymph nodes were investigated, other tumors of the peritoneum were regarded, or another study aim was declared. Studies which explored the effectiveness of chemotherapy and which examined the pathological lymphatic nodal involvement were included (30).

Two studies were rejected because they performed lymph node sampling or selective LNE of bulky nodes (7, 27). This decision minimized bias, because a low number of resected lymph nodes simulates low nodal involvement.

A total of four studies met the inclusion criteria and were evaluated (20, 21, 30, 31).

The most important characteristics such as year of publication, number of patients included, mean or median age, whether or not a systematic LNE was performed, the lymph node basins examined, and the percentage of patients with lymph nodes involved are all shown in Table II.

Eltabbakh and Mount (20) conducted a prospective study, whereas Ayhan et al. (30), Dubernard et al. (31) and Aletti et al. (21) designed a retrospective study. Dubernard et al. (31) investigated the lymph node metastasis in PPC; the other studies compared the lymph node involvement in PPC with PSOC.

Interestingly, each study stated which lymph nodes belonged to the pelvic and para-aortic basins. Despite the fact that this systematic approach perhaps allows reproducible results, the pelvic and para-aortic borders of the studies in fact differed from each other. Eltabbakh and Mount (20) did not mention exactly which lymph node basins they removed. Dubernard et al. (31) performed pelvic LNE while extirpating the common iliac, external iliac and obturator nodes. The para-aortic nodes, paracaval, intercavaoarterial, presacral, infra and supramesenteric nodes up to the left renal vein as upper limit were resected. Ayhan et al. (30) harvested pelvic nodes while extirpating the nodes around the external iliacal vessels, common iliac nodes, internal iliac and obturator nodes, and all tissue around the obturator nerve was removed. To the para-aortic basins they resected all lymph nodes from the bifurcation of the aorta up to the renal vessels that were next to or on the left and right side of the vena cava and aorta. Aletti et al. (21) removed the external, internal, common iliac and obturator nodes and all fatty tissue from the bifurcation of the aorta to the insertion of the ovarian vessels bilaterally.

Eltabbakh et al. (20) stated that just one surgeon and one pathologist performed surgery and pathological examination. Dubernard et al. (31) and Ayhan et al. (30) only mentioned...
that one pathologist examined the tissue. Aletti et al. (21) reported that a dedicated pathologist examined the tissue, but it remains unclear whether it was only one person or not.

FIGO criteria and the grading system were used in every study.

All studies performed systematic pelvic and para-aortic LNE if optimal cytoreductive surgery, defined as RD<1 cm, was achieved.

To summarize all these results, it soon becomes clear that there are a great number of quality differences while comparing the selected studies.

Table III allows an overview of tumor characteristics. It is remarkable that all patients had FIGO III-IV and most of them had grade 2 or 3. Moreover, the number of patients with RD<1 cm is shown.

Tables IV and V illustrate the characteristics of the examined lymph nodes. The number of harvested lymph nodes, lymph node size and capsular integrity are shown. Interestingly, there are no significant differences in these parameters for PPC compared to PSOC.

Eltabbakh and Mount (20) observed that the number of total lymph nodes within the basins did not differ from that in PSOC. It is noteworthy that pelvic lymph nodes were nearly 5 mm larger in PPC when compared to PSOC, but that this was not statistically significant. Also statistically insignificant was the finding that the para-aortal nodes in PPC were nearly about 1.5 mm larger than those of PSOC. Dubernard et al. (31) stated that lymph nodes were not larger than 2 cm. Ayhan et al. (30) and Aletti et al. (21) did not examine size of lymph nodes. Eltabbakh and Mount (20) found intact lymphatic capsule in three quarters of patients. Dubernard et al. (31) used the median value and that is probably why the number of extirpated nodes was higher. In contrast to Eltabbakh and Mount (20), Aletti et al. (21) resected three times as many pelvic nodes and four times as many para-aortal nodes, but there was no significant difference of PPC from PSOC.

Dubernard et al. (31) found a preferred metastatic site: in 72% of the patients with positive para-aortal nodes, the lymph node basins on the left side above the arteria mesenterica inferior were metastatic. Next in statistical significance was the simultaneous lymph node involvement of pelvic and para-aortal nodes, as seen by Aletti et al. (21). They discovered that the number of positive para-aortal nodes in PSOC was significantly higher than that in PPC. Ayhan et al. (30) stated a significantly higher number of
positive left and right pelvic nodes in PSOC, but this
difference was not found in the results of Aletti et al. (21)
and Eltabbakh and Mount (20).

In conclusion, there was no typical spread pattern found,
because the study groups based their systematic lymph node
resection on different retroperitoneal lymph node topography.

Figure 1 illustrates that nearly two-thirds of patients with
PPC had positive retroperitoneal lymph nodes; pelvic nodes
were involved more frequently. Interestingly, the more lateral
of the aorta abdominalis, the lower the number of lymph
nodes found to be involved, but this finding is based on the
results of one study group only (31).

Discussion

Referring to the objectives of this paper and the anatomical
division of the retroperitoneal lymph nodes in different
basins, it stands out that in regard to the papers studied here,
the varying descriptions of pelvic and para-aortic lymph
nodes made it very difficult to write a systematic review and
a synopsis of results. In this context, the variability of the
extent of lymph nodes harvested in the pelvic and para-
aortic region among the four studies appears suspicious.
This goes hand in hand with selection bias, because this
could otherwise have led to confounding results.
Nevertheless, these data were used because all of them
reported systematic pelvic and para-aortic LNE as surgical
procedure. In contrast to the other study groups, Dubernard et al. performed systematic LNE as a part of initial and
interval debulking surgery. This may have confounded the
results of this study, because the extent of nodal
involvement may have been higher. Another relevant fact is
that the taxonomic position of PPC has been unclear for
many years and the useful GOG diagnosis criteria have been
established in routine clinical practice for a few decades. We
acknowledge that the reported biases may have influenced
our results and led to potential weakness.

Moreover, the strength of our review may be reduced
because there were only four relevant papers and the number of
patients examined was small. A plausible reason for this is
that probably not all such data gleaned is ever published,
because it appears to have only a statistically insignificant
diagnostic, prognostic or therapeutic value.

In conclusion, around two-thirds of patients suffering from
PPC appear to have pelvic and para-aortic lymph node
involvement and this is why all four of the papers reviewed
here recommend systematic pelvic and para-aortic LNE when
an optimal cytoreductive surgery (RD≤1 cm) is achieved. This
has to be weighed up against the prolonged operation time as
a risk factor for patients (41).

The challenge for future research is to use a classification
standard for retroperitoneal lymph nodes. In this context, the
classification of lymph nodes by Harter et al. (26) is a useful
tool. Without international agreement on the extent of
retroperitoneal lymph node dissection, the spread pattern of
retroperitoneal lymph node will be difficult to investigate. In
addition to this, it is very often the digestive tract which is
also involved in tumorigenesis and therefore the coverage of
mesenteric lymph nodes should also be scrutinized.

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