The Prognostic Significance Of Angiogenesis in Epithelia Ovarian Carcinoma


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Özet

Amaç: Epitelial over karsinomunda angiogenesisinin prognostik değeri araştırılmıştır.

Materiel ve Yöntem: 1990-1999 yılları arasında primer epitelial over karsinomuna tanısı alınmış 47 hasta (evre IV) şahısına dahil edilmişdir. "borderline" over tümörleri ve primer peritoneal karsino- 
malar şahısına dahil edilmemiştir. Bu bağlamda FIGO kriterlerine göze çarparak revizyon ve evreye göre tümör "debuking" genel kriterlerin alınmıştır. İlk tümör örneklerinde 5 gün kalamıştır. Slaytlar usi- 
rantanarak endoskeletal hücreleri örtüssü veya spesifik ile işaretleyen faktör 
8 ile ilişkili antijen kârısına alınarak kullanılarak mümünhüştürmektedir. 

Bu slaytlar X40 mikroskop altında tanımlanıp en fazla damarı olan olan "hot spot" un seçilmişden sonra 
200x ile birimli mikroskoblar sayılır. Slaytlar yaş, evre, 
grade, LNF nodu tutulum durumu, tümörün tek tutulum veya bilateral olarak 

evleri tutum olma durumu, asit miktarı, tümör büyüklüğü, prooperatif CA 125 düzeyleri, rezidü tümör ve sağkalım süreleri gibi 

Bulgular: MVD sayıları ile klinik patolojik faktörler arasında herhangi 

bir korelasyon saptanmamıştır.

Sonuç: Meme, prostat ve kâğıt hücreli olmayan akciğer kanseri gibi 
solid organ tümörlerinden faktör olarak angiogenesis, over karsinomunda 

dez zamanında değerlendirilebilir.

Anahtar kelimeler: over kanseri, angiogenesis, faktör VIII ile 

ilişkili antijen, prognoz

Introduction

Tumor growth and metastases are dependent on new blood vessel formation. Tumor growth beyond 1-2 mm is known to be strictly dependent on angiogenesis. For a tumor cell to metastasize a series of barriers must be overcome as well as it responds to several cytokines and growth factors. Angiogenesis is the critical step in metastatic process. For a tumor cell to metastasize, tumor cell must gain access to circulation, localize in the target organ, then induce angiogenesis in the target organ. The prognostic importance of tumor angiogenesis is first reported by Sivriavastva in cutaneous malignant melanoma (1). There have been increasing number of reports from that time and established data indicates the prognostic importance of angiogenesis in breast (2), prostat (3), non-small cell lung carcinoma (4), cervical carcinoma (5) and endometrial carcinoma (6). There is little knowledge regarding the association of angiogenesis with tumor growth and metastases in ovarian carcinoma. In this study we aimed to investigate angiogenesis as a prognostic factor in epithelial ovarian carcinoma and correlate angiogenesis with clinicopathological factors.

Material and Methods

47 patients diagnosed as primary ovarian carcinoma (stages I-IV) were included in the study who underwent surgical staging between years 1990-1999 at the Department of Obstetrics and Gynecology of Ankara University Medical School, Ankara, Borderline ovarian tumors and primary peritoneal carcinomas were excluded. Extended surgical staging according to International Federation of Gynecology and Obstetrics (FIGO,1986) (7) was performed in all patients. Total abdomi-
hysterectomy and bilateral salpingo-oophorectomy, pelvic and paraaortic lymph node sampling, omentectomy, peritoneal washings and multiple samplings and tumor debulking according to surgical stage were included in the surgical staging. Since the number of stage I and stage IV tumors was small, stage I tumors were evaluated along with stage II tumors and stage III tumors were evaluated with stage IV tumors. Original diagnoses were confirmed by another pathologist before beginning of the evaluation. Snap thick sections were prepared from the formalin-fixed paraffin embedded tissues of the initial ovarian specimens and were stained using commercially available antibody to factor VIII-related antigen (factor VIII-RAg, Signet, Dedham MA, USA) that labels endothelial cells with high degree of specificity by streptavidin-biotin peroxidase technique. After scanning and selection of the most neovascularized area (hot-spot) in the low power field (40X), microvessels were counted using 200X magnification in three separate areas. Then the mean microvessel density (MVD) calculated. All brown-red stained single endothelial cells or cell clusters which were clearly separated from the adjacent vessels, tumor cells or connective tissue elements were considered and counted as microvessels. Existence of a lumen was not considered mandatory to define a red stained area as a microvessel. In addition dilated venules or bigger vessels with muscular walls were not taken into account and excluded from the counting. Results were correlated with clinicopathological factors such as age, histological type, stage, grade, lymph node involvement, ascite volume, tumor volume, preoperative CA 125 levels, tumor unilaterality or bilaterality, postoperative residue tumor and patient survival.

Results

Tumor samples of 47 patients were evaluated. The mean age of the patients was 54.26±12.60. There were 31 serous papillary cyst adenocarcinoma, 8 mucinous carcinomas and 8 endometrioid carcinomas. According to the FIGO, 6 patients had stage I, 5 patients had stage II, 31 patients had stage III and 5 patients had stage IV disease. According to tumor grade, 15 patients were grade I, 24 patients were grade II and 8 patients were grade III (Table 7). The mean microvessel density (MVD) was 104.9±33.1 ranging between 40 to 190. The mean preoperative serum CA 125 levels was 529.2±348.1 IU/ml ranging between 55 and 2190 IU/ml and ascite volume ranged between 0 and 10 lt. The mean tumor volume was 13.6±6.35 (3-40cm). Nine patients remained without residue tumor, 24 patients had residue tumor ≤2cm and 14 patients had residue tumor >2 cm after surgical debulking.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Stage I+II</th>
<th>Stage III+IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serous</td>
<td>4</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td>Mucinous</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>2</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

Discussion

Table 2: MVD according to tumor stage, type and grade

<table>
<thead>
<tr>
<th>MVD</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Stage</td>
<td></td>
</tr>
<tr>
<td>Stage I+II</td>
<td>114.9 ± 37.8</td>
</tr>
<tr>
<td>Stage III+IV</td>
<td>101.7 ± 31.5</td>
</tr>
<tr>
<td>Tumor Grade</td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>101.1 ± 42.4</td>
</tr>
<tr>
<td>Grade II</td>
<td>102.6 ± 26.8</td>
</tr>
<tr>
<td>Grade III</td>
<td>122.25 ± 27.8</td>
</tr>
<tr>
<td>Histologic Type</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>102.0 ± 29.0</td>
</tr>
<tr>
<td>Mucinous</td>
<td>105.12 ± 51.2</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>114.5 ± 28.7</td>
</tr>
</tbody>
</table>

Although there has been great advance in the field of chemotherapy, ovarian cancer still remains as the most lethal one among gynecologic malignancies. Prognostic factors capable of identifying early recurrences will be the paramount advance in the field of ovarian cancer therapy. Neovascularization is mandatory not only for a tumor cell to grow beyond a critical size, but is also crucial for a tumor cell to metastasize. It constitutes
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an important part in the metastatic process, because it provides access for tumor cells to systemic circulation via microvessels. These newly formed microvessels are known to have fragmented basal membranes which facilitates spread of tumor cells. After establishment of the metastatic focus it is also necessary for metastatic focus to continue its growth and further establishment of new metastatic foci.

Secretion of matrix degrading enzymes such as plasminogen activator and collagenses by endothelial cells facilitates the invasion of tumor cells in to the newly formed microvessels (8). It was also demonstrated that tumor cells could secrete angiogenic substances into the tumor stroma as shown in cervical intraepithelial neoplasia (9). Additionally, angiogenic substances secreted by host immune cells such as macrophages and mast cells contribute to induction of angiogenesis (10,11).

There has been increasing number of reports about angiogenesis and its prognostic value in solid organ tumors recently. It has been reported that microvessel density is related with patient survival in some solid organ tumors (2,3,4). Weidner and associates demonstrated that MVD in the 20X field was an independent prognostic factor for metastases in invasive breast carcinoma (2). In contrast, in studies investigating ovarian carcinoma, angiogenesis was not found to be a new prognostic factor (12,13). Epithelial ovarian cancer spreads by local extension, intraperitoneal seeding, lymphatic involvement and infrequently hematogenously. However, angiogenic properties of ovarian carcinoma cell lines have been demonstrated (14). Nakamichi proposed that angiogenesis is an early event and might be induced differently depending on the tumor type in ovarian cancer (13). We did not confirm this in our study, as we found that angiogenesis was induced equally irrespective of tumor type (Table 2).

Surprisingly, it was demonstrated in the study of Abulafia and associates on ovarian carcinoma that MVD count of mesenchymal metastases significantly correlated with patient survival in stage IIIA and stage IIIB diseases, whereas MVD of primary tumor did not such correlation (12). Nevertheless, it was also suggested that there is a clear cut difference in the MVD of benign and malignant ovarian tumors (15). Importantly it was demonstrated by the same investigators that in the benign group the capillaries tended to be concentrated in the stroma close to epithelium, whereas in malignant epithelial tumors of the ovary they found an increase in the number of microvessels which were distributed heterogeneously in the tumor stroma. This difference is under evaluation by many investigators who indicated that this increased number of blood vessels in malignant epithelial tumors of the ovary resulted in typical changes observed in sonographic blood studies (16,17).

In our study we did not find any correlation between angiogenesis and clinicopathological factors including survival. One possible explanation of this is that the geometrical makeup of these tumors is different from that of other solid organ tumors. For example, in breast carcinoma neovascularization occurs from different directions from the underlying stroma whereas blood supply of ovarian carcinoma arises just from one direction, the hilus. In other words, angiogenesis might vary depending on the distance from the origin of the vascular supply, which has not been studied yet. Secondly, ovarian tumors are so heterogenous that even in the same specimen there may be great differences resulting in substantial individual variation. Thirdly, different from other solid organs, ovarian tissue shows cyclic changes which could have important impacts in MVD formation and assessment. Additionally, in normal nonneoplastic ovarian tissue it was demonstrated that human granulosa and theca lutein cells express vascular endothelial growth factor which is suggested to induce angiogenesis (16).

Although our data did not reveal angiogenesis as prognostic indicator in epithelial ovarian carcinoma, more comprehensive studies are needed to make a more clear-cut conclusion.

References


