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EUROPEAN JOURNAL OF GYNAECOLOGICAL ONCOLOGY (ISSN 0392-2936) publishes original peer reviewed works in the fields of female genital cancers and related subjects and also proceedings of gynecologic oncology society meetings all over the world. The Journal is covered by CURRENT CONTENTS, SCISEARCH, RESEARCH ALERT, INDEX MEDICUS, MEDLINE, EMBASE/Excerpta Medica, CURRENT ADVANCES IN CANCER RESEARCH, BIOSIS.
Effect of collagen powder on lymphorrhea after modified radical mastectomy. A randomized controlled trial

V. Stafyla, E. Dimakakos, A. Koureas, K. Gennatas, D. Voros, I. Vassiliou, V. Smyrniotis, N. Arkadopoulos - Athens, GREECE
This randomized control study demonstrates the effect of collagen type I on lymphorrhea in patients who underwent modified radical mastectomy for breast cancer.

Association of CYP1B1 gene polymorphisms and the positive expression of estrogen \( \alpha \) and estrogen \( \beta \) with endometrial cancer risk

Z.Y. Zhu, Y.Q. Mu, X.M. Fu, S.M. Li, F.X. Zhao - Datong, CHINA
A significant difference in the distribution and allelic frequencies of the codon 432 region of CYP1B was found between patients affected or not by endometrial cancer.

Is postoperative CA125 level in patients with epithelial ovarian cancer reliable to guess the optimality of surgery?

F. Ghaemmaghami, S. Akhavan - Tehran, IRAN
Postoperative CA125 levels do not differ according to optimal or suboptimal cytoreductive surgery.

Alveolar rhabdomyosarcoma originating from the uterine cervix

B. Cakar, U. Muslu, B. Karaca, B. Junushova, R. Uslu, E. Goker - Izmir, TURKEY
A rare case of alveolar rhabdomyosarcoma originating from the uterine cervix.

Metastatic gastric cancer mimicking an advanced cervical cancer: A case report

H. Matsushita, M. Fukase, T. Takayanagi, H. Ikarashi - Yamagata, JAPAN
Metastasis to the uterine cervix from gastric cancer mimicking a Stage IIIB cervical cancer is reported.

Peptide YY producing strumal carcinoid tumor of the ovary

K. Matsunami, H. Takagi, S. Ichigo, T. Murase, T. Ikeda, A. Imai - Gifu, JAPAN
Constipation caused by PYY may help in the diagnosis of ovarian tumors as carcinoids.

Advanced embryonal rhabdomyosarcoma of the uterine cervix: a case report

Š. Smrkolj, S. Rakar, S. Mali, J. Šinkovec, B. Kobal - Ljubljana, SLOVENIA
Patients with advanced embryonal rhabdomyosarcoma of the uterine cervix seem to benefit from a multimodality approach including surgery, adjuvant chemotherapy and radiotherapy.

Borderline mucinous tumor arising in a paratubal cyst: a case report

H.S. Im, J.O. Kim, S.J. Lee, Y.S. Lee, E.K. Park - Korea, KOREA
The first case of a paratubal borderline mucinous tumor.

Primary fallopian tube cancer in term pregnancy: a case report

A. Le, L. Shan, R. Yuan, Z. Liu, H. Yang, Z. Wang - Shanghai, CHINA
The clinical features of a case of primary fallopian tube carcinoma with pregnancy were analyzed.

Prolonged survival after episiotomy recurrence of cervical cancer complicating pregnancy

I. Hafeez, B.D. Lawenda, J.M. Schilder, P.A.S. Johnstone - Indianapolis, IN (USA)
A case of long-term survival greater than ten years following chemoradiation in a patient affected by recurrence of cervical cancer at the site of an episiotomy.

Aggressive ovarian psammocarcinoma: a case report

F.A. Zakkouri, N. Berrada, F. Kettani, H. Mrabti, A. Jalil, H. Errihani - Rabat, MOROCCO
A new case of aggressive serous psammocarcinoma of the ovary, characterized by massive psammoma body formation is reported.

Vertical rectus abdominis myocutaneous flap for vaginal reconstruction after radical pelvic surgery for Stage II vaginal carcinoma

Vertical rectus abdominis myocutaneous flaps may be favorably used for vaginal reconstruction.

Successful salvage treatment of recurrent endometrial cancer with multiple lung and abdominal metastases

L.R. Hsu, Y.P. Chen, H.P. Chang, Y.R. Chen, J.H. Hong, A. Chao, C.H. Lai - Taoyuan, TAIWAN
Chemo-hormone therapy with targeted radiation should be evaluated in recurrent endometrial cancer with positive progesterone receptors for salvage treatment.

Metastatic cervical adenocarcinoma mimicking retroperitoneal sarcoma of the psoas muscle on imaging

Cervical adenocarcinoma with spinal metastasis can mimic retroperitoneal sarcoma originating from the psoas muscle on magnetic resonance imaging.

CT-guided cryoablation of both breast cancer and lymph node axillary metastasis

CT-guided cryoablation of both breast and lymph node metastasis in our case was a safe and feasible technique.
Six-year follow-up without recurrence after a carcinosarcoma of the breast: case report

R. Wernert, G. Yazbek, C. Voisin-Rigaud, G. Ducarme - Clichy, FRANCE

Carcinosarcoma of the breast is a rare entity with a high risk of loco-regional recurrence and poor prognosis. The histogenesis is controversial and optimal treatment modalities remain unknown.

Metastasis from breast cancer to an endometrial polyp; treatment options and follow-up. Report of a case and review of the literature

A.B. Hooker, C.M. Radder, B. van de Wiel, M.M. Geenen - Amsterdam, THE NETHERLANDS

A lobular breast cancer metastatic to the vulva and an endometrial polyp is presented and the literature is reviewed.

Diffuse intraabdominal fibrosis and inflammation mimicking peritoneal carcinomatosis recurred after surgery for borderline ovarian tumor misdiagnosed by 18F-fluorodeoxyglucose-positron emission tomography


Diffuse intraabdominal fibrosis and inflammation can mimic peritoneal carcinomatosis identified with increased metabolic uptake on 18F-fluorodeoxyglucose-positron emission tomography.

A case of bilateral ovarian synchronous tumors (left ovarian serous papillary adenocarcinoma and right ovarian malignant mixed Müllerian tumor)

M.J. Song, C.W. Lee, K.J. Seo, J.A. Kim, J.S. Park, S.Y. Hur - Gyeonggi-Do, KOREA

A case of 58-year-old multiparous with bilateral ovarian synchronous malignant tumors is presented.

Ovarian carcinoma presenting with axillary lymph node metastasis: a case report

F. Ceccarelli, S. Barberi, A. Pontesilli, S. Zancla, E. Ranieri - Rome, ITALY

Primary papillary serous cystadenocarcinoma of the ovary, initially presenting with right axillary lymph node involvement.

Papillary serous adenocarcinoma of the uterine cervix: a case report

H. Yüksel, S.D. Sezer, M. Kâşapk, A. Rıza Obadaşı, F.K. Döger - Aydın, TURKEY

The present study seeks to report a case of papillary serous adenocarcinoma originating from the endocervix.

Rare case of an ovarian monodermal teratoma with functional stroma and extensive ovarian decidualization in a 74-year-old woman

E. Vouza, Ch. Dastamani, Ch. Iavazzo, K. Bakalianou, D. Hasiakos, A. Kondi-Pafiti - Athens, GREECE

Struma ovarii and ovarian decidualization in an 74-year-old woman.

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F. Mantzos, P. Vanakara, S. Samara, G. Wozniak, P. Kollias, I. Messinis, C. Hatzitheofilou

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A systemic review of human papillomavirus studies: global publication comparison and research trend analyses from 1993 to 2008

H.W. Lin1,2,3, T.C. Yu4, Y.S. Ho4,5

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Introduction

Infection with the human papillomavirus (HPV) has been determined to be the main cause of cervical cancer [1, 2]. After HPV was identified on cervical swabs, the relationship between HPV and cervical cancer has been extensively and thoroughly explored. It was found that cervical cancer is mainly caused by HPV [3-5]. The HPV vaccine has since been developed and its clinical trial has indeed shown favorable results [6-8]. Following the discovery of the correlation between HPV and cervical cancer, numerous studies have been conducted on the subject, but nobody has yet looked at a global comparison of the research trends for such studies.

Methods

Documents used in this study were extracted from the online database of the Science Citation Index (SCI) retrieved from the ISI Web of Science, Philadelphia, USA. Journal Citation Reports (JCR) indexed 6,620 major journals with citation references across 173 scientific disciplines during the year of 2008. “Human papillomavirus” was used as a keyword in order to perform the global comparisons and trend analyses. Research performance has been analyzed and ranked across countries and institutes. Research trends of prominent areas were assessed by words cluster analyses. These were obtained from a combination of author keywords, keywords plus, and words in title.

Summary

The term “human papillomavirus” has been used as the keyword during searching titles, abstracts, and keywords based on the online version of Science Citation Index (SCI), Web of Science from 1993 to 2008. Twelve document types were found among the 14,943 papers published in 1,072 journals that were listed in 99 SCI subject categories. All the articles referring to human papillomavirus were assessed by using the following aspects: characteristics of publication output, distribution of output in journals, publication output of source country, source institute, and analysis of word clusters in title, author keywords, and keywords plus. The results have shown that the USA ranked first using five publication indicators including total, single country, international, first author, and corresponding author publications. China has had the sharpest rise of publications since 2004. The top four European countries in 2008 were France, Germany, the UK, and Italy, respectively. Trend studies with word cluster analysis were performed with regards to the areas of immunology, screening methodology, behavioral sciences, economics, and meta-analysis. All those areas have shown a sharp upward rise since 2004. In addition, hypermethylation-induced inactivation of the p16 gene in the early stages of oncogenesis has been getting more interest in recent years.

Key words: Human papillomavirus; Bibliometric; Research trend; Cervical cancer.

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tries. The term “single institute publication” was assigned if the researchers’ addresses were from the same institute. The term “inter-institutionally collaborated publication” was assigned if authors were from different institutes.

All the articles referring to HPV from 1993 to 2008 were assessed using the following aspects: document types and language of publication, characteristics of publication outputs, distribution of outputs in journals, publication outputs of source country, source institute, and analysis of words in title, author keywords, and keywords plus.

Results and Discussion

Document type and language of publication

The distribution of document types identified by ISI was analyzed. From this study, 12 document types were found in the total of 14,943 publications during the 16-year study period. Articles (11,159) contained the most frequently used document type with 75% of all publications. They were followed by reviews (1,324; 8.9%) and the remainder having less significance, were proceedings papers (754), meeting abstracts (667), letters (401), editorial materials (388), notes (160), corrections (39), news items (25), additional corrections (18), reprints (6), and biographical items (2). Journal articles represented the majority of document types. Only 11,159 original articles were used for further analysis, whereas all others were discarded. Ninety-eight percent of all these journal articles were published in English. Several other languages were also used, including French (99), German (98), Spanish (40), Portuguese (7), Chinese (6), Polish (5), Korean (4), Turkish (2), Russian (2), and one in Italian, Romanian, and Serbian, respectively.

Publication output

The amount of SCI journal articles including the ones with “human papillomavirus” in the title only, since 1975, were counted and are displayed in Figure 1. The first paper on the “human papillomavirus DNA-physical map” was published in the Proceedings of the National Academy of Sciences of the United States of America, by Favre et al. from France. These authors also published HPV-related papers in the following years [10-12]. Figure 1 shows that there is an obvious increase in trends between 1984 and 1992. After plateau periods between 1992 and 2004, another sharp increase in trend was revealed. In the early 1980s, studies displayed great milestones in the detection of HPV in genital lesions [13] as well as, DNA sequence of HPV-6 [14,15] and HPV-11 and genome organization [14]. From the identification of the HPV on cervical swabs, the relationship of HPV type-16 and cervical cancer were clearly shown [16]. Physical characteristics of the virus, its DNA sequence and the prevalence of HPV-16 as well as the DNA sequence of HPV-18 were demonstrated [17]. In addition, there was progress in the study of HPV, demonstrating that the E6 protein of HPV-16 is capable of binding to the cellular p53 protein [3]. This confirmed the suspected role of genital HPV infections as the central etiologic factor [18] and justified the need for invasive cervical cancer worldwide [2]. Furthermore, the efficacy, safety and immunogenicity of the HPV vaccine were proved [7] as were its long-term effects [8]. Above all, the authors of these findings have historically contributed to HPV research.

Publication patterns: subject categories and journals

Based on the classification of subject categories of JCR in 2008, the publication output data of HPV research is distributed in 99 SCI and 16 SSCI subject categories. Subject categories containing more than 700 HPV-related articles were statistically analyzed and are shown in Figure 2. The number of scientific articles per category exhibited consistently grew during the time period covered. This indicates that HPV research has developed steadily in various categories. Oncology was the most common category included in 141 journals in JCR 2008. In earlier years, characteristics of the lesions and risk of malignant conversion were associated with the type of HPV involved in epidermodysplasia verruciformis [12]. This was classified in the oncology category. HPV is associated with cervical lesions and its malignant changes was firstly reported in oncology papers. Moreover, prominent articles containing topics on the prevalence of HPV and its relationship to cervical cancer were also published in the area of oncology [2,18].

For 16 years, 11,159 articles were published in 1,072 different journals, including specialty journals and journals about other disciplines. Table 1 presents the 20 journals which contain more than 100 HPV-related articles. Journal of Virology listed HPV in the category of virology. It ranked first with 483 (4.3%) papers. The International Journal of Cancer listed it in the category of oncology, ranking second with 376 (3.4%) publications. The ten journals in Table 1 were listed under oncology followed by obstetrics and gynecology with five journals and virology with four journals. Twenty percent of the articles can be found in these seven core journals. According to JCR, the impact factor (IF) of Cancer Research reached 7.514, which was higher than in any other journal. In addition, five articles were published in the CA-A Cancer Journal for Clinicians, a journal which is ranked as the best of the 6,598 journals listed in SCI with an impact factor 74.575.

Publication performances: countries and institutes

The contribution provided by different countries/territories was estimated by focusing on the location of the affiliation of at least one author of the published papers. There were 37 articles without any author address information on the ISI Web of Science. Of all the articles with author addresses, 8,693 (78%) were single country publications and 2,429 (22%) were internationally collaborated publications. The top 30 countries/territories were ranked according to their number of total publications. This includes the number and percentage of total publications, single country publications, internationally collaborated publications, first author publications, and corresponding author’s publications. Also considered were the country’s collaboration percentage (%C) and the percent-
A systemic review of human papillomavirus studies: global publication comparison and research trend analyses from 1993 to 2008

The age of collaborated publications in total publications for each country (Table 2). Six of the G7 (seven major industrial countries of the world) countries ranked as the top six of the world publications. These were France, Germany, Italy, Japan, the UK, and the USA. Canada came in at number nine. The Netherlands (581; 7th) and Sweden (466; 8th) also ranked in the top ten. Moreover, the G7 had high productivity in independent papers (66%), first author publications (64%), and corresponding author publications (63%). Similar results were also found within medical research topics in terms of stem cell [19], asthma in children [20], and patent ductus arteriosus treatments [21]. The USA showed the greatest number of world publications (41%), followed distantly by other countries. It also had the most frequent partnered publications. This accounted for 54% of the internationally collaborated publications. However, compared to its total publications, the USA presented a very low percentage (29%) of internationally collaborated publications with authors from other countries. Japan held 23% of the world publications, but only 5.7% of all internationally collaborated publications. Table 2 shows that 15 European countries, seven American countries, and seven Asian countries were ranked in the top 30 based on their publications. Only one country from Africa and one from Oceania were in the top 30; South Africa and Australia, respectively. When looking at the percentage of European articles that contained internationally collaborated content, the average was 51% with a range of 29% (Greece) to 68% (Switzerland) while American articles had an average of 60% and a range of 29% (USA) to 100% (Costa Rica). However, in Asian countries, a low average of 32% was found, with a range of 21% (South Korea) to 45% (China).

Table 1. — The top 20 most published journals on the topic of HPV.

<table>
<thead>
<tr>
<th>Journal name</th>
<th>IF</th>
<th>TP (%)</th>
<th>Subject category</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Journal of Virology</td>
<td>5.308</td>
<td>483 (4.3)</td>
<td>Virology</td>
<td>3/27</td>
</tr>
<tr>
<td>International Journal of Cancer</td>
<td>4.734</td>
<td>423 (3.8)</td>
<td>Oncology</td>
<td>30/141</td>
</tr>
<tr>
<td>Gynecologic Oncology</td>
<td>2.919</td>
<td>376 (3.4)</td>
<td>Oncology</td>
<td>65/141</td>
</tr>
<tr>
<td>Oncogene</td>
<td>7.216</td>
<td>270 (2.4)</td>
<td>Obstetrics &amp; Gynecology</td>
<td>12/61</td>
</tr>
<tr>
<td>Virology</td>
<td>3.539</td>
<td>261 (2.3)</td>
<td>Virology</td>
<td>8/27</td>
</tr>
<tr>
<td>Cancer Research</td>
<td>7.514</td>
<td>242 (2.2)</td>
<td>Oncology</td>
<td>12/141</td>
</tr>
<tr>
<td>British Journal of Cancer</td>
<td>4.846</td>
<td>209 (1.9)</td>
<td>Oncology</td>
<td>28/141</td>
</tr>
<tr>
<td>International Journal of Gynecological Cancer</td>
<td>1.932</td>
<td>186 (1.7)</td>
<td>Oncology</td>
<td>105/141</td>
</tr>
<tr>
<td>Journal of General Virology</td>
<td>3.092</td>
<td>181 (1.6)</td>
<td>Obstetrics &amp; Gynecology</td>
<td>29/61</td>
</tr>
<tr>
<td>Journal of Medical Virology</td>
<td>2.576</td>
<td>176 (1.6)</td>
<td>Virology</td>
<td>14/27</td>
</tr>
<tr>
<td>Vaccine</td>
<td>3.298</td>
<td>168 (1.5)</td>
<td>Immunology</td>
<td>42/121</td>
</tr>
<tr>
<td>Cancer Epidemiology Biomarkers &amp; Prevention</td>
<td>4.770</td>
<td>149 (1.3)</td>
<td>Oncology</td>
<td>29/141</td>
</tr>
<tr>
<td>Journal of Clinical Microbiology</td>
<td>3.945</td>
<td>148 (1.3)</td>
<td>Microbiology</td>
<td>18/91</td>
</tr>
<tr>
<td>Journal of Biological Chemistry</td>
<td>5.520</td>
<td>129 (1.2)</td>
<td>Biochemistry &amp; Molecular Biology</td>
<td>41/276</td>
</tr>
<tr>
<td>Anticancer Research</td>
<td>1.390</td>
<td>127 (1.1)</td>
<td>Oncology</td>
<td>119/141</td>
</tr>
<tr>
<td>American Journal of Obstetrics and Gynecology</td>
<td>3.453</td>
<td>122 (1.1)</td>
<td>Obstetrics &amp; Gynecology</td>
<td>7/61</td>
</tr>
<tr>
<td>European Journal of Gynaecological Oncology</td>
<td>0.641</td>
<td>114 (1.0)</td>
<td>Oncology</td>
<td>138/141</td>
</tr>
<tr>
<td>Cancer</td>
<td>5.238</td>
<td>114 (1.0)</td>
<td>Obstetrics &amp; Gynecology</td>
<td>59/61</td>
</tr>
<tr>
<td>Sexually Transmitted Diseases</td>
<td>2.863</td>
<td>109 (1.0)</td>
<td>Infectious Diseases</td>
<td>20/51</td>
</tr>
<tr>
<td>Obstetrics and Gynecology</td>
<td>4.397</td>
<td>107 (1.0)</td>
<td>Obstetrics &amp; Gynecology</td>
<td>2/61</td>
</tr>
</tbody>
</table>

IF: impact factor; TP: total published articles in the 16 years; %: percentage of all articles published in the years.
Figure 1. — Number of SCI papers referring to “human papillomavirus” in the title only (since the first paper was published in 1975).

Figure 2. — Growth trends of seven subject categories containing more than 700 publications.

Figure 3. — Publication growth of the top five countries compared to China.

Figure 4. — Trends between the research areas of immunology and screening methodology.

Figure 5. — Trends between the research areas of behavioral sciences, economics, and meta-analysis.
The data also shows that around 2005 China had a sudden sharp increase in publications. To illustrate this, a time series analysis was done comparing China to the top five publications producing countries (Figure 3). From 1993 until the end of the period covered, a fluctuating slight rise can be seen in the numbers of articles related to HPV research from Germany, France, and Italy. Germany had the greatest number of articles appearing in 2008. One can conclude that Germany had an observable but slightly increasing trend whereas, the UK, being at the top in 1993, remained steady. By contrast, with the lowest production of articles, China had a rapidly increasing trend after 2005. This phenomenon was also found in the field of oncology. The annual mean increase in publications is noticeable in Asian countries, especially in China (23%) [22].

The length and number of key words per title were used to compare the complexity of titles between countries [23]. Distributions of words per title within different blocks were used to evaluate research trends [24].
keywords analysis provided the information on research trends. These could be found in recent years [25]. Analyzing the authors’ keywords was much more frequently applied in the trends research [19,26]. Keywords and search terms were extracted from titles of papers cited in each new article in the database in ISI [27]. Each of them represents the authors’ main ideas in a different fashion. When analyzing each word contained in titles, the phrase in source titles was segmented into single words. On the contrary, in the author keywords analysis, the exact words expressed by the authors were preserved. Also, the keywords plus, an independent supplement, revealed the contents in more detail. In order to analyze the historical development and trends of the research, the keywords and keywords plus can be differentiated into several research topics, for example aerosol [24] and immunology, screening methodology, behavioral sciences, economics, and meta-analysis. First, immunology was comprised of p53, E6, E7, immunization, immune response, immunogenicity, vaccine, immunohistochemistry, vaccine efficacy, prophylactic vaccine, P16 protein, E5 oncoprotein, and host immunity. Second, the screening methodology was composed of the following words: screen, HPV DNA testing, Pap smear, DNA chip, hypermethylation, and viral load.

Table 3. — Top 30 most productive institutes based on the number of articles published.

<table>
<thead>
<tr>
<th>Institute</th>
<th>TP</th>
<th>TPR (%)</th>
<th>SPR (%)</th>
<th>CPR (%)</th>
<th>FAR (%)</th>
<th>RPR (%)</th>
<th>%C</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Cancer Institute, USA</td>
<td>453</td>
<td>1 (4.1)</td>
<td>3 (1.5)</td>
<td>1 (5.5)</td>
<td>1 (2.1)</td>
<td>1 (2.2)</td>
<td>86</td>
</tr>
<tr>
<td>Harvard University, USA</td>
<td>283</td>
<td>2 (2.5)</td>
<td>3 (1.5)</td>
<td>3 (3.1)</td>
<td>4 (1.2)</td>
<td>4 (1.0)</td>
<td>78</td>
</tr>
<tr>
<td>University of Texas, USA</td>
<td>266</td>
<td>3 (2.4)</td>
<td>1 (2.4)</td>
<td>5 (2.4)</td>
<td>2 (1.6)</td>
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Similarly, Pap smear, sexually transmitted infection, cer-

ly more importantly, this was done in order to discover the directions of science in the future.

Table 4 lists the 30 most used author keywords with their ranks and percentages in various blocks. There are 9,577 author keywords appearing in 6,580 articles. Among them, 6,847 (71%) keywords appeared only once and 1,173 (12%) keywords appeared twice. The large number of once-only author keywords probably indicates a dim continuity in the research and a wide variety in research focuses [28]. Similar results were also reported in several research topics, for example aerosol [24] and stem cell research [19].

The study trends obtained from words in titles, author keywords and keywords plus can be differentiated into five disciplines including immunology, screening methodology, behavioral sciences, economics, and meta-analysis. First, immunology was comprised of p53, E6, E7, immunization, immune response, immunogenicity, vaccine, immunohistochemistry, vaccine efficacy, prophylactic vaccine, P16 protein, E5 oncoprotein, and host immunity. Second, the screening methodology was composed of the following words: screen, HPV DNA testing, Pap smear, DNA chip, hypermethylation, and viral load. Similarly, Pap smear, sexually transmitted infection, cer-
vical cancer prevention, and sexual behavior were referred to as behavioral sciences. Cost, decision analysis, and screen programming were considered as belonging to economics. Finally, due to the sharp rise of articles during the last four years, we were also interested in the topic of meta-analysis including systemic review.

The comparison of trends in immunology and screening methodology is shown in Figure 4. This revealed a sharp rise of articles from 2002 until the end of the period covered. Upward trends could be seen in the areas of behavioral sciences and economics from 2004 and meta-analysis from 2005 (Figure 5). These upward trends may be due to the study of efficacy, safety, and immunogenicity of the HPV vaccine studied in 2004 and its long-term effects discovered in 2006 [7,8]. Figures 4 and 5 demonstrate that five disciplines all showed an upward trend, firstly immunology and screening methodology, then behavioral sciences and economics, and finally meta-analysis.

The number of articles related to HPV shows an upward trend having two stages. Oncology was the most common category. The top three productive journals were *Journal of Virology*, *International Journal of Cancer* and *Gynecologic Oncology*. The top ten countries were the seven major industrial countries (G7: the USA, the UK, Germany, France, Italy, Japan, and Canada), the Netherlands, Sweden, and Australia. The G7 produced almost two-thirds of single country publications. The American National Cancer Institute was the dominant institute in the total, inter-institutional, first author, and corresponding author publications. However, the University of Texas ranked first in single institute publications. In author keywords, p53, polymerase chain reaction, and apoptosis were popular. We artificially and innovatively analyzed the distribution and change of words in the title, author’s keywords, and keywords plus. In doing so, we discovered five trends that were related to HPV and had increased in time series order. These were immunology, screening methodology, behavioral sciences, economics, and meta-analysis.

**Conclusions**

The result of this analysis by the bibliometric method can help researchers envision the panorama of HPV research. The results of the examination of the number of publications over time can exhibit the nation’s performance. Once important findings are documented and pub-

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TP: the number of total publications; R (%): the rank and percentage of author keywords in total publications.
lished, it is expected that there will be a rapid rising slope of publications. The achievement in cell biology, biochemistry and molecular biology can enhance the research on oncology, obstetrics and gynecology and immunology. The research trends can be traced to the trajectory of number of publications. Study trends could very well be effortlessly detected by words cluster analyses.

References


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Taichung (Taiwan)
e-mail: ysho@asia.edu.tw
Prognosis and role of postmastectomy radiotherapy in patients with T1-T2 breast cancer with one to three positive axillary nodes

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¹Department of Radiotherapy, Tianjin Cancer Institute and Hospital; Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education; Key Laboratory of Cancer Prevention and Therapy, Tianjin
²Department of Radiotherapy, Shandong Cancer Institute and Hospital, Jinan (China)

Summary

Purpose: To evaluate the prognosis and role of postmastectomy radiotherapy (PMRT) in T1-T2 breast cancer with one to three positive axillary nodes. Methods: The 10-year Kaplan-Meier locoregional recurrence (LRR), distant recurrence (DR), disease-free survival (DFS) and overall survival (OS) were compared between the N0 and 1-3N+ cohorts. The role of PMRT was evaluated in the 1-3N+ cohort. Results: The 10-year LRR, DR, DFS, OS rates in N0 and the 1-3N+ cohorts were as follows: LRR 7.5% vs 19.4% (p = 0.011); DR 14.4% vs 23.0% (p = 0.029); DFS 71.3% vs 51.2% (p = 0.001) and OS 77.0% vs 58.7% (p = 0.001). Of the 192 1-3N+ patients not treated and treated with PMRT, the outcomes were: LRR 20.1% vs 18.4% (p = 0.047); DR 26.4% vs 21.5% (p = 0.743); DFS 40.2% vs 55.4% (p = 0.260) and OS 40.7% vs 66.0% (p = 0.344), respectively. Conclusion: PMRT reduces the 10-year LRR rate for such patients, but further examination is needed.

Key words: Postmastectomy radiotherapy; Breast cancer; Positive axillary nodes.

Introduction

It is well known that postmastectomy radiotherapy (PMRT) is indicated for patients with advanced primary tumors of > 5 cm or with four or more positive axillary nodes. Adjuvant PMRT is used in patients with breast carcinoma chiefly to reduce the risks of locoregional recurrence [1-5]. However, the role of PMRT in patients with tumors ≤ 5 cm with one to three positive axillary nodes is controversial; the use of PMRT in node-negative patients with tumor size < 5 cm has also not been widely accepted and the long-term effect on overall survival of local tumor control improved by adjuvant PMRT continues to be debated [4, 6]. This retrospective study aimed to evaluate locoregional recurrence (LRR), distant recurrence (DR), disease-free survival (DFS) and overall survival (OS) in patients with T1-T2 breast cancer with one to three positive nodes in comparison with patients with node-negative disease, and to discuss the role of PMRT in such patients.

Methods and Materials

Patients

The charts and final pathologic reports of female patients with T1-T2 breast cancer with zero to three positive axillary lymph nodes (0-3N) who underwent mastectomy between May 1997 and March 2002 at Tianjin Cancer Hospital were reviewed retrospectively after approval by the institutional review board. Patients with established indications for PMRT, including pT3-4 tumors and/or four or more positive nodes, patients presenting with distant metastasis and patients with unknown pTN stage were excluded. The remaining 540 Chinese women with stage T1-T2 breast cancer with zero to three positive axillary nodes (0-3N+) formed the cohort for this analysis.

Treatments

Of the 540 patients, 512 underwent a modified radical mastectomy – that is, removal of the breast plus level I+II+III axillary dissection; 28 patients underwent radical mastectomy. Before surgery, no patients had distant metastasis, and no tumors were present at the margins of excision as confirmed by postoperative pathology. Before surgery, 119 patients had received chemotherapy (79 of N0 patients and 40 of 1-3N+ patients): cyclophosphamide 600 mg/m², methotrexate 40 mg/m², 5-fluorouracil 600 mg/m² (CMF regimen) on either day 1 and day 8 every four weeks or day 1 every three weeks. Of these patients, 63 received one cycle of chemotherapy; 30 patients received two cycles; 20 patients received three cycles and 6 patients received four to six cycles. After surgery, 504 patients received chemotherapy (323 of N0 patients and 181 of 1-3N+ patients): 493 received the CMF regimen (162 patients received one to five cycles; 194 patients received six cycles; 112 patients received seven cycles and 25 patients received eight to nineteen cycles); 9 patients received a CAF (cyclophosphamide, adriamycin and fluorouracil) regimen and 2 patients received NF treatment (navelbine and fluorouracil).

Radiation therapy was followed by mastectomy and chemotherapy. A total of 275 patients underwent radiation therapy after four to six cycles of CMF chemotherapy (140 of N0 patients and 135 of 1-3N+ patients). One hundred and sixty-two patients were given postmastectomy radiation therapy that included axillary apex/supraclavicular fossa and internal mammary lymph nodes; 84 patients received radiation treat-

Summary

Purpose: To evaluate the prognosis and role of postmastectomy radiotherapy (PMRT) in T1-T2 breast cancer with one to three positive axillary nodes. Methods: The 10-year Kaplan-Meier locoregional recurrence (LRR), distant recurrence (DR), disease-free survival (DFS) and overall survival (OS) were compared between the N0 and 1-3N+ cohorts. The role of PMRT was evaluated in the 1-3N+ cohort. Results: The 10-year LRR, DR, DFS, OS rates in N0 and the 1-3N+ cohorts were as follows: LRR 7.5% vs 19.4% (p = 0.011); DR 14.4% vs 23.0% (p = 0.029); DFS 71.3% vs 51.2% (p = 0.001) and OS 77.0% vs 58.7% (p = 0.001). Of the 192 1-3N+ patients not treated and treated with PMRT, the outcomes were: LRR 20.1% vs 18.4% (p = 0.047); DR 26.4% vs 21.5% (p = 0.743); DFS 40.2% vs 55.4% (p = 0.260) and OS 40.7% vs 66.0% (p = 0.344), respectively. Conclusion: PMRT reduces the 10-year LRR rate for such patients, but further examination is needed.

Key words: Postmastectomy radiotherapy; Breast cancer; Positive axillary nodes.
Tamoxifen was given to premenopausal patients, and aromatase inhibitor to postmenopausal women.

Study assessments

The primary outcomes were LRR and DR, and the secondary end points were DFS and OS. LRR was defined as the first site at which a tumor recurred involving the ipsilateral chest wall and/or axillary, supraclavicular, infraclavicular and internal mammary lymph nodes. LRR events occurring > 1 month after DR were not recorded. DFS was computed from the date of the diagnosis to the first recurrence of all types or breast cancer-related death by the end of follow-up. OS was estimated from the date of diagnosis to the date of breast carcinoma-related death.

In addition to radiotherapy, hormonal therapy was indicated for 235 patients with estrogen receptor (ER)- or progesterone receptor (PR)-positive breast cancer (159 of N0 patients and 76 of 1-3N + patients). Tamoxifen was given to premenopausal patients, and aromatase inhibitor to postmenopausal women.

Figure 1. — Comparisons of (a) locoregional recurrence (b) distant recurrence (c) disease-free survival and (d) overall survival between patients with node-negative and node 1–3-positive axillary lymph nodes.
Statistical analysis

Tumor and treatment characteristics of N0 and 1-3N+ patients with breast cancer were compared using chi-square tests. Ten-year rates of LRR, DR, DFS and OS of the N0 and 1-3N+ cohorts were computed by the Kaplan-Meier method and the log-rank test. Ten-year rates of LRR, DR, DFS and OS of the N0 and 1-3N+ cohorts were compared for those undergoing and not undergoing PMRT.

Results

Clinicopathologic characteristics

The median follow-up time was 7.2 years (range 0.25-10.7 years), median age 48 years (range 25-83 years) and median tumor size 3.0 cm (range 0.3-5.0 cm). The median number of lymph nodes in dissected tissue was 19 (range 2-44). In comparison with N0 patients, patients with 1-3N+ were older (71% vs 46% aged ≥ 50), had more T2 disease (89% vs 62%), more lateral tumors (60% vs 51%) and a greater proportion underwent radiotherapy (76% vs 51%) (Table 1).

Comparisons of 10-year LRR, DR, DFS, OS rates in N0 and 1-3N+ groups

The 10-year Kaplan-Meier LRR and DR rates were higher in 1-3N+ than in N0 patients: LRR 19.4% vs 7.5% (p = 0.011); DR 23.0% vs 14.4% (p = 0.029); and the 10-year Kaplan-Meier DFS and OS rates were lower in 1-3N+ than in N0 patients: DFS 51.2% vs 71.3% (p = 0.001); OS 58.7% vs 77.0% (p = 0.001). Of 48 LRRs, 25 (52.1%) involved the chest wall, 16 (33.3%) the clavicular nodes and seven (14.6%) the axillary nodes. DR occurred in 76 (14.1%) of the two groups (Table 2, Figure 1).

Comparisons of 10-year LRR, DR, DFS and OS rates in the 1-3N+ cohort treated and not treated with PMRT

The 10-year Kaplan-Meier LRR and DR rates were lower in 1-3N+ patients who underwent radiotherapy than in those who did not, and the 10-year KM DFS and OS rates in the 1-3N+ cohort who underwent radiotherapy were higher than in those who did not (Table 3, Figure 2). However, only the comparison of the 10-year Kaplan-Meier LRR rate had statistical significance.

Table 1. — Clinicopathologic characteristics of the entire cohort and comparisons between N0 and 1-3N+ patients with breast cancer.

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<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>154 (28)</td>
<td>106 (31)</td>
<td>48 (25)</td>
<td></td>
</tr>
<tr>
<td>Progesterone receptor status</td>
<td></td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Positive</td>
<td>196 (36)</td>
<td>126 (36)</td>
<td>70 (36)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>200 (37)</td>
<td>121 (35)</td>
<td>79 (41)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>144 (27)</td>
<td>101 (29)</td>
<td>43 (23)</td>
<td></td>
</tr>
<tr>
<td>Positive nodes (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>≤ 20</td>
<td>533 (99)</td>
<td>348 (100)</td>
<td>185 (96)</td>
<td></td>
</tr>
<tr>
<td>&gt; 20</td>
<td>7 (1)</td>
<td>0 (0)</td>
<td>7 (4)</td>
<td></td>
</tr>
<tr>
<td>Nodes removed (n)</td>
<td></td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>≤ 5</td>
<td>4 (1)</td>
<td>3 (1)</td>
<td>1 (0)</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>22 (4)</td>
<td>13 (4)</td>
<td>9 (5)</td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>110 (20)</td>
<td>77 (22)</td>
<td>33 (17)</td>
<td></td>
</tr>
<tr>
<td>≥ 16</td>
<td>404 (75)</td>
<td>255 (73)</td>
<td>149 (78)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>275 (51)</td>
<td>140 (40)</td>
<td>135 (70)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>265 (49)</td>
<td>208 (60)</td>
<td>57 (30)</td>
<td></td>
</tr>
<tr>
<td>Systemic therapy</td>
<td></td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>218 (40)</td>
<td>144 (41)</td>
<td>74 (39)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19 (4)</td>
<td>10 (4)</td>
<td>9 (5)</td>
<td></td>
</tr>
</tbody>
</table>

Results are shown as number (%).

Table 2. — Crude rates and 10-year Kaplan-Meier rates of LRR, DR, DFS and OS in patients between N0 and 1-3N+ patients with breast cancer.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N0 (n = 548)</th>
<th>1-3N+ (n = 348)</th>
<th>Log-rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude rate N (%)</td>
<td>10-year KM rate (%)</td>
<td>Crude rate N (%)</td>
<td>10-year KM rate (%)</td>
</tr>
<tr>
<td>LRR</td>
<td>23 (6.6)</td>
<td>7.5</td>
<td>25 (13.0)</td>
</tr>
<tr>
<td>DR</td>
<td>41 (11.8)</td>
<td>14.4</td>
<td>35 (18.2)</td>
</tr>
<tr>
<td>DFS</td>
<td>272 (78.2)</td>
<td>71.3</td>
<td>123 (64.1)</td>
</tr>
<tr>
<td>OS</td>
<td>303 (87.1)</td>
<td>77.0</td>
<td>140 (72.9)</td>
</tr>
</tbody>
</table>

LRR = locoregional recurrence; DR = distant recurrence; DFS = disease-free survival; OS = overall survival.
Discussion

As expected, patients with T1-T2 breast cancer with one to three positive axillary lymph nodes had higher 10-year LRR and DR rates and lower 10-year DFS and OS rates than patients with negative nodes. Differences in the 10-year LRR, DR, DFS and OS rates between the two groups were statistically significant. It is well known that nodal status is one of the strongest predictors of overall survival and metastasis and also a strong predictor of postmastectomy chest wall relapse when radiation is not used [2, 9, 10]. Although outcomes will continually

Table 3. — Crude rates and 10-year Kaplan-Meier rates of LRR, DR, DFS and OS in 1-3N+ patients between with radiotherapy and without radiotherapy.

<table>
<thead>
<tr>
<th></th>
<th>RT (n = 135)</th>
<th>No RT (n = 57)</th>
<th>Log-rank p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude rate N (%)</td>
<td>14 (10.4)</td>
<td>24 (17.8)</td>
<td>0.047</td>
</tr>
<tr>
<td>10-year KM rate (%)</td>
<td>18.4</td>
<td>21.5</td>
<td>0.743</td>
</tr>
<tr>
<td>LRR</td>
<td>11 (19.3)</td>
<td>11 (19.3)</td>
<td>0.260</td>
</tr>
<tr>
<td>DR</td>
<td>34 (59.6)</td>
<td>39 (68.4)</td>
<td>0.344</td>
</tr>
<tr>
<td>DFS</td>
<td>40.2</td>
<td>40.7</td>
<td></td>
</tr>
<tr>
<td>OS</td>
<td>101 (74.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| LRR = locoregional recurrence; DR = distant recurrence; DFS = disease-free survival; OS = overall survival.

Figure 2. — Ten-year (a) locoregional recurrence, (b) distant recurrence, (c) disease-free survival and (d) overall survival in 1-3N+ patients treated and not treated with postmastectomy radiotherapy (PMRT).
survival. Further investigation with randomized trials and distant recurrence and improves disease-free and overall survival that PMRT combined with systemic therapy is important. However, the clinical outcomes obtained strongly suggest that PMRT improves not only locoregional control, but also disease-free and overall survival, possibly when distant micrometastasis is controlled by systemic therapy and the locoregional tumor burden is reduced by radiation therapy, the effects combine to enhance disease control and survival [12]. The differences of 10-year DR, DFS and OS rates between the groups treated or not treated with PMRT did not reach statistical significance, possibly owing to the small number of patients with T1-T2 breast cancer with one to three positive nodes enrolled in this retrospective trial.

As in our study, many trials have shown that in women receiving systemic therapy, PMRT improves not only LRR but also disease-free and overall survival [13]. In the Danish Breast Cancer Cooperative Group 82b and 82c trials, 3,083 high-risk patients with breast cancer were followed-up for 18 years. The 18-year probability of LRR (with or without distant metastasis (DM)) was 49% and 14% (p < 0.001) after no RT and RT, respectively; the 18-year probability of DM subsequent to LRR was 35% and 6% (p < 0.001) after no RT and RT, respectively, whereas the probability of any DM was 64% and 53% (p < 0.001) after no RT versus RT, respectively. The trials suggested that RT not only improves local control rate but also reduces the DM rate [14]. Regrettably, no randomized trial designed to study the role of PMRT in patients with breast cancer with one to three positive nodes has yet been carried out [15]. Thus the role of PMRT in women with breast cancer with one to three positive nodes is currently undefined, but possibly our study may shed some light on its role in such patients.

As with other retrospective analyses, our study was subject to biases in patient and treatment selection. However, the clinical outcomes obtained strongly suggest that PMRT combined with systemic therapy is important in controlling local recurrence and potentially reduces distant recurrence and improves disease-free and overall survival. Further investigation with randomized trials and a greater number of patients is needed.

Conclusion

Patients with T1-T2 breast cancer with one to three axillary lymph nodes have a worse prognosis than patients with negative lymph nodes. PMRT reduces the 10-year LRR rate for such patients, but its influence on 10-year DR, DFS and OS rates needs further observation.

Acknowledgments

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References


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Expression of hypoxia-inducible 2 (HIG2) protein in uterine cancer

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²Department of Obstetrics and Gynecology, School of Medicine, Keio University, Tokyo (Japan)

Summary

For both cervical cancer (UCC) and endometrial cancer (EMC) there are no effective prognostic markers. In this study, we evaluated HIG2 protein expression in 332 uterine cancers (186 UCCs and 146 EMCs) and examined the relationship between HIG2 protein expression and clinical factors, including prognosis. Totally, HIG2 expression was detected in 58% of UCC and 66% of EMC. However, there was no significant relationship between HIG2 expression and age, clinical stage and histology in either UCC or EMC. In addition, HIG2 protein expression was not related to prognosis of UCC or EMC. The positivity rate of HIG2 protein was 56% and 61% in early-stage UCC and EMC, respectively and 67% in non-squamous cell carcinoma of UCC. The positivity rate of HIG2 protein was high even in early-stage UCC and EMC.

Key words: Endometrial cancer; Cervical cancer; Adenocarcinoma; HIG2.

Introduction

Carcinoma of the uterine cervix (UCC) is a common malignant neoplasm in Japanese women and its incidence in young women is increasing [1]. Endometrial cancer (EMC) is also increasing in Japan [1]. It is very important to find prognostic markers or effective serum tumor markers, however in both UCC and EMC there are no effective prognostic or serum tumor markers. In previous reports we performed gene expression profiles in epithelial ovarian cancer (EOC) using cDNA microarrays and suggested that the HIG2 gene might be a new biomarker for EOC [2]. Furthermore, we generated a polyclonal antibody for HIG2 protein and further validated the expression of HIG2 in EOC and clear cell carcinoma of the endometrium and concluded that HIG2 might be used as a marker for ovarian and endometrial clear cell adenocarcinoma or for prediction of chemotherapy response of clear cell carcinoma of the ovary [3]. In this study we evaluated HIG2 protein expression in uterine cancer (UTC) and examined the relationship between HIG2 protein expression and clinical factors, including prognosis.

Materials and Methods

Clinical samples

A total of 332 UTCs (186 UCCs and 146 EMCs) and 14 normal endometriums (proliferative phase: 7, secretory phase: 7) and seven normal cervical epitheliums were included in the study. The median age of UCCs was 52 years old (range: 22-92). Among the UCCs, FIGO Stage was: I: 99, II: 48, III: 21, IV: 18 and histology: squamous cell carcinoma: 150, adenocarcinoma: 23, and adenosquamous carcinoma: 13. The median age of EMCs was 55 years old (range: 25-83). Among the EMCs, the histologic grade was as follows: FIGO stage: I: 93, II: 5, III: 41, IV: 7 and histologic grade: G1: 66, G2: 64, G3: 16. Of 146 patients, 115 patients had estrogen receptors. All patient-derived paraffin sections were collected and archived under protocols approved by the institutional review boards (IRBs) of the parent institutions based on the Declaration of Helsinki.

Immunohistochemistry

Establishment of a polyclonal anti-HIG2 antibody was reported previously [3]. Immunolocalization of the HIG2 protein was performed using a polyclonal anti-HIG2 antibody generated by injecting the purified full-length HIG2 fusion protein into rabbits. In brief, histological sections (4 µm) were affixed to glass slides, dewaxed, and rehydrated. The sections were then incubated in 3% hydrogen peroxide for 10 min at room temperature to quench endogenous peroxidase activity. The sections were reacted with the HIG2 antibody (× 5000) at 4ºC overnight. Peroxidase activity for all proteins was visualized by applying diaminobenzidine chromogen containing 0.05% hydrogen peroxide for 2-10 min at room temperature. The sections were then counterstained with hematoxylin. The slides were observed by two independent pathologists who were blinded to the clinical background of the patients. Judgement was performed based on the cytoplasmic staining [3]. HIG2 cytoplasmic staining was divided into positive or negative. Slides of EOC known to be either positive or negative for HIG2 expression were used as positive and negative controls.

Statistical analysis

The relationship between HIG2 expression and age, clinical stage and histologic grade were analyzed using t-test and chi-square test. Overall survival (OS) distribution was calculated using the Kaplan-Meier method. A value of \( p < 0.05 \) was considered statistically significant.
Expression of hypoxia-inducible 2 (HIG2) protein in uterine cancer

HIG2 protein was weakly expressed in two of seven cervical intraepitheliums. In all cases, HIG2 protein expression was detected in 108/186 (58%) UCCs. There was no significant relationship between age, clinical stage, histologic type and HIG2 expression. HIG2 protein was weakly expressed in two of seven proliferative endometriums and four of seven secretory phase endometriums. In all cases, HIG2 protein expression was detected in 96 of 146 (66%) EMCs. There was no significant relationship between age, clinical stage, histologic grade, estrogen receptor status and HIG2 expression (Table 1). There was no significant difference in overall survival between HIG2 positive and negative cases in either UCC or EMC.

Results

Immunolocalization of HIG2 protein

Previously we reported that immunohistochemical analysis demonstrated strong cytoplasmic HIG2 staining as well as weak nuclear staining, and that the anti-HIG2 antibody is specific to the HIG2 protein, which is predominantly located in the cytoplasm of the cells. Typical images of HIG2 immunohistochemical staining are shown in Figure 1.

HIG2 expression in normal cervical intraepithelium, normal endometrium, UCC and EMC

Figure 1. Typical images of HIG2 immunohistochemical staining. (a) cervical intraepithelium, (b) proliferative phase endometrium, (c) secretory phase endometrium, (d) cervical cancer, (e) endometrial cancer. Weak nuclear staining and cytoplasmic staining were observed.
Table 1. — HIG2 expression and clinical factors.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIG2 expression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervical cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt; median</td>
<td>51% (47/93)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>66% (61/93)</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
</tr>
<tr>
<td>I+II</td>
<td>56% (83/147)</td>
</tr>
<tr>
<td>III+IV</td>
<td>64% (25/39)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>squamous cell</td>
<td>56% (84/150)</td>
</tr>
<tr>
<td>non-squamous cell</td>
<td>67% (24/36)</td>
</tr>
<tr>
<td><strong>Endometrial cancer</strong></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt; median</td>
<td>64% (47/73)</td>
</tr>
<tr>
<td>&gt; median</td>
<td>67% (49/73)</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
</tr>
<tr>
<td>I+II</td>
<td>61% (61/100)</td>
</tr>
<tr>
<td>III+IV</td>
<td>76% (35/46)</td>
</tr>
<tr>
<td>Histologic grade</td>
<td></td>
</tr>
<tr>
<td>G1+G2</td>
<td>66% (85/129)</td>
</tr>
<tr>
<td>G3</td>
<td>65% (11/17)</td>
</tr>
</tbody>
</table>

Discussion

We previously reported that HIG2 might be used as a marker for ovarian and endometrial clear cell adenocarcinoma and for prediction of chemotherapy response of clear cell carcinoma of the ovary [3]. Togashi et al. reported that HIG2 plays an essential role in proliferation of renal CCC cells in an autocrine manner and HIG2 protein is highly expressed in renal clear cell carcinoma [4]. In this study we evaluated HIG2 protein expression in UCC and EMC and examined the relationship between HIG2 expression and clinical factors including prognosis. HIG2 protein expression was detected in cervical intraepithelium, (2/7) proliferative endometrium (2/7) and in secretory phase endometrium (4/7). Totally, HIG2 expression was detected in 58% of UCC and 66% of EMC. However, there was no significant relationship between HIG2 expression and age, clinical stage and histology in either UCC or EMC. In addition, HIG2 protein expression was not related with prognosis of UCC and EMC. However, the positivity rate of HIG2 protein was 56% and 61% in early stage of UCC and EMC and 67% in non-squamous cell carcinoma of UCC.

In both UCC and EMC, there are no effective tumor markers. For example, elevated serum levels of SCC are found in 57% and 65% of women with primary squamous cell carcinoma of the UCC [5, 6]. Especially the incidence of elevated serum levels of SCC is low in poorly differentiated squamous cell tumor or early stage tumor [7]. In addition, the incidence of elevated serum levels of CA125, CA19-9 and CEA are low in adenocarcinoma of the UCC [8]. A low incidence of patients with early-stage EMC also have elevated serum CA125 or CEA levels [9-11]. A previous immunohistochemical study reported that CEA was detected in 64% of adenocarcinoma of UCC [12] and, the positivity rate of CA125, CEA and CA19-9 was 65%, 58% and 60%, respectively, in EMC [13-15] and the positivity rate of CA125 was 88% in benign endometrium [16]. In our study, the positivity rate of HIG2 was similar with previous reports, however, positivity rates of HIG2 were slightly high in early-stage UCC and EMC, and low in benign cervical intraepithelium and endometrium, compared with previous reports [12-16]. HIG2 is a secretory molecule and an ELISA system using polyclonal antibody for HIG2 protein has been developed [4]. In the future, HIG2 may be used as a serum marker.

Conclusions

The positivity rate of HIG2 protein was high even in early stages of UCC and EMC. We are planning to measure serum HIG2 protein by using the new ELISA system by monoclonal antibody for HIG2 protein in gynecologic malignancies in future studies.

Acknowledgements

The authors are grateful to Dr. Naoki Kawamura of Osaka City General Hospital for his critical review of the manuscript and to Ms. Asami Nagata and Ms. Nozomi Tsuji for their technical assistance. This study was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Japan (20014024, Keio University) and a Grant from Osaka City General Hospital.

References

Expression of hypoxia-inducible 2 (HIG2) protein in uterine cancer

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The role of p16<sup>INK4a</sup> immunostaining in the risk assessment of women with LSIL cytology: a prospective pragmatic study

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Summary

Background: The detection of high-grade cervical intraepithelial neoplasia (CIN2 or worse) among patients with low-grade cytology (LSIL) is challenging. The aim of this study was to assess the efficacy of p16<sup>INK4a</sup> in the risk assessment of women with LSIL cytology.

Methods: Consecutive liquid-based cytology specimens of 95 LSIL smears were selected and stained for p16<sup>INK4a</sup>. All patients had colposcopically directed punch biopsies or large loop excision of the transformation zone of the cervix. The endpoint was detection of a biopsy-confirmed CIN2 or worse.

Results: The overall sensitivity and specificity of p16<sup>INK4a</sup> for diagnosis of CIN2+ among LSIL smears were 41% and 86%, respectively. The positive predictive value of the biomarker was 62% and the negative predictive value 72%.

Conclusions: The study shows that p16<sup>INK4a</sup> has low sensitivity but acceptable specificity for evaluation of LSIL smears harbouring high-grade lesions. The marker needs to be further assessed as an adjunct to other tests in an attempt to improve the triage of LSIL cytology smears.

Key words: p16<sup>INK4a</sup>; Immunostaining; Cervix; Liquid-based cytology; LSIL, CIN.

Introduction

The majority of low-grade intraepithelial lesions (LSIL) represent minor cellular changes due to acute or transient human papillomavirus (HPV) infection that tends to regress. However, there are lesions that harbour high-grade histology and are at risk of progressing to cervical cancer if left untreated [1].

The current management options for women presenting with LSIL are repeat cytology, and referral for colposcopic evaluation if the abnormality persists, or immediate referral to colposcopy, or finally, triage with high-risk HPV DNA (hr-HPV) testing. The main disadvantage of cytological surveillance only, is the risk of women defaulting on follow-up. On the other hand, women referred immediately to colposcopy are at risk of overtreatment with potential adverse pregnancy outcomes [2, 3]. High-risk HPV DNA testing has been shown to have a role in the triage of atypical squamous cells of undetermined significance (ASCUS) smears [4] however, its value in the triage of LSIL is limited [5]. The test’s role and limitations were presented in a recent review that concluded that future research should focus on methods that will improve the test’s specificity [6].

Numerous epidemiologic and molecular studies have demonstrated that hr-HPV genotypes are etiologic agents for the overwhelming majority of cases of invasive cervical squamous cell carcinoma [7, 8]. New biomarkers associated with infection by hr-HPV could be used to distinguish those cases that are at risk of progression. p16<sup>INK4a</sup> is one of the biomarkers for transforming HPV infection because it accumulates in the nucleus and cytoplasm of affected cells and can be detected by immunostaining [9].

This present study aimed to assess the efficacy of p16<sup>INK4a</sup> (p16) immunocytochemistry to predict a histological diagnosis of CIN2 or worse (CIN2+) in women with LSIL cytology.

Materials and Methods

This was a prospective diagnostic pragmatic study that assessed women referred to colposcopy for the first time, from October 2008 to February 2010, with a pap test or liquid-based cytology (LBC) sample of LSIL. We excluded women who had had treatment (loop excision of the transformation zone or cone biopsy of the cervix) in the past or had been previously reviewed in colposcopy for abnormal smears. We also excluded women who had had no cervical biopsies taken.

Eligible participants were referred to colposcopy with a sample showing LSIL in the context of cervical cancer screening and were included in the study after giving informed consent. A LBC specimen was obtained prior to the colposcopic examination for p16 immunostaining. A single experienced operator performed all colposcopies and was blinded to the results of the p16 immunostaining. Women with normal colposcopic impressions did not have biopsies taken and were referred for a repeat cytological and colposcopic assessment in...
six months. Women with high-grade colposcopy and those women with low-grade colposcopy who had completed their family or were too anxious to return just for repeat cytological and colposcopic surveillance, had either punch biopsies or loop excision of the transformation zone (LLETZ). The remaining women with low-grade colposcopy, after being fully informed about the options, were referred for repeat cytology and colposcopy in six months.

The primary outcome was the sensitivity of p16 to detect CIN2+ in a population of LSIL samples and it was defined prior to the start of the study.

p16 immunostaining was performed using the Dako CINtec cytology kit (Dako Cytomation, Glostrup, Denmark) according to the manufacturer’s instructions. All slides were counterstained with hematoxylin (Dako Cytomation) to allow for assessment of the nucleus. We considered as positive p16 staining if at least one dysplastic cell was stained for the marker.

We correlated the accuracy parameters of p16 immunostaining such as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to the study gold standard (colposcopically directed punch cervical biopsies or LLETZ biopsies), on the basis of detecting CIN2 or worse [10].

Results

A series of 95 women with LSIL cytology who underwent either punch [4] or LLETZ biopsies (91) at the Department of Colposcopy of the University Hospital of Ioannina in Ioannina, Greece were included during the period assessed.

The characteristics of the study population are shown in Table 1. All women had histological specimens taken after the colposcopic assessment. Among the 95 LSIL samples 34 (36%) harboured high-grade histology (CIN2+).

In Table 2 the correlation between the results of immunostaining for p16 and the histological diagnosis are presented. The vast majority of those within normal limits (WNL) and low-grade biopsies (CIN1, HPV) were negative for p16. The results were equivocal for CIN2+ biopsies as 58% of CIN2 lesions stained negative for the biomarker. Moreover, the number of CIN3 lesions that stained positive for p16 was similar with those non-stained for the marker (Table 2). We furthermore assessed the accuracy parameters for the value of p16 in detecting CIN2+ in LSIL cytology. As shown in Table 3, the marker had low sensitivity (41%) but better specificity (86%) for CIN2+ in LSIL smears.

Discussion

Since hr-HPV is consistently associated with premalignant and malignant lesions of the uterine cervix, the use of molecular techniques to detect infection by hr-HPV has been proposed as a way to improve the results of conventional diagnostic strategies. The use of p16 marker has been suggested to compensate for the lack of specificity of the HPV DNA test and advocated as an adjunct tool for routine use [11]. Physiologically, p16 blocks the activity of cyclin-dependent kinases CDK4/6. In a transforming hr-HPV infection the viral oncogenes E6 and E7 interfere substantially with apoptosis and cell cycle regulation. Most importantly, E7 disrupts the protein of retinoblastoma (pRb) from its binding to E2F transcription factor and thereby promotes cell cycle progression, a molecular switch that is usually activated by CDK4/6. Affected cells strongly express p16 to counteract irregular cycle activation; however, since E2F is not released though CDK4/6 action, but by E7, p16 expression has no effect on cell cycle activation. Over time, p16 accumulates in the nucleus and cytoplasm of affected cells and can be detected by immunostaining [9].

Our work was an attempt to assess whether p16 immunostaining is useful for the evaluation of the malignant potential of LSIL smears. We conducted a pragmatic study choosing a primary outcome that is relevant to everyday life. The greatest strength of such a study is that it can deliver evidence of effectiveness in everyday clinical context.

There are several reports in the literature that assessed p16 in LSIL samples. The sensitivity of the marker to detect CIN2+ varies from 35% [12] to 100% [13] in different studies. In our study the sensitivity of the marker for detection of CIN2+ was low (41%) for a gain in specificity (86%). We have shown in a previous review that there are significant discrepancies among various authors on the interpretation of p16 immunostaining [14]. The discrepancies on the interpretation of p16 positivity, as
well as the variations on the population investigated by each study, add to the difficulty in assessing the clinical effectiveness of the biomarker.

Although the present study was based on a selected number of cases, it correlates p16 immunostaining to the gold standard, which is the histological diagnosis. Furthermore, the quality of the cells stained positive for the biomarker was assessed. p16 immunostaining was considered positive only if dysplastic cells stained for the marker, thus reducing the false-positive results.

Conclusion

The current study does not support the use of p16 as a single marker for the assessment of LSIL smears due to its low sensitivity. The biomarker could however have a place as an adjunct test to other markers in order to increase the specificity in the triage of LSIL cytology.

References


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Long-term topotecan therapy in recurrent or persistent ovarian cancer

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Summary

Background: The objective of this study was to evaluate feasibility, safety and clinical outcome of long-term therapy with topotecan (Hycamtin) in recurrent or persistent ovarian cancer. Patients and Methods: A retrospective chart review was conducted on all patients treated with topotecan (TPT) at the Department of Obstetrics and Gynecology, University of Bari, Italy between 1999 and 2007. Pertinent clinicopathologic information, response and toxicity following treatment with TPT were collected. TPT was given at a dosage ranging between 1.5 and 1.0 mg/m² every three to four weeks. All patients were evaluated for toxicity according to the CTC and response according to the RECIST response criteria. Time to progression (TTP) was calculated from initiation of TPT treatment and start of the next chemotherapy regimen. Results: A total of 30 patients received TPT for at least eight cycles for recurrent ovarian (22), fallopian tube (3) or primary peritoneal carcinoma (5). A total of 432 cycles of chemotherapy were given, with an average of 14.4 cycles per patient (range 8-22). Dose reduction was necessary in 20 patients (66%). About half of the patients required blood transfusions and growth factors. Non hematologic toxicity was mild and manageable. Responses were observed in 16/30 patients (53%), the remaining having SD. Median time to treatment progression was 28 months (range 9-88). Conclusion: Long-term treatment with topotecan in recurrent/persistent ovarian cancer is feasible with limited evidence of cumulative toxicity. The results of this retrospective analysis suggest a potential role for late response and survival benefit for those patients without disease progression who continue topotecan therapy beyond six cycles of treatment.

Key words: Recurrent ovarian cancer; Topotecan; Ovarian carcinoma.

Introduction

Ovarian carcinoma is the most common cause of death from gynecologic malignancy in Europe and the United States [1]. Despite high overall response rates to induction platinum and taxane-based chemotherapy, the majority of patients with advanced ovarian cancer will develop recurrent disease within two years, thereafter becoming candidates for further chemotherapy [2].

Several cytotoxic agents have shown good activity in recurrent ovarian cancer, with response rates ranging between 15 and 40%, but none were able to induce durable remission in the absence of continued treatment [3].

A recently published meta-analysis has proved that duration of chemotherapy with topotecan influences survival in recurrent ovarian cancer. In fact, patients who continued chemotherapy for more than six cycles had a statistically significant longer survival (107.0 vs 83.6 weeks) compared to those who stopped treatment after six cycles [4].

The aim of this retrospective study was to evaluate response rate, toxicity and outcome of patients who received long-term treatment (at least 8 cycles) of topotecan for recurrent ovarian carcinoma.

Patients and Methods

The clinical records of all patients treated with topotecan (Hycamint GlaxoSmithKline, Philadelphia PA) at the Gynecologic Oncology Unit of the Department of Gynecology, Obstetrics and Neonatology (DiGON), University of Bari, Italy between 1999 and 2007 were reviewed. Those patients who received at least eight cycles of chemotherapy were selected and form the basis of our report.

The following data were retrieved from the files of the patients: age, FIGO stage and histology at ovarian cancer diagnosis, previous chemotherapy, details of topotecan treatment (number of cycles, dosages, delays, toxicity, use of growth factors, transfusions, response) and time to treatment progression defined as the interval between initiation of TPT administration and beginning of the following chemotherapy. All patients were staged according to the revised International Federation of Gynecology and Obstetrics (FIGO) staging system [5].

Topotecan was administered intravenously (IV) at a dose of 1.5-1.25 mg/m², on days 1-5, as a 1-hour infusion in 250 ml of 5% dextrose. Chemotherapy was repeated every 21 days. In case of severe toxicity (WBC count less than 1,000/µl, platelet count less than 50,000/µl, and organ toxicity), topotecan was reduced to 1.0 mg/m² and/or interval between cycles was lengthened to 28 days. Antiemetic medication consisted of ondansetron 8 mg IV plus dexamethazone 20 mg. Patients received G-CSF only in case of grade 4 neutropenia after nadir.

Responses were evaluated according to RECIST criteria [6]. In patients who achieved an objective response or disease stabilization after six cycles, therapy was continued until disease progression, and interrupted in case of unacceptable toxicity.

Results

A total of 50 patients were treated with topotecan for their recurrent or persistent ovarian, primary peritoneal and fallopian tube cancer. Of these patients, 30 (22
ovarian, 5 primary peritoneal and 3 fallopian tube carcinomas) were identified as receiving long-term topotecan (at least 8 cycles). Characteristics of these patients at the time of diagnosis are summarized in Table 1. Median age of the patients was 54 years (range 31-81), and most patients had FIGO Stage III, G3 cancers at the time of diagnosis. All had received primary radical surgery followed by first-line chemotherapy with platinum and paclitaxel. A median of 2.1 (range 1-4) previous chemotherapeutic regimens before topotecan treatment had been delivered (one line in 10, two lines in 13 and more than 2 lines in 7). All but six patients (20%) were considered to have platinum-sensitive disease (recurrent disease more than 6 months after completion of first-line chemotherapy).

A total of 432 cycles of topotecan were administered with a median of 11 cycles (range 8-20 cycles). Topotecan cumulative doses ranged from 35 mg/m² to 72.5 mg/m². All patients were assessable for toxicity. There was no death related to treatment. Grade 3 leukopenia occurred in 20% of patients and grade 3 neutropenia in 40% (Table 2); six patients required G-CSF support for febrile neutropenia. Grade 4 anemia was observed in only three patients and 15 received blood transfusions and erythropoietin (EPO) support during chemotherapy. Non-hematologic toxicity was generally mild; as expected nausea, vomiting, alopecia and neurotoxicity were the most frequent side-effects of the treatment (Table 3). Due to toxicity, six patients (20%) required dose reduction to 1.0 mg/m² and in three patients (10%) chemotherapy was administered at 28-day intervals. Furthermore, nonhematologic and hematologic toxicity never caused therapy interruption.

Six patients (20%) had a complete response (CR), 11 (37%) a partial response (PR), and 13 (43%) had disease stabilization (Table 4). The median duration of response in patients with complete response was 38 months. Responses were observed also in third-line and more than third-line chemotherapy. The median time to treatment progression (TTP) for the entire series was 28 months (range 9-88). The PFI was significantly longer for patients who had been only on one prior regimen compared to those who had two or three prior regimens (39.4 vs 18.4 months). There was only one response in the group of patients with platinum-resistant disease.

### Table 1. — Patient characteristics at the time of ovarian cancer diagnosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number or percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median)</td>
<td>54 years (range 31-81)</td>
</tr>
<tr>
<td>Stage of disease</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>II</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>III</td>
<td>22 (73%)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Grading</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>G2</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>G3</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>18 (60%)</td>
</tr>
<tr>
<td>Endometroid</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Others</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Carbo-taxol (1st line)</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>9 (33%)</td>
</tr>
<tr>
<td>Taxanes and or platinum</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Others</td>
<td>6 (20%)</td>
</tr>
</tbody>
</table>

### Table 2. — Hematologic toxicity according to WHO grade.

<table>
<thead>
<tr>
<th>Variable</th>
<th>WHO grade (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 13 37 40 3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17 43 33 7 4</td>
</tr>
<tr>
<td>Anemia</td>
<td>20 7 43 17 13</td>
</tr>
</tbody>
</table>

### Table 3. — Nonhematologic toxicity according to WHO grade.

<table>
<thead>
<tr>
<th>Variable</th>
<th>WHO grade (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>7 13 37 43 3</td>
</tr>
<tr>
<td>Peripheral neurotoxicity</td>
<td>20 60 13 7 3</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>100 7 33 40 20</td>
</tr>
<tr>
<td>Alopecia</td>
<td>7 13 37 40 20</td>
</tr>
<tr>
<td>Local reactions and phlebitis</td>
<td>90 3 7 3 4</td>
</tr>
</tbody>
</table>

### Table 4. — Response rate according to previous lines of treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-line</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Third-line</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>More than third-line</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

6 (20%) 11 (37%) 13 (43%) 30
patients achieving CR to second-line chemotherapy has not been established [10].

A prescribed number of cycles is reasonable for platinum-based treatment because some long durations of response may be anticipated and continuing beyond six cycles leads to progressive intolerance. Nonplatinum drug regimens, however, should not be subjected to such limitations since they rarely result in CRs, are generally better tolerated, and have no appreciable worsening of toxic effects with repeated cycles [11]. For these reasons maintenance long-term therapy may be an attractive alternative for several second- or third-line drugs as topotecan, caelyx and gemcitabine, that have non-cumulative dose-limiting myelosuppression [3, 4, 9, 10]. Taxanes are also generally well tolerated except for the problematic sensory neuropathy, edema, extensive chronic alopecia and nail changes.

The current experience documents the feasibility of prolonged topotecan therapy in patients who achieve CR, PR or stable disease in recurrent ovarian cancer. In fact, in this study patients tolerated topotecan quite well, with absence of significant cumulative myelosuppression. Nonhematologic toxicity was also mild and manageable. Similarly to our study a previous report has documented a limited toxicity (particularly cardiac toxicity) in a group of patients who received one year administration of liposomal doxorubicin as maintenance treatment for recurrent ovarian cancer [12].

In our study response rate was remarkable even in some cases after the second recurrence or in those patients heavily pretreated. It is, however not possible to state how long treatment should be continued in responding patients.

“Long-term” administration of topotecan is feasible with a moderate toxicity and results in a good response rate both in platinum sensitive and resistant patients with recurrent gynecological cancer.

References
The value of TOP2A, EZH2 and paxillin expression as markers of aggressive breast cancer: relationship with other prognostic factors

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Summary

Introduction: The immunocytochemical expression of topoisomerase II alpha (TOP2A), enhancer of zeste homologue 2 (EZH2) and paxillin has recently gained increasing attention. Although previous studies have commented on the clinical usefulness of these markers, their role remains controversial. Aim: The purpose of the study was to investigate the expression of TOP2A, EZH2 and paxillin in relation to classic prognostic parameters and their significance as prognostic markers in imprints of resected breast carcinomas. Methods: Imprint smears from 55 patients who underwent surgical treatment for primary carcinoma in our department between 2005 and 2006 were studied immunocytochemically with the use of TOP2A, EZH2 and paxillin antibodies. Results: The expression of TOP2A correlated with higher histologic grade, tumor size and negative PR expression. High intensity staining for EZH2 expression was associated with higher histologic grade, negative ER and PR expression and positive Ki-67 expression. The expression of paxillin showed no correlation with estrogen/progesterone and HER2 expression nor with tumor grade and stage. Conclusion: Our data indicate that TOP2A and EZH2 expression are related to a more aggressive tumor phenotype. The expression of paxillin failed to correlate with any of the studied clinicopathologic factors. Further studies are needed to verify these results.

Key words: TOP2A; EZH2; Paxillin; Tumor markers; Breast cancer.

Introduction

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer deaths among women in Western societies. Prompt diagnosis and selection of appropriate treatment play an important role in reducing mortality [1]. In order to plan specific therapies several prognostic/predictive markers have been evaluated over the last years [2]. Although molecular profiling has shown promise in refining treatment decision making, to date, immunohistochemistry remains a validated and less expensive method for the investigation of new prognostic and predictive markers [3]. In view of this notion the immunohistochemical expression of topoisomerase II alpha (TOP2A), zeste homologue 2 (EZH2) and paxillin has recently gained increasing attention. TOP2A IIa is a key enzyme in DNA replication and the polycomb group protein enhancer of EZH2 is a major component for the maintenance of cell identity and cell cycle regulation [4, 5]. Both these factors have been proposed as potential markers for targeted therapy [6, 7]. Paxillin is a focal adhesion protein that regulates various biologic pathways such as cell migration and proliferation [8]. Although previous studies have commented on the clinical usefulness of these three markers, their role remains controversial. In this prospective study we examine the association between TOP2A, EZH2 and paxillin with other clinicohistopathological parameters and discuss the clinical implications of our findings.

Materials and Methods

Imprint samples were obtained from 55 patients who underwent surgery for breast cancer immediately after tumor removal in the operating room. Mean age of the patients was 56.7 years old at the time of diagnosis. Imprint smears were taken from different areas of macroscopically estimated breast carcinoma. We prefer to use imprint smears instead of paraffin-embedded tissue sections, as the latter present a lot of difficulties regarding immunoreactivity. Depending on the thickness of the section, there will always be a number of cells sliced or overlapped, thus leading either to false low or false high immunoreactivity, respectively [9-11]. Furthermore, tissue fixation and to a lesser degree tissue processing are potential causes of variation in the reproducibility of immunohistochemical staining [12]. Besides that, in cytologic preparations, the cells are whole, a large surface of the tumor is sampled and tissue is preserved for subsequent pathologic and molecular analyses [11, 13]. Its now firmly established that a wide variety of markers can be applied on cytologic preparations and that immunocytochemistry correlates well with immunohistochemistry [14-16]. After air drying, smears were fixed in buffer formalin 5% for 20 min and stored at ~7°C until used for an immunocytochemical procedure. All histological

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Statistical analysis

A standard statistical software package SPSS (SPSS Inc, Chicago IL) was used in the analysis. Descriptive statistics were calculated for all variables. The chi-square test or Fisher’s exact test as appropriate, was used to examine the association between TOP2A, paxillin and EZH2 expression and the steroid hormones, c-erbB-2, EGFR, p53 and Ki-67 status, as well as the correlation of the former markers with tumor type, grade and stage. The one-sample Kolmogorov-Smirnov test was used to test if a variable was normally distributed. All data were normally distributed, and the association between TOP2A, paxillin and EZH2 expression and patient age and tumor size was analyzed by two independent cytologists. In cases where staining was heterogeneous in the slide examined fields included those with the highest and those with the lowest percentage of stained cells. The immunostaining for each protein was determined as positive or negative. Staining was interpreted as positive when >10% of the tumor cells showed cytoplasmatic or nuclear staining.

Results

Mean age of the patients was 56.7 years old (SD ± 13.4 years) during the time of diagnosis. Tumor characteristics are presented in Table 1. Immunocytochemical analysis revealed that 32 (58.2%) patients were positive for paxillin expression, 35 (74.5%) out of 47 tested patients were positive for TOP2A expression and nine (16.4%), 11 (20%) and 14 (25.5%) patients were categorized as having high, moderate and weak staining, respectively, for EZH2 expression. Ki-67 expression and patient age and tumor size was analyzed with the Student’s t-test and with the one-way ANOVA with post-hoc LSD analysis; p values less than 0.05 were considered statistically significant.

Table 1. — Tumor characteristics

<table>
<thead>
<tr>
<th>Tumor size (mean ± SD)</th>
<th>2.3 ± 1.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological type I, number (%)</td>
<td>46 (83.6%)</td>
</tr>
<tr>
<td>Invasive</td>
<td>9 (16.4%)</td>
</tr>
<tr>
<td>Histological type II, number (%)</td>
<td>50 (90.9%)</td>
</tr>
<tr>
<td>Ductal</td>
<td>5 (9.1%)</td>
</tr>
<tr>
<td>N stage, number (%)</td>
<td>30 (54.5%)</td>
</tr>
<tr>
<td>NO</td>
<td>14 (25.5%)</td>
</tr>
<tr>
<td>N1</td>
<td>6 (10.9%)</td>
</tr>
<tr>
<td>N2</td>
<td>5 (9.1%)</td>
</tr>
<tr>
<td>N3</td>
<td>6 (10.9%)</td>
</tr>
<tr>
<td>Tumor grade, number (%)</td>
<td>3 (5.5%)</td>
</tr>
<tr>
<td>1</td>
<td>25 (45.5%)</td>
</tr>
<tr>
<td>2</td>
<td>27 (49.1%)</td>
</tr>
<tr>
<td>3</td>
<td>19 (34.5%)</td>
</tr>
<tr>
<td>4</td>
<td>13 (23.6%)</td>
</tr>
<tr>
<td>Positive tumors for [number (%)]</td>
<td>43 (78.2%)</td>
</tr>
<tr>
<td>ER</td>
<td>37 (67.3%)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (10.9%)</td>
</tr>
<tr>
<td>HER2</td>
<td>5 (9.1%)</td>
</tr>
<tr>
<td>EGFR</td>
<td>23 (41.8%)</td>
</tr>
<tr>
<td>p53</td>
<td>27 (49.1%)</td>
</tr>
<tr>
<td>Ki-67</td>
<td>35 (65.5%)</td>
</tr>
</tbody>
</table>

Negative PR expression (48.6% vs 8.3%, p < 0.05). High intensity staining for EZH2 expression was associated with higher histologic grade (88.9% vs 21.4%, p < 0.05), negative ER and PR expression (55.6% vs 7.1% and 66.7% vs 7.1% respectively, p < 0.05) and positive Ki-67 expression (77.8% vs 7.1%, p < 0.05) (Table 2). The expression of paxillin failed to correlate with estrogen/progesterone and HER2 expression as well as with tumor grade and stage.

Discussion

This prospective study evaluated the role of the immunocytochemical expression of three different novel markers in invasive breast carcinomas.

TOP2A is a key enzyme in DNA replication which catalyzes the unwinding of DNA by inducing single-stranded breaks on both DNA strands [20]. Considering the pivotal role of this enzyme in the modification of DNA topology it would appear logical to assume that TOP2A overexpression should correlate with high cell proliferation rate. Although this study revealed a strong correlation between TOP2A expression and tumor grade in several countries, including ours, the mitotic count, a well established proliferation index is incorporated into the tumor grading systems [21] no correlation was found with Ki-67 expression. This discrepancy may be the result of the small sample size of this study. Probably for the same reason, although we showed a significant association with PR-
negative tumors, no correlation was found with ER-negative tumors. Overall, it appears that TOP2A overexpression is related to a more aggressive tumor phenotype [22, 23]. Furthermore, in addition to its role as a proliferative and subsequently possibly prognostic marker, TOP2A has been proposed as a potential molecular target of several chemotherapy agents, including anthracyclines. Nonetheless, to date, its role as a predictive biomarker for chemotherapy remains controversial [24].

The polycomb group protein (PcG) enhancer of EZH2 is a major component for the maintenance of cell identity and cell cycle regulation [25]. Previous studies have shown that EZH2 promotes cell proliferation and tumor progression [26]. In this study we showed that the expression of EZH2 was strongly associated with increased tumor cell proliferation (as indicated by the Ki-67 expression) and higher tumor grade. These findings are indicative of the aggressive biologic behavior of EZH2 positive tumors and indirectly suggest the possible role of EZH2 overexpression in local tumor invasion and possible distant metastases. Due to lack of data no survival analysis was done, nevertheless according to previous published studies although EZH2 expression was inversely correlated with prognosis it does not appear to be an independent prognostic factor [27]. Furthermore we found that EZH2 overexpression was negatively correlated with ER and PR expression. Although previous investigators have also documented this association between EZH2 expression and hormone receptor status its role in oncogenesis remains largely unknown [28]. We should also highlight that this increasing interest regarding PcG proteins including EZH2 is also derived from the recently published studies regarding their potential role as markers for targeted therapy [7, 29].

Paxillin is a phospho-tyrosine-containing protein which is located at specific cell structures, called focal adhesions sites [30]. It is the member of a family of proteins that also contains hic-5 and leupaxin [31, 32]. Paxillin has several binding sites for other proteins with which it interacts into complexes able of transmitting signals downstream of integrins. The N-terminal half of paxillin contains several peptide sequences, such as the LD motifs, which serve as a docking site for various actin-binding and signaling proteins [33]. The C-terminal half contains the LIM domains, sequences that play an important role in the binding of paxillin to the focal adhesion sites [34].

Paxillin regulates various biological events such as cell migration and proliferation. Despite the extensive research to date, the precise function of paxillin remains elusive [35]. Although many reports implicate paxillin as a positive regulator of motility some investigators have published opposite results suggesting that paxillin could in fact inhibit cell motility [36, 37]. In the same manner the role of paxillin in breast cancer remains controversial. A study by Vadlamudi et al in human breast cancer cells demonstrated an increase in paxillin expression with HER2/HER3 pathway and grade 3 breast cancer tumors [38]. Similarly in a recent report by Hicks et al. paxillin expression correlated well with HER2 amplification, but failed to show any association with tumor grade [39]. On the other hand Madan et al., although also failing to show any correlation between paxillin and tumor grade, found no association between paxillin and HER2 expression [40]. Interestingly, however, the latter researchers demonstrated that high paxillin expression was associated with lymph node negative status and thus less aggressive forms of breast cancer. In agreement with the previous studies we failed to show any association between paxillin and estrogen/progesterone expression as well as between paxillin and HER2 expression or tumor grade and stage. We assume that the reasons for these discrepancies could be the relatively small number of patients that were enrolled in these studies and the analysis of a heterogeneous group of breast neoplasms.

In conclusion, we demonstrated a significant association between EZH2 and TOP2A expression with unfavorable prognostic markers such as higher tumor grade. These data indirectly support the possible prognostic role of these two markers. On the other hand this study failed to show any correlation between paxillin and other clinicopathologic factors. Further studies are needed to confirm our results and help us better understand the biologic role and possible clinical implications of these markers.

### References


The value of TOP2A, EZH2 and paxillin expression as markers of aggressive breast cancer: relationship with other prognostic factors


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The chemosensitivity of nodal metastases in recurrent epithelial ovarian cancer


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Summary

Purpose: In this study, we compared second-line chemotherapy effects of nodal metastases with other metastases sites. Methods: The medical records of 44 women with recurrent ovarian cancer who received second-line chemotherapy were retrospectively reviewed. Results: Median age at the time of second-line chemotherapy was 55 years (range: 31-74). Recurrent sites were as follows: 29 patients had a solitary site (abdominal cavity: 8; lymph node: 3; pelvic cavity: 10; liver: 4; lung: 4) and 15 patients had multiple sites (in total, the response rate was 30% (CR: 8, PR: 5). The response rate in sensitive cases was 50% vs 5% vs 5% p = 0.002. However, age, chemotherapy regimen, histologic type and number of diseases were not related with chemotherapy effect. In all diseases, response rate tended to be higher in lymph node disease than in the others (44% vs 27%). In both sensitive and refractory/resistant cases, response rate tended to be higher in lymph node disease. Conclusion: The response rate for lymph node diseases tended to be relatively high. Further study analyzing survival will be required to conclude the chemotherapy effect.

Key words: Second-line chemotherapy; Recurrence; Lymph node; Recurrent site.

Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecologic malignancy, accounting for 7,000 new diagnoses and 4,000 deaths annually in Japan. Patients are usually treated with cytoreductive surgery, followed by platinum and paclitaxel chemotherapy. The initial response rate to standard treatment exceeds 70% [1]. Despite initial high responses, the majority of cases experience relapse, with a median disease-free interval of 18 to 24 months. Some retrospective studies demonstrated a survival benefit for patients undergoing optimal secondary cytoreductive surgery [2-8]. Based on NCCN guidelines, secondary cytoreductive surgery may be considered as a treatment option for clinically focal recurrence after a disease-free interval > 6 months. Recently, retrospective studies have shown that secondary cytoreductive surgery for isolated nodal recurrence is effective [9-12]. Morice et al. reported that nodal metastases of EOC are chemoresistant lesions [13]. However, Blanchard et al. reported that good chemotherapy response rates could be obtained in recurrent nodal metastases [10]. Thus, it is controversial if chemotherapy is effective for lymph node disease.

Cancer consists of founder cancer cells and stroma including blood and lymph endothelial cells, inflammatory cells, immunocytes and macrophages, and fibroblasts. Recently, the role of stroma is thought to be associated with tumor progression including invasion or metastasis as well as response to therapy [14-16]. In addition, the chemotherapy effect is thought to be related to drug delivery status. From these findings, it can possibly be deduced that chemotherapy effects may differ among the locations of target disease. In this study, we compared the chemotherapy effect of nodal metastases with other metastases sites.

Materials and Methods

Patients

We retrospectively reviewed the medical records of women with recurrent ovarian cancer who received second-line chemotherapy. Recurrent cases who received surgery were excluded from the study. Forty-four patients who initiated second-line chemotherapy between February 1998 and October 2008 were included in this study. All patients underwent initial surgery and primary chemotherapy consisting of a platinum/taxane regimen. All patients were followed-up at the Department of Obstetrics and Gynecology, Keio University Hospital, Tokyo. Treatment decisions for second-line chemotherapy were usually made by the attending clinician. Data were collected on age, International Federation of Obstetricians and Gynecologists (FIGO), histologic type, the extent and outcome of surgery, prior chemotherapeutic treatments, recurrent sites, intervals between primary and secondary treatments and overall survival after receiving the second-line drug.

Definition of chemotherapy sensitivity of primary chemotherapy

Refractory, resistant, and sensitive in the first recurrence were defined as follows. Refractory: partial response, progression or stable disease on primary chemotherapy; Resistant: complete remission and relapse < 6 months after stopping primary chemotherapy; Sensitive: complete remission and relapse ≥ 6 months after stopping primary chemotherapy.

Evaluation of response of second-line chemotherapy

Response was based on two-dimensional measurements of the lesions on computed tomography (CT) or magnetic resonance imaging (MRI) images. Complete response (CR) was
The chemosensitivity of nodal metastases in recurrent epithelial ovarian cancer

defined as no evidence of disease on imaging studies, with normalization of the serum CA125 level. Partial response (PR) was defined as a > 50% decrease in tumor size. Progressive disease (PD) was defined as a > 25 increase in tumor size or the appearance of a new lesion. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The CA125 response criteria were not used; however, patients were not considered as having PR or SD if there was an increase of CA125.

Statistical analysis

The relationship between response rate or non-PD rate and chemosensitivity, age, regimen, histology, and disease site were analyzed by Fisher’s exact test. Statistical calculations were performed using SPSS Statistics software version 17.0 for Windows (SPSS, Chicago, IL).

Results

Patients

Median age at the time of second-line chemotherapy was 55 years (range: 31-74). Clinical stage and histology were as follows: clinical stage (I: 5; II: 3; III: 24; IV: 12); histology (serous: 22; clear cell: 12; endometrioid: 8; undifferentiated: 2). At first recurrence, 24 patients were platinum-sensitive and 20 patients were platinum-resistant. Recurrent sites were as follows: 29 patients had a solitary site (abdominal cavity: 8; lymph node: 3; pelvic cavity: 10; liver: 4; lung 4) and 15 patients had multiple sites. Performance status (PS) was zero-one in 40 cases, and two in four cases at second-line chemotherapy. Twenty-four patients received a platinum/taxane regimen, 13 patients received cisplatin+irinotecan, four patients received cisplatin+doxorubicin+cyclophosphamide, and three patients received irinotecan, doxil or topotecan as second-line chemotherapy.

Relationships between clinical factors and the response rate or non-PD rate

Relationships between clinical factors and the response rate or non-PD rate of second-line chemotherapy are shown in Table 1. In total, response rate and non-PD rate were 30% and 51% (CR: 8, PR: 5, SD: 9), respectively. The response rate in sensitive cases was higher than in refractory/resistant cases (50% vs 5% \( p = 0.002 \)) and the non-PD rate in sensitive cases was higher than in refractory/resistant cases (67% vs 30% \( p = 0.03 \)). However, age, chemotherapy regimen, histologic type and number of diseases were not related with the chemotherapy effect.

Relationship between chemotherapy response and recurrent site

The relationship between response rate or non-PD rate and recurrent sites is shown in Table 2. In all diseases, the response rate and non-PD rate tended to be higher in recurrent sites.
lymph node disease than in other diseases; however, this
difference was not significant (44% vs 27%, 89% vs
50%), respectively. CR was achieved in two cases of
lymph node disease and in ten cases of other disease
sites. In both sensitive and refractory/resistant cases,
response rate and non-PD rate tended to be higher in
lymph node disease. The relationship between chemother-
apy response and recurrent sites in 12 multiple recurrent
cases is shown in Table 3. In eight of 12 cases, similar
chemotherapy responses were obtained despite differing
disease sites. In four of 12 cases (case 8, 9, 10, 11),
chemotherapy responses were different among recurrent
sites. In two cases (10 and 11) chemotherapy responses
for lymph node disease were stable, however, responses
for other recurrent sites were PD.

Discussion

Recurrence of EOC are almost always fatal. For recur-
rent EOC, therapeutic options consist of surgery,
chemotherapy, and radiotherapy. The NCCN guidelines
recommend surgical treatment for clinically focal recur-
rence after a disease-free interval > 6 months. Recently,
retrospective studies have shown that secondary cytore-
ductive surgery for isolated nodal recurrence was effec-
tive [9-12]. However, there have been no high-quality
reports which compared salvage chemotherapy with
surgery for focal recurrence after a disease-free interval >
6 months. Before 1990, lymphadenectomy was often
performed at a second-look operation after chemotherapy;
positive nodes were found just as frequently at second-
look operations as in patients undergoing lymphadenec-
tomy at primary surgery [17-19]. Recently, Morice et al.
examined the rates of nodal involvement in 205 EOC
patients and reported that the rates of nodal involvement
in patients who underwent lymphadenectomy prior to or
after chemotherapy were not statistically different [13].
These findings may indicate that chemotherapy may have
little effect against the retroperitoneal lymph nodes
metastases. In contrast, Banchard et al. reported that a
good response rate could be obtained for lymph node
metastasis (11 CR out of 20 treated patients) [10]. In this
study, response rate and non-PD rate for lymph node dis-
cases were 100% and 100% for sensitive cases, and 0%
and 80% for refractory/resistant cases, and the chemother-
apy effect for lymph node disease tended to be better than
that for other recurrent sites.

In contrast, response rate and non-PD rate for liver
diseases were 33% and 33% for sensitive cases, and 0%
and 29% for refractory/resistant cases. Kusumoto et al.
examined the chemosensitivity of 16 pairs on samples
obtained simultaneously from primary and metastatic
lesions of clinical gastric cancer by in vitro chemo-
sensitivity test (succinate dehydrogenase inhibition test)
and reported that the lymph nodes were more chemosen-
sitive to carboploone, doxorubicin, mitomycin C, cis-
platin, aclacinomycin A and 5-FU, while the liver was
less sensitive than the primary lesions to carboploone,
doxorubicin, mitomycin C, cisplatin, aclacinomycin A
and 5-FU [20]. These findings are concordant with the
findings of this study.

The effect of chemotherapy on survival for isolated
lymph node relapse was thought to be essential to con-
clude the chemotherapy effect. However, there were only
three cases who had isolated lymph node relapse in this
study. The remaining six cases with lymph node relapse
were accompanied by other recurrent diseases. Isolated
lymph node relapse of EOC is reported to be a rare event
and its prevalence has been reported to be about 5% [5,
9-12, 21].

In conclusion, response rate and non-PD rate for lymph
node disease tended to be relatively high. Further study
analyzing survival will be required to conclude the
chemotherapy effect.

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Twelve-month follow-up detection of high-risk human papillomavirus (HPV) DNA for 93 cases with cervical intraepithelial neoplasia grade 2 or 3 (CIN 2-3) after a loop electrosurgical excisional procedure (LEEP)


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Summary

Purpose: The purpose of this study was to follow-up cervical intraepithelial neoplasia grades 2 or 3 (CIN2/3) cases after a loop electrosurgical excisional procedure (LEEP) by liquid-based cytology (LBC) and detection of HPV DNA. Methods: LEEP was performed for the first diagnosed CIN2/3 cases. Six and 12 months after LEEP, LBC and HPV DNA detection were performed. Results: The number of cases with CIN2 accounted for 64.5% (60/93) of the total cases before LEEP. Six months post LEEP, the number of cases with normal LBC and negative HPV DNA accounted for 63.4% (59/93). Cases with abnormal LBC accounted for 17.2 (16/93), and cases with persistent positive HPV DNA accounted for 11.8% (7/93). Two cases had both persistent positive HPV DNA and abnormal LBC. A vaginal intraepithelial neoplasm (VAIN2) was found in one of the HPV DNA persistent positive cases. Twelve months post LEEP, 4.3% (8/93) of the cases were HPV DNA positive. Abnormal LBC was observed in four cases (of which 2 cases were HPV DNA positive) with normal LBC and negative HPV DNA at six months post LEEP. Conclusion: HPV DNA examination is instrumental for the detection of VAIN.

Key words: Loop electrosurgical excisional procedure; Human papillomavirus; Follow-up.

Introduction

Cervical cancer is the second malignant tumour threatening the health of women globally. Treatment of patients with cervical intraepithelial neoplasia grades 2 or 3 (CIN 2-3) is the most important approach to prevent the occurrence of late-stage cancer. The loop electrosurgical excisional procedure (LEEP) is the main operation for patients with CIN2/3 and previous studies showed that the curative rate of LEEP was up to 67-90% [1-4]. Follow-up examinations after operation include cytology and colposcopy. High-risk HPV has been recognized as a reason for cervical cancer [5]. With the development of the Hybrid Capture II (HCII) technique, detection of HPV DNA has been introduced in the follow-up examinations after surgery is performed for CIN patients. To evaluate the role of HPV DNA detection in follow-up examinations, we performed a 12-month follow-up examination with both liquid-based cytology (LBC) and HPV DNA detection for the patients who underwent surgery from November 2006 to January 2008.

Materials and Methods

Subjects

LEEP was performed for the first diagnosed CIN2/3 cases with the lesion areas being less than 50% of the cervix. All cases with LEEP were included during the study period.

Patients living in different locations were excluded from the study because follow-up examinations could not be performed for these patients. A total of 132 cases were included in the study and 93 cases were completed with follow-up examinations. This study was approved by the Ethics Board of Beijing University Third Hospital and patients were informed about the aims of the study and gave their informed consents.

LEEP

Wallech electric knife with a power of 50W was used for LEEP. Lugol’s solution was used to display the cervical transformation areas before LEEP. The complete region with cervical transformation was excised for pathological examination.

Follow-up examinations

Six months post LEEP, LBC and HPV DNA examinations were performed. Twelve months post LEEP, both LBC and HPV DNA examinations were performed for those patients with positive HPV DNA in the first follow-up examination. HPV DNA-negative patients in the first follow-up examination underwent LBC 12 months after LEEP. Biopsy was performed for those patients with either abnormal LBC or positive HPV DNA in the follow-up examination. LBC examination was performed using Surepap (TriPath Imaging Inc., Burlington, NC). HPV DNA examination was performed using the HCII method (Digene Orporation, Gaithersburg, MD).

Statistical analysis

Statistical analysis was performed with the Student’s t-test and p values < 0.05 were considered statistically significant.
Twelve-month follow-up detection of high-risk human papillomavirus (HPV) DNA for 93 cases with cervical intraepithelial etc.

Results

General information for the patients with CIN2/3 before LEEP

The average age of the patients included in this study was 37.3 ± 6.7 and the average time of giving birth was 0.9 ± 0.7. Diagnoses of CIN2/3 were made for 91 cases by abnormal cytological changes and the remaining two cases were diagnosed by HPV DNA positive results with a cytological report of “no intraepithelial lesion or malignant change”. The number of the cases with CIN2 and CIN3 accounted for 64.5% (60/93) and 35.5% (33/93), respectively. The lesion area in the patients did not exceed 50% of the total cervical areas by colposcopy examination.

Pathological observation of patients after LEEP

After LEEP, 41.9% (39/93) of the patients had similar pathological changes compared to pre-LEEP pathology, while 10.8% (10/93) of the initially diagnosed CIN2 cases were upgraded to CIN3. In contrast, 47.3% (44/93) of the patients had lower grade pathology after LEEP. Approximately 12% (11/93) of the initially diagnosed CIN3 were downgraded to CIN2. There was no invasive cervical carcinoma detected in any of these 93 cases.

Follow-up examinations six months after LEEP

LBC and HPV DNA examinations were performed for the patients six months after LEEP. Biopsy was performed for some of the patients under the direction of a colposcope. All the patients were divided into four groups based on the LBC and HPV DNA examination results. The first group contained only patients with abnormal LBC; the second group contained only patients with positive HPV DNA; the third group contained patients with both abnormal LBC and positive HPV DNA; and patients in the fourth group were normal in both LBC and HPV DNA examinations. Pathological analyses for the patients in all these four groups are shown in Table 1. Colposcopy examination was not performed for six abnormal patients due to personal reasons (pregnant or leaving the country, etc.). These six patients were involved in the late-stage examination and no CIN2 or high grade was detected.

The number of cases with normal LBC and negative HPV DNA accounted for 63.4% (59/93) six months after LEEP. The number of cases with negative HPV DNA accounted for 80.6% (75/93) of the total cases. Two cases were detected with CIN2 and one case was detected with VAIN2. The percentage of the persistent CIN2/3 after LEEP was 2.2% six months after LEEP.

Both LBC and HPV DNA examination can detect patients with CIN2 or higher grade pathological changes. The sensitivity and specificity of a single HPV DNA examination was not lower than those of a single LBC examination or combination with both LBC and HPV DNA examinations (Table 2).

Discussion

LEEP uses a thin wire loop electrode which is attached to an electrosurgical generator to excise tissue with abnormal pathological changes. During the LEEP procedure, the tip of the electrode produces super high-fre-
quency electric wave. Instant contact between the tissues and electric wave produces high heat due to absorption of the electric wave by the tissue, which achieves the purpose of incision and hemostasis. Recently, LEEP has been widely used for the treatment of the cervical precancerous lesions [6-8]. The advantage of LEEP to treat CIN2/3 is that (1) LEEP can completely remove the cervical transformed regions; (2) the samples from LEEP can be used for pathological examinations; (3) the procedure produces less bleeding; (4) the anaesthesia procedure is simple; and (5) LEEP can be easily performed in an outpatient department. Therefore, LEEP has replaced to a large extent the procedure of cold knife conisation (CKC). Previous studies have shown that the curative rate of cervical lesions by operation is approximately 67-90% [1-4]. Our studies showed that the rate of disease persistence was 2.2% after CIN2/3 patients with lesion areas less than 50% of the cervical area underwent LEEP, which is consistent with the results in the literature.

Persistent infection with HPV is one of the critical factors affecting the occurrence of persistence or recurrence of disease. Application of HPV detection in the follow-up examinations after operation displays many advantages. Some studies have shown that the changes of HPV detection results between postoperation and preoperation can predict the prognosis of persistence or recurrence of disease. High loads of HPV before operation would indicate a high chance of operation failure [9]. If the HPV can be cleared immediately after operation, the chance of operation success would be increased, otherwise the chance of operation failure would be increased due to the persistent infection with the same type of HPV [10, 11]. Because the predicative value of HPV negative is approximately 100%, researchers suggest that HPV detection be used as a single follow-up examination. For those HPV-negative patients after surgery, the intervals between follow-up examinations can be longer [12]. However, due to the fact that the operation failed in a few cases, the value of the HPV loads on the prognosis of disease persistence or recurrence in our study could not be analysed.

Cytological analysis is also an important follow-up examination. Cytological examination has higher specificity, while HPV DNA examination has higher sensitivity for the prognosis of disease [13]. Combined cytological and HPV DNA examination decreases the examination times, which is also recommended for clinical applications [14]. In our study both LBC and HPV DNA testing had a sensitivity of 100%. HPV DNA testing had a higher specificity, but was not statistically different.

Studies have shown that persistence or recurrence of disease after surgery are related to the residual tissue around the edge of the lesion, pathological changes in the glands caused by the original lesions, and multiple distribution of the lesions [15-18]. Some studies showed that cases where the cutting edge had positive pathological changes after LEEP/CKC had a higher recurrence rate when lesions remained in the cervical canal [19, 20]. When complete hysterectomy was performed for those patients with positive pathological changes in the cutting edge, only a small number of patients still had high-grade pathological changes in the cervix. This might be due to the edge thermal effect of LEEP and heating haemostasis, which further disrupts the lesions. Therefore, in the guidelines of the American Society for Colposcopy and Cervical Pathology, individual treatment should be applied for patients with a positive cutting edge in the surgical samples. Firstly, cytological analysis can be used for the follow-up examinations. However, cytology should include a sample from the cervical tube because lesions may be deeper once the new transformation regions are developed after LEEP. Secondly, for those patients with positive cutting edges in the samples from operations, diagnostic conisation can be performed. Thirdly, if it is not appropriate to perform diagnostic conisation, complete hysterectomy can be performed [21]. Lastly, previous reports showed that persistent CIN occurred after conisation for those CIN patients with a failed LEEP operation. For patients who do not want to have complete hysterectomy, partial trachelectomy can be performed and satisfactory prognosis is achieved [22]. All patients undergoing the procedure should have ten years of follow-up examinations.

Among the 93 cases investigated in this study, two patients had persistent lesions but no infiltration carcinoma was detected. One of the reasons that the operation had a high rate of success was that the lesion areas were relatively small (< 50%). In the two patients with persistent lesions, one sample from the operation had positive pathological changes in the outer edge and the other one was negative. More cases are needed in this regard.

Close follow-up examination should be performed for patients undergoing the procedure. Combination examinations should be applied for patients with high-risk disease factors. Our two patients were diagnosed six months after the operation. Previous studies show that persistence or relapse of lesions normally occurred within two years after operation. Thus, follow-up examination in the early stage is most important to prevent and detect recurrence of disease [23, 24].

It is worth noting that infection with high-risk HPV is not only related to the high grade of CIN, but also closely related to the occurrence of VAIN. During the follow-up examinations, VAIN was detected in this study. Therefore, follow-up examination should be performed for the whole lower genital tract. We also found that LBC results were negative, while HPV DNA was positive for the VAIN2 patients, indicating that HPV DNA has a higher sensitivity.Statistical analysis was not performed because the number of these cases was low.

In conclusion, persistent lesions were observed in 2.2% (9/93) of the CIN2/3 cases with LEEP treatment during the one-year follow-up with HPV DNA and LBC examinations. Both HPV DNA and LBC analyses can efficiently detect CIN2 or higher grade for post surgical patients during follow-up examinations. In addition, HPV DNA examination has a high specificity for the detection of CIN2/3.
References


Efficiency of postoperative pain management after gynecologic oncological surgeries with the use of morphine + acetaminophen + ketoprofen versus morphine + metamizol + ketoprofen

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Summary

Surgical treatment used in gynecological oncology involves acute postoperative pain which requires efficient treatment. This study covered a group of 128 patients who were randomly divided into two groups. In the postoperative period patients in group I were administered morphine subcutaneously, acetaminophen intravenously and naproxen per rectum. Patients in group II were administered morphine, naproxen, and metamizole instead of acetaminophen and ketoprofen additionally. In group I after the administration of morphine and acetaminophen 22 patients (34.37%) needed additional doses of ketoprofen. In group II 33 women (51.56%) required ketoprofen after the administration of morphine and metamizol (N1 = 22 vs N2 = 33, p < 0.05). The use of metamizol with morphine (without ketoprofen) gave worse analgesic results than acetaminophen with morphine, but the combination of morphine, acetaminophen and ketoprofen or morphine, metamizol and ketoprofen gave satisfactory analgesic results.

Key words: Postoperative analgesia; Morphine; Acetaminophen; Metamizol; Ketoprofen; Genital carcinomas.

Introduction

The foundation of the treatment process for carcinomas of the female genitals is the surgery where the main objective is maximum cytoreduction. It is very often connected with extensive surgery during which not only appendages and the uterus are removed, but also lymph nodes, the greater omentum, the appendix and sometimes sections of the intestines. These operations belong to category III and IV of surgeries and involve significant or extensive tissue injuries, which in turn involves acute postoperative pain which requires an efficient treatment process and appears when intraoperative analgesia stops working [1]. Acute or uncontrolled postoperative pain may cause persistent postoperative pain and complications. Efficient analgesia, apart from patient satisfaction, reduces the time of hospitalization and enables earlier rehabilitation [2, 3].

Basic pharmaceuticals used to overcome pain after gynecological surgeries of the third and fourth category include: weak or strong opioids (tramadol, pethidine, morphine), metamizol, ketoprofen and acetaminophen [4].

The aim of the research was to evaluate the efficiency of the management schemes of postoperative pain in women after gynecologic oncological surgeries.

Materials and Methods

The study covered a group of 128 patients aged from 42 to 82 years who underwent surgeries between 2007-2009 at the Department of Gynecology of the Regional Hospital in Kalisz due to malignant carcinomas of the genitals: cervix carcinoma, endometrial carcinoma, ovarian carcinoma. Each patient underwent laparotomy, accompanied by an intraoperative examination in the instances of ovarian carcinomas.

The scope of each surgery depended on the type of carcinoma. For cervix carcinoma Wertheim’s procedure was performed, for endometrial carcinoma – extended removal of the uterus together with lymphadenectomy, for ovarian carcinoma – maximum cytoreduction together with the removal of the greater omentum and in one instance also removal of sections of the small intestine.

The patients were randomly divided into two groups (64 patients in each group).

In the postoperative period and on the day of operation patients in group I were administered morphine subcutaneously (SC) in the dose of 1 mg per 10 kg of body mass every four hours, 1 g of acetaminophen intravenously (IV) every six hours and from the first day after the operation 500 mg of naproxen per rectum in suppository form, per rectum every 12 hours. During the whole hospitalization period, the pain intensity level was checked by means of the pain intensity numeric rating scale (NRS; 0-10), where 0 indicates no pain, 5 – moderate pain and 10 – the worst pain that can be imagined. In the instances of pain rated 5 or more, patients were additionally administered 100 mg of ketoprofen IV.
On the day of operation patients in group II were administered morphine SC in the following dose: 1 mg per 10 kg of body mass every four hours, 1 g of metamizol IV every six hours and from the first day after the operation 500 mg of naproxen per rectum every 12 hours. In the instances of pain rated 5 or more, patients were additionally administered 100 mg of ketoprofen IV.

Results

The average age of patients was 68 years. The hospitalization period lasted between five and seven days (mean 5.7 days). On the day of surgery and prior to administration of the first analgesics 48 patients in group I rated their pain at 8 on the scale, 12 patients rated the pain at 7, and four at 6. After administration of morphine and acetaminophen the pain eased off in all patients but 22 still rated it at 6 on the scale. Thus it was necessary to provide these patients with additional doses of ketoprofen IV. Other patients from group I rated the pain at 4 after being administered morphine and acetaminophen. On the first day after the surgery ten patients from group I who rated the pain at 6 and were administered ketoprofen IV. The other 54 patients rated the ailments at 4 and were routinely administered naproxen per rectum. On the second day after the surgery four patients required administration of ketoprofen, and on the third day two patients. On the fourth day no patient required any additional analgesics.

On the day of the surgery 50 patients in group II rated the pain at a score of 8 and 14 rated it at 7. After administering morphine and metamizol, the pain eased off in all patients but still 22 patients who were administered PCA suffered from pain rated at 6 on the scale. Therefore it was necessary to provide these patients with additional doses of ketoprofen IV. Other patients from group I who rated the pain at 4 after being administered morphine and acetaminophen. On the first day after the surgery ten patients who were administered ketoprofen IV. The other 54 patients rated the ailments at 4 and were routinely administered naproxen per rectum. On the second day after the surgery four patients required administration of ketoprofen, and on the third day two patients. On the fourth day no patient required any additional analgesics.

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Not only the efficiency of analgesics was observed but also side-effects, patients’ satisfaction and the influence on surgical effects. The superiority of CEA over PCA was proved as far as relieving pain was concerned. However, patients who were administered CEA suffered from intense pruritus.

Comparison of the use of patient-controlled analgesia by means of PCA with patient-controlled epidural analgesia (PCEA) after gynecologic oncological surgeries was made by Chen et al. [6]. They did not report any superiority of PCEA over PCA in oncological patients but better pain relieving effects after the application of PCEA.

Hudcova et al. [7], Bell et al. [8] as well as Pearl et al. [9] studied the efficiency of analgesics by means of opioids administered in various ways. Hudcova et al. [7] reported better control of pain in patients being administered PCA than in patients being administered conventional analgesics (“on request”). However, higher consumption of morphine was reported as well as intense pruritus with the use of PCA. In their random study, Bell et al. [8] did not report any difference as far as analgesic effects and patients’ satisfaction were concerned in any group in which opioids were administered, either in the PCA system or intravenously or subcutaneously. Similarly to Hudcova et al. [7], Bell et al. [8] reported higher consumption of pharmaceuticals and the occurrence of pruritus in the group with PCA. Pearl et al. [9] studied the efficiency of early (since the first 24 hours) oral application of morphine and proved no difference as far as pain relieving effects and side-effects were concerned between the oral and intravenous PCA system with the application of morphine.

Numerous side-effects of opioids make researchers look for new analgesic treatment schemes and application of non-opioid pharmaceuticals in multimodal analgesia which makes use of the possibility of multidirectional inhibition of nociception as well as modulation of pain-related information flow [10, 11]. Mugabure Bujedo et al. [12] as well as Buvanendran et al. [13] proved that multimodal analgesia enables convalescence and first of all reduces demand for opioids, limiting side-effects typical for them. Many researchers reported the efficiency of the application of non-steroid anti-inflammatory drugs in multimodal analgesia, as well as metamizol and acetaminophen administered intravenously, both in combination with opioids and without [14-16]. McNicol et al. [17] studied the usefulness of the application of non-steroid anti-inflammatory drugs and acetaminophen together with opioids or without them in pain resulting from

<table>
<thead>
<tr>
<th>Group</th>
<th>Day of operation</th>
<th>First day</th>
<th>Second day</th>
<th>Third day</th>
<th>Fourth and following days</th>
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<td>I</td>
<td>34.37 (N 22)</td>
<td>15.62</td>
<td>6.25</td>
<td>3.12</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>51.56 (N 33)</td>
<td>21.87</td>
<td>9.37</td>
<td>4.69</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 1.—Percentage of patients, in each group and day, suffering from pain rated > 4 points in NRS, requiring the administration of additional doses of ketoprofen, [%].
malignant carcinomas. However, the results obtained were ambiguous and did not allow any final conclusions to be formulated.

Analgesic treatment after gynecologic oncologic surgeries applied by us and presented in this paper was compliant with the rules of multimodal analgesia, gave satisfactory results in the form of inhibition of very acute pain and at the same time allowed many side-effects connected with the application of only one group of medications to be avoided.

Conclusions
The combination of morphine, acetaminophen and ketoprofen or morphine, metamizol and ketoprofen gives satisfactory analgesic results even when it comes to operations belonging to category III and IV of surgeries.

The use of metamizol with morphine in the treatment scheme on the day of operation (without ketoprofen) gave worse analgesic results than acetaminophen with morphine, and the difference proved to be statistically significant ($p < 0.05$).

Application of multimodal analgesia prevents side-effects from appearing when only one group of medication is administered.

References


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Multivariate analysis by Cox proportional hazard model on prognosis of patient with epithelial ovarian cancer

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Summary

Purpose of investigation: To evaluate the influence of various clinicopathological and biochemical factors on the survival of patients with epithelial ovarian cancer (EOC) after radical resection. Methods: A retrospective analysis was made for 183 cases of epithelial ovarian cancer treated from January 1997 to January 2001. Six clinicopathological factors, including menopause, histological type, histological grade, lymph node metastasis, FIGO stage and chemotherapy that could possibly influence survival were selected. The expression of COX-2 and VEGF protein as two biochemical factors were detected in EOC tissues using immunohistochemical staining. Independent variables were first analyzed by univariate methods. A multivariate analysis of these variables was performed using the Cox proportional hazard regression model. Results: The ovarian cumulative survival rate was 48.71% for three years and 30.71% for five years. Univariate analysis of overall survival involving all the patients indentified five factors that were associated with a significant outcome: menopause, histological grade, FIGO stage, COX-2 or VEGF expression level (p < 0.05). The expression of COX-2 was positive in 140 (76.5%) of these 183 cases, but was not associated with menopause, histological type, histological grade, lymph node metastasis or FIGO stage. Median survival time was 24.56 months for the patients with COX-2 positive expression, and 47.52 months for those with COX-2 negative expression (p < 0.05). VEGF protein overexpression was examined in 117 (63.93%) of all 183 cases, and was associated with lymph node metastasis (p < 0.05), but not associated with menopause, histological grade, histological type or FIGO stage. The median survival time was 23.36 months for the patients with VEGF detected expression, and 42.09 months for those with no VEGF detected expression (p < 0.05). When the interactive effects of these factors were taken into account, COX-2 expression, FIGO stage, VEGF expression and histological grade were the four most important prognostic factors by multivariate analysis using the Cox proportional hazards model. Risk of death for the patients with COX-2 positive expression was 2.8 times than that with COX-2 negative expression, and for FIGO stage, VEGF expression and histological grade, risk of death was 2.2, 2.1, and 1.84 times, respectively. Conclusion: COX-2 expression, FIGO stage, VEGF expression and histological grade are the most important prognostic factors for EOC after curative resection.

Key words: Ovarian cancer; Clinical pathological factors; COX-2; VEGF; Prognosis; Cox’s proportional hazard regression model.

Introduction

Ovarian cancer is one of three gynecologic malignancies. Although current treatment of ovarian cancer entails a combination of surgery and chemotherapy, the prognosis has not changed. The 5-year survival rate is still 20%–30%. Thus it is necessary to research and analyze the operative prognosis factor and to entail suitable methods to improve prognosis. Recently early diagnostic surveillance of disease and evaluation of prognosis has become an important subject and has achieved some advancement [1].

The prognosis of ovarian cancer is difficult and complex. Clinicopathological and biochemical factors are more strictly related to prognosis [2]. Many studies have noted that poor prognosis is associated with highly malignant biochemical characteristics and behavior [3-5]. In addition clinicopathological and biochemical parameters can reflect and express the biologic behavior of ovarian cancer systematically, especially biochemical parameters which have more clinical value [5].

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Materials and Methods

Clinical materials
A selected 183 patients with EOC underwent surgery at the Chinese Medical University Affiliation Shengjing Hospital between January 1997 and January 2001. All patients were diagnosed by the pathologist. Median age was 43.15 (range 20-74). All patients were not treated by chemotherapy or radiotherapy before surgery, and 147 of 183 cases were followed-up completely. All tissues were fixed in 10% formalin and paraffin-embedded according to standard procedures.

Biological factors
Immunohistochemical examination was performed for determination of expression of COX-2 and VEGF on ovarian epithelial cancer tissue samples.

Main reagent
Rabbit anti-human COX-2 monoclonal antibody, rabbit anti-human VEGF monoclonal and S-ABC were used according to the manufacturer’s instructions (Boster Co.).

Immunohistochemical studies
Immunohistochemical staining with antibodies to COX-2 and VEGF was performed using a standard protocol according to laboratory manual instructions. Staining steps were carried out strictly according to standard procedures. The COX-2 and VEGF were heated in a microwave oven to retrieve masked antigens. Colon carcinoma sections showing immunoreaction were scored as positive. PBS replaced the first biotin as negative.

For the assessment of COX-2 and VEGF expression levels, the staining intensity and the percentage of stained cells were analyzed. Staining intensity was scored as 0 (negative), 1 (weak), 2 (medium), or 3 (strong), and percentage of stained cells was scored as 0 (0), 1 (< 30%), 2 (30%-60%), 3 (> 60%); both combined, 0-1 was negative, and 2 or more was positive.

Clinicopathological factors
1. Menopause: 94 cases were in premenopause and 89 in postmenopause.
2. FIGO stage: I + II; 72; III + IV, 111.
3. Histological grade: high = 54 cases; median and low = 129 cases.
4. Histological type: There were 120 serous cystadenocarcinomas (SCAC), 29 mucinous cystadenocarcinomas (MAC), 34 others (including 16 endometrioid carcinomas, 12 clear cell carcinomas, 4 of Wolfian duct origin cystadenocarcinomas and 2 undifferentiated carcinomas).
5. Lymph node transmission: 88 cases had involvement and 95 did not.
6. Chemotherapy: 151 cases underwent chemotherapy and 32 did not.
7. Quantified clinicopathological and biochemical factors are shown in Table 1.

Follow-up
In the 183 EOC patients, 147 were followed-up completely, and 36 were lost. The follow-up cases had the same survival time.

Statistical analysis
The χ² test was used to analyze the distribution of COX-2 positive and VEGF positive cases according to the clinicopathological features. Median and life tables were computed using the product-limit estimate by the Kaplan-Meier method. Comparison of survival time of both (or more groups) was analyzed by the Wilcoxon method or Kruskal-Wallis test. Cox’s proportional hazard regression model was used to analyze the role of the clinicopathological and biochemical parameters (COX-2 and VEGF).

Results
COX-2 and VEGF expression in EOC
COX-2 and VEGF immunostaining was observed mainly in the cytoplasm of tumor cells. One hundred and forty cases (76.5%) were scored as COX-2 positive and 117 (63.93%) were scored as VEGF positive (Figures 1 and 2).

Correlation with clinicopathological parameters
Table 2 shows the distribution of positive COX-2 and VEGF according to clinicopathological characteristics. COX-2 positive was not distributed differently according to menopause, FIGO stage, histological grade, lymph node transmission, or histological type. The expression rate of VEGF was 68.18% and 60.0% for lymph node transmission and no lymph node transmission, respectively. The difference was significant. However, VEGF posi-
The 3-year cumulative survival rate was 19.11% for patients with tumors positive for COX-2 and 69.11% for negative tumors. The 3-year and 5-year survival rate for patients with negative tumors was higher than for patients with positive tumors.

In 147 follow-up cases, patients with tumors negative for VEGF had an increased median survival time (42.09 months, n = 56) compared to patients with tumors positive for VEGF (23.36 months, n = 91). The comparison survival was significantly different. Figures 3 and 6 show the 3-year and 5-year survival curves according to VEGF status in EOC cases. The 3-year cumulative survival rate was 18.75% for patients with tumors positive for VEGF and 59.75% for negative tumors. The 3-year and 5-year survival rate for patients with negative tumors was higher than for patients with positive tumors.

**Univariate analysis**

We compared the survival among all patients with EOC by univariate analysis according to the six clinicopathological parameters (menopause, FIGO stage, histological grade, lymph transmission, histological type, and chemotherapy) and two biochemical parameters (COX-2, VEGF). Significant prognostic markers in univariate analysis were menopause, FIGO stage, histological grade, histological grade, COX-2 positive and VEGF positive. Lymph node transmission, histological type, and chemotherapy were not significant (Table 3).

Three clinicopathological factors were selected: menopause, FIGO stage, and histological grade. Figure 7 shows the 5-year Kaplan-Meier curves for each factor. Figure 7A shows the different survival curves for patients in premenopause (median survival, 34.9 months) and postmenopause (median survival, 25.7 months). Postmenopausal patients had a 5-year survival rate of 67.61%, whereas premenopausal patients had a 5-year survival rate of 27.61%.

Figure 7B shows the different survival curves for patients with earlier FIGO stage (median survival, 47.18 months) and later stage (median survival, 20.52 months). Early-stage patients had a 5-year survival rate of 67.71%, whereas premenopausal patients had a 5-year survival rate of 47.18%.

Figure 7C shows the different survival curves for patients with high diffusion (median survival, 46.36 months) and median and low cases (median survival, 23.04 months). High diffusion patients had a 5-year survival rate of 67.21%, whereas the median and low diffusion patients had a 5-year survival rate of 38.18%.

**Multivariate analysis**

We used a multivariate regression analysis based on Cox’s proportional hazard regression model to test the independent value of each parameter selected by univariate analysis. The variables used in Cox’s model are shown in Table 4. Expression of COX-2 was an independent value of each parameter selected by univariate analysis.
Figure 1. — Expression of COX-2 in ovarian epithelial cancer investigated by immunohistochemistry (SABC x 400).

Figure 2. — Expression of VEGF in ovarian epithelial cancer investigated by immunohistochemistry (SABC x 400).

Figure 3. — Three-year Kaplan-Meier curves to COX-2 status in ovarian epithelial cancer.

Figure 4. — Five-year Kaplan-Meier curves to COX-2 status in ovarian epithelial cancer.

Figure 5. — Three-year Kaplan-Meier curves to VEGF status in ovarian epithelial cancer.

Figure 6. — Five-year Kaplan-Meier curves to VEGF status in ovarian epithelial cancer.
Multivariate analysis by Cox proportional hazard model on prognosis of patient with epithelial ovarian cancer

prognostic factor for poor survival (relative risk (RR) 2.825; 95% CI 1.506 to 5.299). Other independent prognostic factors associated with poor prognosis were FIGO stage (RR, 2.292), expression of VEGF (RR, 2.051), histological grade (RR, 1.873).

Discussion

**COX-2/VEGF expression in EOC**

COX-2 is the rate-limiting enzyme in prostanoid biosynthesis and is involved in tumor progression. Several functions of inducible COX-2 have been described in the biology of various carcinomas: increased cell proliferation [9], inhibition of apoptosis, stimulation of angiogenesis, as well as inhibition of immnosurveillance [10]. VEGF can stimulate normal epithelial cell increases as well as promote some tumor cell growth.

Numerous studies show COX-2 is rapidly inducible when cells are stimulated and plays a role in pathology, physiology, and procession, including inflammatory processes as carcinogenesis [11]. COX-2 and VEGF overexpression have been described in various malignancies. Trifan and Hla showed COX-2 plays a role in carcinogenesis [12]. Gupta et al. showed COX-2 overexpression in prostate adenocarcinoma [13].

In our study COX-2 and VEGF both overexpressed in EOC, 76.5% and 63.93, respectively. We failed to demonstrate an association between COX-2 status and any of the clinicopathological characteristics (menopause, FIGO stage, histological grade, lymph node transmission, and histological type). VEGF status did have an association with lymph node transmission, but not with menopause, FIGO stage, histological grade, and histological type. Lee et al. had results similar to ours [14]. VEGF status is associated with lymph nodes and can be a helpful marker in determining lymph node transmission.

Recent experimental evidence indicates that carcinogenesis is a multi-factoral and multi-stepped procedure [15, 16]. More than two proteins were involved and different proteins play different roles in different stages. In our studies COX-2 and VEGF both expressed cases is 95 (51.90%) and neither is 18 (9.84%). There are some studies that show COX-2 and its product, prostaglandin E$_2$ (PGE$_2$), promote carcinogenesis together. COX-2 was found to be up-regulated VEGF expression to promote the vessel [17].

![Figure 7A](image1)

Survival functions (%)

![Figure 7B](image2)

Survival functions (%)

![Figure 7C](image3)

Survival functions (%)

Figure 7. — Menopause (A), FIGO stage (B), histological grade (C) 5-year survival.
Association between COX-2 and VEGF protein expression in EOC and prognosis

In our study, patients with tumors negative for COX-2 had an increased median survival time compared to patients with tumors positive for COX-2 and increased cumulative survival time compared to patients with tumors positive for COX-2. The cumulative survival rate for COX-2 negative expression was higher than COX-2 positive expression showing that the expression of COX-2 protein is associated with prognosis in EOC patients. It could be a good parameter to determine the prognosis of ovarian cancer [18]. As is now known, COX-2 and PGE\textsubscript{2} can promote increased cells to inhibit apoptosis, enhance tumor transformation, and enhance tumor invasion, all of which can affect carcinoma prognosis.

VEGF can regulate vascular permeability and is an important mediator of vasculogenesis and angiogenesis. Our study shows the median survival time for VEGF negative-expression was longer than VEGF positive expression. The accumulation of negative VEGF was higher than that of positive VEGF showing VEGF can be a parameter for ovarian carcinoma [19].

Factors affecting surgical prognosis of EOC and future application

The research shows that the rate of three-year survival was 45.71% and the rate of five-year survival was 30.71% in the 147 cases with precise follow-up records. According to the latest reports about EOC we found that the rate of three-year survival is from 35.74% to 49.06% and the rate of five-year survival is from 25% to 40% [20, 21]. From the data we can see that although both basic research and clinical diagnosis have been improved in recent years, the prognosis shows little change, and the survival rate remains the same.

Cox’s proportional hazard regression model is a mathematical model in survival analysis which was put forward by British biological statistician D.R. COX [22]. This model is a perfect solution to the three main problems that once existed in survival analysis, and the analysis has had breakthrough progress to be a more comprehensive system. Now the COX proportional hazard regression model has become one of the most important mathematical models in survival analysis and has been applied worldwide as a multivariate analysis method [23].

Univariate analysis showed that the surgical prognosis of epithelial ovarian cancer is influenced by many factors, including menopause, FIGO stage, histological grade, COX-2 protein positive expression, and VEGF protein positive expression ($p < 0.05$). In order to remove the mixed or overlapping factors in this study, Cox’s proportional hazard regression model was used to give further multivariate analyses to the factors above. The results indicated that COX-2 protein positive expression, FIGO stage, VEGF protein positive expression, and histological grade are the four most significant factors which affect the surgical prognosis of EOC. The menopause factor in multivariate analysis was removed because its role does not appear significant when many factors have mutual influence on the surgical prognosis of EOC.

COX-2 protein positive expression is the most important factor. According to the data we can see that the COX-2 protein positive expression death risk is 2.83 times as COX-2 protein negative expression death risk. A study by Fujimoto et al. [18] found that patients with epithelial ovarian cancer who had positive COX-2 protein expression have poor prognosis, in line with our report. The reason may be that the COX-2 protein in tumor tissues has high proliferative activity and poor biological action.

FIGO stage has always been considered an important factor affecting the surgical prognosis of ovarian cancer. Indeed, Cox’s model analysis proved pathologic staging to be the second most important factor. Survival time between early stage (phase I + phase II) and advanced stage (phase III + IV) revealed significant differences ($p < 0.05$). The latter death risk is 2.29 times higher as for early stage. Research shows that the sooner EOC is pathologically staged, the better the prognosis. Ovarian cancer patients in phase I have a 5-year survival rate of about 87%, while phase III-IV patients have a 5-year survival rate of only 5-10% [24], showing that early diagnosis and treatment can improve the prognosis.

VEGF protein positive expression has been proved to be the third most important factor affecting the surgical prognosis of EOC. VEGF positive protein expression and negative expression have significant differences in the median survival period ($p < 0.05$). The former has a risk which is 2.051 times higher than for negative expression. It could be that the poor prognosis of VEGF protein positive expression is because VEGF stimulates peripheral blood vessels and growth of lymphatic endothelial cells, which plays an important role in cancer growth and metastasis. The investigation on 83 cases of Phase III ovarian cancer patients launched by Raspollini et al. [25] found that microvessel density and VEGF are directly related to survival rate, also confirmed in this study.

According to Cox’s model analysis, the importance of the histological grading factor is in fourth place. Highly differentiated EOC shows great differences in the median survival period of the medium and low differentiated period with the latter risk of death 1.87 times higher than the former. EOC histological grading has always been considered to be related to prognosis. Scorilas et al.’s [26] study confirmed that the five-year survival rate of a highly differentiated patient group was higher than the rate of the medium and low differentiated group. The results of this study are also consistent with our results in that the prognosis of medium and low differentiated EOC cases is poor.

The results mentioned above are instructive to clinical practice. The four factors (COX-2 protein positive expression, FIGO stage, VEGF protein positive expression, and histological grade), which have been confirmed to be the most influential on the surgical prognosis of EOC by COX multivariate analysis, are all related – with inherent biological characteristics and action of the tumor itself. Thus, in order to improve the surgical prognosis of EOC, it is necessary to adopt comprehensive treatment measures which use surgery as the main stay method to deal...
with EOC. In accordance with the research, we suggest that COX-2 protein positive expression is the most important factor to prognosis. Our study used immunohistochemical methods which can detect COX-2 protein expression. This method is very easy to adopt and will hopefully be applied in routine pathologic examination. Other researches have also confirmed that COX-2 selective inhibitors, e.g. NS398, have a proliferative inhibition function on human ovarian cancer cells and can induce apoptosis in ovarian cancer cells; this suggests COX-2 is likely to be an effective chemical control target in ovarian cancer and NS398 is expected to become an effective chemoprophylactic drug in ovarian cancer though further development in detailed treatment methods and measures are necessary. Furthermore, although there are many clinical pathologic factors which affect the surgical prognosis of EOC, pathologic staging is the most simple and important. Thus, emphasis on the importance of early diagnosis and early treatment of EOC can improve the prognosis. Finally, what needs to be pointed out is that there are many factors which influence the surgical prognosis of EOC besides the ones which have been analyzed in this report, and further researches on their function and significance is needed.

References

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Women’s knowledge and utilization of gynecological cancer prevention services in the Northwest of Greece

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Summary

Purpose of investigation: In Greece an organized cervical or breast cancer screening program does not exist and the population coverage is unknown. Methods: Women of all ages completed a questionnaire, which assessed women’s awareness of and participation in breast and cervical screening and human papillomavirus (HPV) vaccination. The women were randomly approached in public areas. Results: 1,012 women completed the questionnaire. 52% of the women over 39 years old had undergone mammography in the last year and 76% of the women over 20 years old had a cervical smear test within the last three years in an opportunistic basis. In addition, the likelihood of having regular mammograms was positively associated with the likelihood of having regular cervical smears. Fifty percent of the responders did not identify HPV as the cause of cervical cancer and 38% were not aware of the HPV vaccine. From the women aged 16 to 28 years old, 11% had been vaccinated against HPV and an additional 23% intended to have the vaccine in the next six months. Conclusion: Knowledge and utilization of mammography and cervical screening was quite satisfactory, although HPV vaccination coverage was low. Preventive services could be improved through the development of a plan for the information of the public and the distribution of the HPV vaccine.

Key words: Cancer; Breast; Cervix; HPV vaccine; Cytodiagnoses; Mammography.

Introduction

The effectiveness of cervical (Papanicolaou test) and breast (mammography) screening has been established. In countries where an organized, routine and widespread screening program exists like in Australia and the UK, mortality from cervical and breast cancer is considerably reduced [1, 2].

Cervical screening aims at secondary prevention which is based on the diagnosis and treatment of premalignant lesions before they progress to invasive cancer. Breast screening aims at tertiary prevention which is based on the early diagnosis and treatment of invasive disease. In Greece screening for both cancers is opportunistic and there are no reliable statistics concerning the participation of Greek women. However, in a recent paper regarding cervical cancer mortality in South Eastern European countries, it appears that the relevant frequency in Greece is the best among its neighbors [3].

Lately the hopes for reduction in the incidence of cervical cancer are focused on the newly introduced and promising HPV vaccine, which aims not at secondary but at primary prevention. The vaccine protects from the cause of cervical cancer, which is the sexually transmitted infection with certain types of HPV (16 and 18 mainly). According to studies [4, 5], it is extremely effective in preventing premalignant lesions but in order to have a major effect on mortality, a wide female population coverage is essential. In Greece the HPV vaccine was introduced in the national immunization program in 2007. However, it is provided free up to the age of 26.

The aim of this study is to provide data on Greek women’s knowledge and utilization of gynecological cancer prevention services, which could be used by policy makers for service improvement.

Materials and Methods

Respondents

The study population was comprised of randomly selected women of all ages and levels of education from the North-West of Greece. They all received a one-page questionnaire with 13 items (Table 1).

Procedure

Either of the two main researchers approached the women. Settings where the study took place were: the university campus of Ioannina, the waiting areas of one of the biggest hospitals in the region (University Hospital of Ioannina), outside the national election centers (the study was conducted during the 2009 national elections in Greece), other places like Civil Services, private offices and central markets. The women who were willing to answer were given the questionnaire to complete it without particular guidance from the researcher. Participants were assured of complete anonymity.

The aim of the questionnaire was to assess the awareness, knowledge and utilization of breast and cervical screening and HPV vaccine. Women were be asked whether they were aware of the particular prevention method and if they were utilizing it. In case they were not utilizing it, they were asked to give the main reason why in a multiple choice format. For instance, if they were not having cervical smears, they were asked “why are you not having cervical smears?” and they were given the following options: “a. Fear b. Ignorance c. I believe it does not help d. It does not concern me because of my age e. Other”. The questionnaire was concise and short so that women would not get tired or decline completing it because of lack of time.
Data analysis

Basic descriptive statistics and frequency calculations were performed on all variables. Comparisons were made using the chi-square test.

Results

Study sample

A total of 1,012 women participated, with a mean age of 39 years (range: 16-89 years). As far as the educational level is concerned, 49% (n = 496) had a higher education, 35% (n = 357) secondary, 13% (n = 132) primary, 2% (n = 23) none and 1% (n = 4) did not mention. Regarding the place, 30% (n = 303) of the questionnaires were filled in at the waiting areas of the hospital, 15% (n = 132) at the national election centers, 9% (n = 96) at the university campus and 48% (n = 481) at other public places. The main results are summarized in Table 2 and comparisons between age groups and educational levels are represented in Table 3.

Mammography

Although the majority (97%; n = 986) knew what a mammography was, only 52% (n = 529) were aware of the age women should start mammography screening (40 years). The rest chose “30 years old” (26.88%; n = 272), “20 years old” (8.7%; n = 88), “I don’t know” (8.3%; n = 84), “50 years old” (3.85%; n = 39) and “60 years old” (0%; n = 0). Age influenced the possibility of giving a correct reply to this question in a statistically significant degree. Women who did not know, were mainly under 30 years or over 60 years old (p < 0.05). Regarding the frequency of having mammography, 80.28% (n = 812) answered once a year which is in agreement with the guidelines [6], 8.7% (n = 88) did not know, 7.81% (n = 79) answered every six months, 3.26% (n = 33) every five years or over 60 years old (0%; n = 0). Age influenced the possibility of giving a correct reply to this question in a statistically significant degree. Women of any age who stated knowledge about HPV 50% 501/1012 a Pap smear in the last 3 years 76% 678/898 a Pap smear in the last 3 years 76% 678/898 Women over 39 who have had a Pap smear in the last 3 years 76% 768/1012 Women over 20 who have had a Pap smear in the last 3 years 76% 678/898 Women of any age who stated correct knowledge about HPV 50% 501/1012 Women of any age who stated correct knowledge about HPV 50% 501/1012 Women over 39 who have had a Pap smear in the last 3 years 76% 768/1012 a Pap smear in the last 3 years 76% 678/898 a Pap smear in the last 3 years 76% 678/898

Table 1. — The 13 items of the questionnaire.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Percentage</th>
<th>Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women of any age who stated knowledge about mammography</td>
<td>97%</td>
<td>986/1012</td>
</tr>
<tr>
<td>Women over 39 who have had a mammogram in the last 3 years</td>
<td>67%</td>
<td>308/458</td>
</tr>
<tr>
<td>Women of any age who stated knowledge about the Pap smear</td>
<td>99%</td>
<td>1001/1012</td>
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<td>678/898</td>
</tr>
<tr>
<td>Women of any age who stated correct knowledge about HPV</td>
<td>50%</td>
<td>501/1012</td>
</tr>
<tr>
<td>Women of any age who stated correct knowledge about the HPV vaccine</td>
<td>56%</td>
<td>568/1012</td>
</tr>
<tr>
<td>Women 16-28 who have had the HPV vaccine</td>
<td>11%</td>
<td>35/330</td>
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</tbody>
</table>

Table 2. — Main results.

<table>
<thead>
<tr>
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<th>Numbers</th>
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<tbody>
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<td>11%</td>
<td>35/330</td>
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</table>

Table 3. — Comparisons between age groups and educational levels.

<table>
<thead>
<tr>
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<th>Better respondents</th>
<th>Worse respondents</th>
<th>p value</th>
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<tr>
<td>30-60 y.o.</td>
<td>30-60 y.o.</td>
<td>&lt; 30 &amp; &gt; 60 y.o.</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>mammography</td>
<td>Primary &amp; Secondary E.</td>
<td>Higher E.</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Utilization of mammography</td>
<td>Secondary &amp; Higher E.</td>
<td>Primary E.</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Knowledge of frequency</td>
<td>22-60 y.o.</td>
<td>&lt; 22 &amp; &gt; 60 y.o.</td>
<td>0.05</td>
</tr>
<tr>
<td>Knowledge of frequency</td>
<td>Secondary &amp; Higher E.</td>
<td>Primary E.</td>
<td>0.05</td>
</tr>
<tr>
<td>Utilization of Pap test</td>
<td>Secondary &amp; Higher E.</td>
<td>Primary E.</td>
<td>0.05</td>
</tr>
<tr>
<td>Knowledge of HPV</td>
<td>&lt; 51 y.o.</td>
<td>≥ 51 y.o.</td>
<td>0.05</td>
</tr>
<tr>
<td>Knowledge of HPV</td>
<td>Higher E.</td>
<td>Primary &amp; Secondary E.</td>
<td>0.05</td>
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<tr>
<td>Knowledge of HPV</td>
<td>&lt; 50 y.o.</td>
<td>≥ 50 y.o.</td>
<td>0.05</td>
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<tr>
<td>Knowledge of HPV</td>
<td>Secondary &amp; Higher E.</td>
<td>Primary E.</td>
<td>0.05</td>
</tr>
<tr>
<td>Positive attitude</td>
<td>16-18 y.o.</td>
<td>19-28 y.o.</td>
<td>0.05</td>
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<tr>
<td>to the HPV vaccine</td>
<td>Secondary E.</td>
<td>Higher E.</td>
<td>0.05</td>
</tr>
</tbody>
</table>

* years old; † Education.
From the women over 39 years old who had undergone mammography screening one year before (n = 238), 90% (n = 214) had also had a smear test in the last three years. In contrast, from the women over 39 years old who had not undergone mammography screening one year before (n = 215), 54% (n = 117) had had a smear test in the last three years (p < 0.05).

Pap test

A high percentage (98.91%; n = 1001) of the responders declared that they knew what a Pap test was. Regarding the response to the recommended frequency for a smear test, 77.47% (n = 784) of the women answered every one to three years with a further 17.98% (n = 182) every six months and only 3.85% (n = 39) did not know, 0.59% (n = 6) every five years, and 0.1% (n = 1) every ten years. There was a significantly statistical difference in the educational level and the age (p < 0.05) between the women who knew and those who did not know. As for the two last questions of this section 75.59% (n = 678) of the women over 20 had had a cervical smear test in the last three years. Women over 60 years old and women of lower education were statistically significantly less likely to have had a Pap smear the last three years. The reasons why one quarter of the responders over 20 (n = 219) did not have a smear test were 20% (n = 39) negligence, 13.7% (n = 30) ignorance, 10.05% (n = 22) fear, 9.59% (n = 21) age, 6.39% (n = 14) hysterectomy, 5.02% (n = 11) disbelief in the benefit and 37.9% (n = 83) unspecified reason.

From the women over 39 years old who had had a smear test in the last three years (n = 331), 65% (n = 214) had also undergone mammography screening one year before. On the other hand, from the women over 39 years old who did not have a smear test in the last three years (n = 122), 20% (n = 24) had undergone mammography screening one year before (p < 0.05).

HPV-HPV vaccine

Only half (n = 501) of the responders identified HPV as the cause of cervical cancer. From the other half most of the women (35.28%; n = 357) had never heard of HPV, 13.6% (13.44%) thought it was the cause AIDS and 18 (1.78%) the cause of pneumonia. Higher education and age less than 51 years old was statistically significantly associated with knowledge of HPV (p < 0.05). Having had a recent cervical smear was also positively associated with knowledge of HPV (p < 0.05).

Regarding the recommended age for HPV vaccination, 389 (38.44%) of responders were not even aware of the vaccine, whereas 568 (56.13%) knew that the recommended age for the vaccination was from 12 to 26 years old, which is the target group according to Greek guidelines. The rest chose one to six years old (n = 28; 2.77%), above 26 years old (n = 17; 1.68%) and two to six months after birth (n = 9; 0.89%). There was a significant correlation between knowledge of the vaccine and both education and age (p < 0.05). Ignorance of the vaccine was mostly observed in women with only a primary education or over 49 years old.

The two last questions referred to the responders’ attitude towards HPV vaccination. From the women aged 16 to 28 years old (n = 330), only 10.61% (n = 35) had been vaccinated against HPV. Regarding the 294 women (89.09%) who had not been vaccinated, only 67 (22.79%) intended to have the vaccination in the next six months. The reasons for being against vaccination included ignorance 38.33% (n = 87), fear 21.16% (n = 48), other 18.94% (n = 43), age 13.22% (n = 30), and disbelief in the benefit 9.25% (n = 21). There was also a very small portion of the responders over 28 years old who were positive to being vaccinated with two women having had and eight intending to have the vaccine. Being in favor or against the vaccine was not affected by educational levels (p = 0.189).

Discussion

Since in Greece there are limited epidemiological data and no official statistics concerning cervical and breast screening, our study was an attempt to shed light on this subject.

A screening programme must achieve high population coverage in order to have an effect on mortality. High population coverage usually requires an organised setting. Examples of countries with such program especially for cervical screening are the UK, New Zealand and the Nordic countries [7]. In countries where screening is opportunistic the coverage rates are usually not high enough to influence mortality rates [8]. Surprisingly it appears from this study that despite the fact that mammography and cervical screening in Greece are opportunistic, they both have a very high percentage of population coverage. The reasons are not evident, although they might be related to the very well developed private gynecologic practice in Greece. It is considered socially and medically appropriate for Greek women to have a private appointment with their gynecologist every year. One might assume that this process is essential for the achievement of these high coverage rates, as in this annual visit the gynecologists take the smear test and recommend a mammography according to the age and history. Towards this direction an important role could also have been played by the promotion of information about breast cancer prevention on the mass media and the campaigns of non state associations. The high cervical screening participation rates could explain why Greece appears to have one of the lowest mortality rates from cervical cancer in Southern Europe [3].

Interestingly, a large number of women thought that the frequency of cervical screening was every six months. This might be due to the lack of Greek guidelines, leaving a margin for “overscreening”.

As expected the likelihood of having regular mammograms was positively associated with the likelihood of having regular cervical smears. This could mean that
there is a common motivating factor for both tests. This factor could either be the private gynecologist who in Greece has a role similar to the general practitioner/family physician for gynecological issues or the educational level. Lower education increased the risk of not utilizing the screening services. This suggests that coverage could be improved if some information regarding screening services were given to girls during the final years of primary education. The sample size in this study is not particularly large, but it is random and compares favorably to another Greek study in which 1,000 people of both sexes together were included [9].

Our questionnaire did not inquire whether the responders were sexually active because it was thought this might discourage them from completing it. So, the population coverage for cervical screening was calculated assuming that the vast majority of women over 21 years old are sexually active. This assumption was based on the fact that the mean age of sexual activity in Greece is 19.2 years [10].

As far as HPV vaccine coverage is concerned, there are no officially published data, as it was only recently introduced. Our figures are disappointing, since only 11% of the target group had been vaccinated. This is not surprising, as Greek Health authorities did not make any provision for an organized vaccination service similar to the school based programs in the UK and Australia. Apart from the ignorance of HPV and the vaccine it seems that fear triggered by media releases is another deterrent. Eventually, unfounded statements of the side-effects dispersed disbelief and mistrust to the public.

In conclusion, despite the surprisingly satisfactory results regarding the participation in mammography and cervical screening, our study highlights that there is room for improvement. It is essential that screening guidelines are published and the government settles a plan for the distribution of the vaccine and public education. Last but not least, the media, including the major TV channels, should take care to report news regarding the HPV vaccine with responsibility and extreme caution based on medical evidence.

References


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Malignant changes in adenomyosis in patients with endometrioid adenocarcinoma

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Summary

Objective: The aim of our retrospective study was to evaluate pathological changes in adenomyotic foci in hysterectomy specimens, and point out a possible mechanism of carcinogenesis in adenomyotic foci inside the myometrium. Methods: Retrospective analysis of clinical data; 219 patients were operated at our departments from 2003-2008 with the diagnosis of early endometrial cancer. Standard staging operation was used in all cases and all hysterectomy specimens were afterwards routinely analyzed. Results: Adenomyosis was found in 88 of a total of 219 hysterectomy specimens, while 205 of these 219 were affected by endometrioid adenocarcinoma. In 87 cases it coexisted with endometrioid adenocarcinoma, in one case with clear cell carcinoma and it was not found in the hysterectomy specimen affected by papillary serous carcinoma. All cases of malignant changes (n = 6) in adenomyosis were found exclusively with coexisting endometrioid adenocarcinoma: adenocarcinoma in adenomyosis was well or moderately differentiated in five cases, and poorly differentiated in just one case. Differentiation of the tumor in adenomyosis correlated with differentiation of the eutopic endometrial cancer in 50%. Hyperplastic changes like benign glandular hyperplasia, or atypical complex hyperplasia (ACH) were identified simultaneously in all cancer-positive adenomyotic foci. Conclusion: Malignant changes in adenomyosis were present in 6.8% of patients with endometrial cancer. All malignancy-positive cases of adenomyosis were associated with endometrioid adenocarcinoma of the eutopic endometrium. Interestingly, in all these cases, different stages of hyperplastic changes were also simultaneously identified. This observation suggests a similar pathway of carcinogenesis in adenomyosis as is known in estrogen-responsive endometrial cancer type I.

Key words: Hysterectomy; Myometrium; Adenomyosis; Endometrial cancer; Adenocarcinoma; Carcinogenesis.

Introduction

Endometrial adenocarcinoma and adenomyosis are hormone-dependent uterine lesions affecting the uterine corpus with increased frequency today [1-4]. The precise etiology of adenomyosis is still unknown while endometrial cancer shows two elucidated pathways of carcinogenesis [2, 3, 5, 6]. Case reports describe de novo malignant transformation inside adenomyotic foci while the eutopic endometrium was unaffected [7-11]. On the other hand, simultaneous malignant changes of the eutopic endometrium and adenomyosis have been described as well [12-15]. Adenocarcinomas involving adenomyosis are characterized by frequent preceding estrogen use, low histological grades, and excellent prognosis [15]. According to some studies coexisting adenocarcinoma arising from adenomyosis did not worsen the prognosis of the disease [6, 16], but is more often connected with deep myometrial invasion [13]. The distinction between true myoinvasion and malignant changes inside adenomyosis is very difficult, however crucial since the patient can be upstaged and inappropriately treated [17].

Materials and Methods

A total of 219 patients were operated in our department between the years 2003 and 2008 with the diagnosis of early endometrial cancer. The average age was 61.4 years (45-85) and the average body mass index (BMI) 31.4 (17.1-57.3). Standard staging operation was used and all hysterectomy specimens were afterwards routinely analyzed in the Department of Pathology. The formalin-fixed uterus was cut in a standard manner and the whole specimen was histologically analyzed. Isolated malignant changes in adenomyosis were strictly distinguished from the secondary invasion of endometrial cancer. Adenomyosis was defined as the presence of endometrial glands and stroma in the myometrium, disconnected from the native endometrium and fulfilling the criteria of Colman and Rosenthal [18].

Results

Of the 219 patients operated for early endometrial cancer, endometrioid adenocarcinoma was confirmed in 205 cases, clear cell carcinoma in ten cases, and papillary serous carcinoma in four cases. Adenocarcinoma was found in 88 cases of 219 specimens (40.2%); in 87 cases it coexisted with endometrioid adenocarcinoma, in one case with clear cell carcinoma, and it was not found in the hysterectomy specimen affected by papillary serous carcinoma (Table 1).

The histopathological changes in adenomyosis in our cases were as follows: common structure - 17 patients...
Table 1. — Presence of adenomyosis in different types of endometrial cancer (n = 88).  

<table>
<thead>
<tr>
<th>Endometrial cancer</th>
<th>Adenomyosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrioid adenocarcinoma</td>
<td>87 (97.8%)</td>
</tr>
<tr>
<td>Clear cell carcinoma</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Papillary serous carcinoma</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2. — Histopathological changes of adenomyosis in patients with endometrioid adenocarcinoma (n = 87).  

<table>
<thead>
<tr>
<th>Pathological changes</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glandular hyperplasia without atypia</td>
<td>25 (28.7%)</td>
</tr>
<tr>
<td>Atrophy</td>
<td>21 (24.1%)</td>
</tr>
<tr>
<td>Atypical complex hyperplasia (ACH)</td>
<td>18 (20.7%)</td>
</tr>
<tr>
<td>Malignant changes</td>
<td>6 (6.8%)</td>
</tr>
<tr>
<td>No pathological changes</td>
<td>17 (19.5%)</td>
</tr>
</tbody>
</table>

Table 3. — Correlation between the final staging of endometrial cancer and malignant changes in adenomyosis (n = 6).  

<table>
<thead>
<tr>
<th>Endometrial cancer final staging</th>
<th>Malignant changes in adenomyosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG2</td>
<td>moderately differentiated</td>
</tr>
<tr>
<td>IgG2</td>
<td>well differentiated</td>
</tr>
<tr>
<td>IgG3</td>
<td>poorly differentiated</td>
</tr>
<tr>
<td>IgG2</td>
<td>well differentiated</td>
</tr>
<tr>
<td>IgG1</td>
<td>well differentiated</td>
</tr>
<tr>
<td>IbG2</td>
<td>well differentiated</td>
</tr>
</tbody>
</table>

Table 4. — Correlation between the final staging of endometrial cancer and malignant changes in adenomyosis (n = 6).  

<table>
<thead>
<tr>
<th>a</th>
<th>Age</th>
<th>BMI</th>
<th>HRT</th>
<th>Myometrial invasion &gt; 50%</th>
<th>Final staging</th>
<th>Hyperplastic changes in adenomyosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76</td>
<td>25.2</td>
<td>–</td>
<td>+</td>
<td>IgG2</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>32.8</td>
<td>–</td>
<td>+</td>
<td>IgG2</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>25.4</td>
<td>+</td>
<td>+</td>
<td>IgG3</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>28.2</td>
<td>–</td>
<td>+</td>
<td>IgG2</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>33.4</td>
<td>–</td>
<td>+</td>
<td>IgG1</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>33.5</td>
<td>–</td>
<td>–</td>
<td>IbG2</td>
<td>+</td>
</tr>
</tbody>
</table>

(19.5%), atrophy – 21 patients (24.1%), glandular hyperplasia without atypia – 25 patients (28.7%), ACH – 18 patients (20.7%), and malignant changes – six patients (6.8%) (Table 2). All cases of malignant changes in adenomyosis were found in patients with estrogen-dependent type I endometrioid adenocarcinoma (Table 3). The average age of this group of six patients was 63.5 (55-76) and average BMI was 29.8 (25.2-33.4). Only one patient with cancer-positive adenomyosis had a history of hormone replacement therapy (HRT). The malignant changes in adenomyosis were in four well differentiated cases, in one moderately differentiated case, and in one poorly differentiated case. No stromal invasion into the adjacent myometrium was found. In the group with malignant changes in adenomyosis there were five cases where deep myometrial invasion of the tumor into the eutopic endometrium was proven (Table 4). In all cancer-positive adenomyotic lesions, other hyperplastic changes like benign glandular hyperplasia or atypical complex hyperplasia (ACH) were simultaneously identified.

Discussion

The risk factors for malignant transformation in adenomyosis are poorly defined [12, 13, 19, 20]. Systemic exogenous or endogenous hyperestrogenism, local overproduction of estrogens and other conditions, such as p53 mutation and increased activity of cyclooxygenase-2 are mostly discussed [9, 10, 20, 21]. In several studies, the usual findings are concomitant malignant changes of the endometrial epithelium located inside the myometrium and in normally located endometrium [9, 12, 15, 20]. We observed such findings in six cases (6.8%) of our study group (n = 87) (Tables 2 and 3). All patients in our study with cancer-positive adenomyosis were overweight or obese with possible endogenous hyperestrogenism as a risk factor. However one patient did have a history of increased systemic exogenous hyperestrogenism by HRT.

It is often difficult to distinguish myometrial invasion from the extension of carcinoma into adenomyosis, especially in the cornual area of the uterus [6, 9, 22, 23]. The presence of carcinoma in adenomyosis deeper than the maximum depth of the true tumor invasion does not worsen the prognosis [6]. Colman and Rosenthal proposed criteria for the diagnosis of carcinoma arising within adenomyosis [18]. These were: a) the carcinoma must be absent from the normal surrounding endometrium, b) the carcinoma must be seen to arise from the adenomyotic epithelium without invasion from another source, and c) endometrial stromal cells supporting a diagnosis of adenomyosis must be present. All our six cases of malignancy inside adenomyosis fulfilled the above-mentioned criteria. Since no myoinvasion of the tumor into the adenomyotic foci was observed, no correlation with stromal invasion of the intrauterine malignancy was proved (Table 3). In all cases of malignant findings in adenomyosis, we observed an increased stromal reaction around afflicted adenomyotic lesions. This reaction probably protects against myoinvasion into the surrounding myometrium [19].

Malignant changes of adenomyosis were confirmed only in the group with endometrioid adenocarcinoma, and they correlated with the tumor grading of the eutopic endometrium – in three cases (50%) (Table 3). In the other three cases the differentiation of the tumor located in the uterine cavity was lower than in the adenomyotic foci. Five of six tumors in adenomyosis were well or moderately differentiated and only one had poor differentiation. In our study the presence of adenocarcinoma in adenomyosis was connected with deep myometrial invasion of the tumor located inside the eutopic endometrium in five of six cases. This is almost the same result as that published by Ismiil [13].

Case reports also present adenocarcinoma arising de novo in an isolated adenomyotic lesion inside the myometrum [7-11]. These isolated ectopic changes are probably more aggressive like type II endometrial cancer [9]. In these specimens no malignancy of the normally located endometrium was observed. There was no such case in our series. In ten patients with clear cell carci-
In summary, we evaluated malignant changes in adenomyosis in patients with concomitant endometrial cancer. Adenomyosis is not a malignant disease, but it can undergo malignant changes. We observed different forms of hyperplasia in adenomyotic foci including ACH. Interestingly ACH as a premalignant lesion was confirmed in 18 hysterectomy specimens (20.7%) and it was present also in already malignant adenomyotic foci in 100%. All cancer-positive cases of adenomyosis in our study were found in the group with endometrioid adenocarcinoma, which is the same observation as published by Mittal and Barwick [15]. This fact may partially explain a better prognosis of these carcinomas. Our results also show malignant changes in adenomyosis with various differentiation (well, moderate, poor). These changes did not correlate with the tumor differentiation inside eutopic endometrium. However, there is no clear study demonstrating the natural transformation of adenomyosis to adenocarcinoma, and the mutual relationship of these two diseases is still speculative. According to published literature and our results, it can arise de novo or copy the model of carcinogenesis of type I endometrial cancer. Therefore it can also possess different biological features with different impact on the prognosis of the disease. Further studies are necessary to elucidate the clinical relevance of distinguishing the two possible pathways of malignant changes in adenomyosis.

References


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Effect of collagen powder on lymphorrhea after modified radical mastectomy. A randomized controlled trial

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Summary

Aim: Postoperative lymphorrhea is a major complication of axillary lymphadenectomy. The aim of our study was to evaluate the impact of type I collagen in postoperative lymphorrhea in mastectomy patients. Methods: Eighty patients that underwent modified radical mastectomy for breast cancer were randomized in two groups. In group A (collagen group, n = 42) collagen type I (Cellerate RX powder) was applied in the axillary cavity after lymphadenectomy while in group B (control group, n = 38) lymphadenectomy was performed in the standard fashion without the use of a sealant. Suction drains remained in place until the daily amount of lymphatic drainage fell under 30 ml. The total amount and the duration of drainage, as well as the morbidity and severity of arm pain were compared in the two groups. Results: There was a non significant trend towards lower overall drainage in the collagen group. The duration of drainage and postoperative pain were similar in the two groups, as was morbidity. Subgroup analysis of patients according to the number of lymph nodes excised, revealed significantly less lymphorrhea in terms of volume and duration in patients who had more than ten lymph nodes excised. Conclusion: Collagen type I (Cellerate RX powder) appears to attenuate postoperative lymphorrhea in patients undergoing axillary lymphadenectomy especially when > 10 lymph nodes are removed.

Key words: Modified radical mastectomy; Lymphorrhea; Collagen.

Introduction

Although it is considered a minor complication of breast surgery, prolonged lymphatic drainage after axillary dissection is the most common cause of long hospitalization for breast cancer patients, who usually have an otherwise uneventful postoperative course [1-4]. Breast surgeons employ many different techniques to achieve reduction of lymphorrhea, like the use of ultrasonic scissors and fixation of skin flaps on the chest wall intraoperatively, or pressure dressings postoperatively [5-9]. In view of the insignificant results of all these methods and having in mind the known action of collagen as a biologic sealant, we tested the effect of type I collagen powder (Cellerate RX, Wound Management Technologies, Inc, USA) on the volume and duration of lymphorrhea in patients with modified radical mastectomy.

Patients and Method

Between 2004 and 2009 we conducted a prospective randomized trial evaluate the impact of collagen type I on axillary drainage after lymphadenectomy. Eighty female patients were enrolled in the study and underwent mastectomy for breast cancer and axillary lymph node dissection level I-II. Exclusion criteria were: A) previous operations on the axilla, B) neo-adjuvant chemotherapy, C) previous chest wall irradiation, D) immediate breast reconstruction, and E) recurrent disease.

After informed consent, each patient was randomized to receive either type I collagen (collagen group) or nothing (control group) in the axillary cavity. Randomization was performed using a web based program. All patients were offered modified radical mastectomy using electrocautery for the breast excision and blunt dissection along with ligation of lymphatics and vessels in the axilla. They were all treated with axillary node dissection level I-II, since sentinel lymph node biopsy had not yet been established as standard of care in our institution at the time of the study. Type I collagen powder (Cellerate RX) was used in the collagen group (42 patients). Three grams of powder were applied on the exposed tissue in the axillary cavity and the mastectomy flaps, after the completion of lymphadenectomy. Before skin closure two soft suction drains (Jackson-Pratt) were used – one for the axilla and one on the chest wall. The wound was covered with simple dressings. Starting from postoperative day 1 each patient was encouraged to use her arm and follow a program of special exercises for arm mobilization. Drainage was monitored on a daily basis and the drain was removed when it fell under 30 ml/day. Monitoring was performed by experienced hospital personnel that was blinded to the treatment assignment. All patients remained hospitalized until the removal of the drains to ensure that monitoring was reliable. The daily amount of drainage was the total volume of axillary and chest wall drainage. Total amount of drainage consisted of the amount in the drains and the amount of serous fluid aspirated, in case of seroma.

On the first and third postoperative day both groups were asked to assess the severity of pain in the ipsilateral arm using a visual analogue scale.

The primary endpoints of the study were the duration and the volume of drainage, and the secondary endpoint was the severity of the pain in the arm and the morbidity in the two groups of patients.

Seroma was defined as a palpable serous collection in the axilla that needed aspiration. Wound infection was defined as erythema of the wound accompanied by collection, and was monitored using wound cultures.
Statistical analysis was performed using SPSS software. Quantitative data were expressed as mean values and the comparison between the two groups was made using the Student’s t-test. A $p$ value $< 0.05$ was considered statistically significant.

### Results

All 80 patients enrolled completed the study. There were no significant differences between the two patient groups (collagen vs control group) with regards to age, body mass index, number of lymph nodes removed and disease stage (Table 1).

The mean overall drainage output for collagen group was $507 \pm 85\text{ml}$ (mean value $\pm$ SD) versus $693 \pm 101\text{ml}$ for the control group. The mean duration of drainage was $5.2 \pm 1.1$ days for collagen group versus $6.8 \pm 1.2$ days for controls (Table 1). Although these results showed a non significant difference between the two groups, there was a trend for lower output and shorter duration of drainage in the collagen group. Postoperative pain measurements on days 1 and 3 were not statistically significant in the two groups (Table 1). The complication rate was similar in both groups. With regard to seromas, the incidence and total volume aspirated showed no statistically significant difference in the two groups. The same was true for wound infection (Table 1).

According to the number of lymph nodes excised, patients were classified into two subgroups: subgroup A included 24 patients with ten or fewer lymph nodes excised whereas subgroup B included 56 patients with more than ten lymph nodes excised. An additional statistical analysis was performed for these subgroups and the results are demonstrated in Table 5. For subgroup A, the use of collagen on the axilla had no impact either on the overall amount or on the duration of drainage ($520 \pm 75\text{ ml}$ versus $643 \pm 65\text{ ml}$ and $5.2 \pm 1.5$ days versus $5.8 \pm 2$ days). For subgroup B, the effect of the use of collagen was statistically significant and reduced both the amount and the duration of lymphorrhea (Table 2). Further subgroup analysis based on lymph node status showed no difference in the amount and duration of drainage in patients with positive or negative lymph nodes.

### Discussion

Although breast surgery is known to have only a few and usually minor complications, prolonged lymphorrhea after axillary dissection is very common. Patients who develop this complication are not only obliged to retain their drains and eventually stay hospitalized for several days, but they are also prone to developing further problems, like seroma, wound infection or even lymphosarcoma [1-3].

Lymphorrhea is attributed to both an acute inflammatory reaction resulting from the surgical stress and to the transaction of lymphatics during axillary dissection. When it seizes a few days (3-4) after surgery it is a well accepted postoperative event that is not regarded as a complication [6-8]. On the contrary, prolonged lymphatic drainage is a rather unpleasant situation caused by certain pathophysiologic mechanisms [3, 7, 8]. The fibrinolytic activity of the plasmin system in serum and lymph may contribute to fluid accumulation and fibrin complexes, that have already formed within and around vessels, may become degraded resulting in further leakage [1]. Bonemima et al., report that seromas do not contain enough fibrinogen, resulting in impaired coagulation [2].

Factors predisposing to prolonged postoperative lymphorrhea are old age, obesity, preoperative chemotherapy and high axillary dissection, while timing of mobilization and type of drains are not important [3-5]. A number of different surgical techniques have been employed to reduce the incidence of lymphorrhea, e.g., the use of ultrasound scissors instead of electocautery, the fixation of flaps with sutures on the thoracic wall, the placement of full or half vacuum suction drains or the use of pressure dressings [6-8]. Many authors have tried fibrin sealant or tetracycline in the axillary cavity and others used subcutaneous octreotide [9-11].

In our study we used porcine hydrolysate collagen type I (Cellerate), that is known to promote and accelerate cellular regeneration by replicating the natural fibroconnec-
tive template. It works by attaching to fibroblasts to the wound bed forming a biologic platform that encourages the healing process. All 60 patients enrolled in the protocol had similar characteristics and the surgical technique was the same. It is noteworthy that all patients underwent modified radical mastectomy and they all followed the same program for arm mobilization, so that the postoperative drainage could be comparable. Although there was no statistically significant effect on the total volume and duration of lymphorrhea between the two groups, there was a trend towards improved outcomes in the collagen group. Subgroup analysis of patients classified according to the number of lymph nodes removed revealed the beneficial effect of collagen. Total amount and duration of drainage was statistically significant in the subgroup of patients that had more than ten lymph nodes excised. This finding is of major clinical importance in the era of therapeutic-only lymphadenectomy for breast cancer. It is widely accepted that complete axillary dissection and axillary sampling as staging procedures for early breast cancer have already been replaced by sentinel lymph node biopsy. Therefore, lymphadenectomy should only be performed for therapeutic reasons either in case of a positive sentinel lymph node for early cancer patients or as a standard treatment for advanced cancers, and many centers around the world advocate even level-III clearance. The minimum accepted number of lymph nodes excised in this case should be at least ten. In this setting, the clinical importance of the beneficial effect of collagen in this specific subgroup of patients is significantly reinforced. Our study included cases of both therapeutic and staging lymphadenectomy, as sentinel lymph node biopsy had not yet been established in our unit at the time of the study.

However, further complications attributed to lymphorrhea, such as postoperative seromas and wound infection, as well as arm pain were not affected by the use of collagen. Our results are in accordance with other studies that report decreased lymphorrhea with no impact on delayed seroma formation and other complications [12-14]. On the other hand, several trials with a small number of patients failed to prove the protective effect of sealants. In addition, a systematic review concluded that there is no strong evidence to support the use of fibrin in axillary surgery [15-17].

Conclusion

Based on our results, the use of type I collagen reduces the overall amount and duration of postoperative lymphorrhea in patients undergoing modified radical mastectomy with standard therapeutic lymphadenectomy and excision of more than ten lymph nodes avoids prolonged hospitalization. However, it does not affect postoperative morbidity and pain.

References


Association of CYP1B1 gene polymorphisms and the positive expression of estrogen α and estrogen β with endometrial cancer risk

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**Summary**

To investigate the relationship between the CYP1B1 L432V polymorphism, ERα and ERβ positivities and the incidence of endometrial cancer. The relationship between CYP1B1 L432V polymorphism, ERα and ERβ positivities and endometrial cancer was investigated using the allele-specific polymerase chain reaction method to analyze gene polymorphism in exon 3 codon 432 (C-G) of CYP1B1. Our results are as follows: in endometrial cancer cases the prevalence rates of CYP1B1 L432V genotypes C/C, C/G, and G/G were 47.2%, 36.1%, and 16.7%, respectively, and 68.8%, 23.8% and 7.5% in the control group, respectively. The frequencies of CYP1B1 C and G alleles were 65.3% and 34.7% in endometrial cancer patients and 80.6% and 19.4% in the control group. A significant difference was found in the genotype distributions or allele frequencies of CYP1B1 L432V polymorphism between the two groups (p < 0.05). Compared with wild-type C/C, the susceptibility of endometrial cancer with homozygotic mutation G/G and heterozygotic mutation C/G increased by 3.235 (95%CI 1.111-9.425) and 2.214 (95% CI 1.067-4.593). Moreover, the positive expression of ERα in genotypes G/G and C/G was higher than in the wild genotype C/C (p < 0.05). In conclusion, allelic polymorphism of CYP1B1 L432V increases the risk of endometrial cancer and has a positive correlation with ERα expression.

**Key words:** Endometrial cancer; L432V polymorphism of CYP1B1 gene; Risk factor; ERα and ERβ.

**Introduction**

Endometrial cancer is one of the common gynecological malignancies of the female urogenital tract, and its incidence is increasingly becoming significant [1]. However, the genetic basis of this disease is not yet well understood. Studies have shown that endogenous and exogenous estrogens are related to endometrial cancer risk. Estrogen production and metabolism play critical roles in the development and pathogenesis of endometrial cancer [2, 3]. Cytochrome P4501B1 (CYP1B1) is a key enzyme in the estrogen metabolism pathway, which results in the hydroxylation and conjugation of estradiol. CYP1B1 converts estrogen to 4-hydroxylated estrogen, which induces DNA damage [4]. Several polymorphisms of the CYP1B1 gene have been described, of which, four result in amino acid substitutions. Exon 3 contains three polymorphic sites at codons 432, 449, and 453. The amino acid replacement occurs at codon 432, leading to the replacement of Leu → Val [5, 6]. Inherited alterations in the activity of CYP1B1 lead to differences in estrogen metabolism in endometrial cancer, indicating estrogen-mediated carcinogenesis [7]. CYP1B1 polymorphisms have been studied in relation to ovarian, prostate, and breast cancers [8-10]. The present study forwards the hypothesis that polymorphisms of the CYP1B1 gene and the activation of estrogen receptors are significant in the pathogenesis of endometrial cancer. The L432V polymorphism of the CYP1B1 gene in endometrial cancer was investigated. The effect of the CYP1B1 polymorphism on the expressions of estrogen α and estrogen β (ERα and ERβ) were also examined.

**Materials and Methods**

**Research subjects**

Seventy-two patients with sporadic endometrial cancer from the Department of Pathology of the Third Hospital in Datong, Shanxi Province, China between April 2000 and June 2005 were used as research subjects. Ages ranged from 38-79 years with a mean age of 59. The histopathological types of these cancers were as follows: 67 cases of endometrioid cancer (9 adenosquamous, 4 adenoacanthoma), two cases of clear cell cancer, and three cases of serous papillary adenocancer. A total of 80 cancer-free control samples were included in the investigation from unrelated, healthy volunteers in the same prefecture. There were no differences between patients and control groups with regards to age, race, family history of cancer, and body mass index (BMI).

**DNA extraction**

Paraffin-embedded endometrial cancer blocks were cut into 20-40 m sections. After deparaffinization by dimethylbenzene, sections were treated with anhydrous ethyl alcohol. Blood samples for the control groups were collected from healthy women who underwent physical examination prior to collection. DNA was extracted from all endometrial cancer and control samples using a DNA extraction kit (Promega Corporation). Quantity and quality of DNA were measured at 260 and 280 nm with the use of a spectrophotometer.
Analysis of CYP1B1 polymorphism

To analyze the L432V polymorphism of CYP1B1, each DNA sample was amplified in two separate reactions using one of two 3’ primers: 5’-TCC GGG TTA GCC CAC TTC AG-3’ or 5’-TCC GGG TTA GCC CAC TTC AC-3’. All reactions included the 5’-ATG CGC TTC AGC TTT GT-3’ primers (YingJun Biotechnology Co., Ltd., Shanghai). The 50 µl reactions were comprised of 50 mmol/l polymerase chain reaction (PCR) buffer, 200 µmol/l deoxynucleoside triphosphates (dNTP), 0.4 µmol/l primers, and 1 U Taq polymerase. After initial denaturation at 95°C for 5 min, the sample underwent 35 cycles at 94°C for 60 sec 60°C for 60 sec, and 72°C for 60 sec before undergoing a final extension at 72°C for 8 min.

Gel electrophoresis genotype analysis

Each of the CYP1B1 genes from the PCR was electrophoretically separated on 2% agarose gels using 180 V at ambient temperature. The products were then visualized by ethidium bromide staining under UV light. The DNA samples were homozygous wild-type and mutated-type genotypes. For genotype verification, some of the PCR products were subjected to direct sequencing.

ERα and ERβ immunohistochemistry

The 72 patients with endometrial cancer were also studied by immunohistochemical analysis. Anti-ERα and anti-ERβ antibodies were used to identify the expressions of these receptors in cancerous endometrium using standard immunohistochemical techniques. Paraffin-embedded endometrial cancer blocks were cut into 5 µm sections and dried at room temperature. After deparaffinization, sections were treated with 2% hydrogen peroxide in methanol for 20 min to inactivate endogenous peroxidase. After blocking with 3% normal goat serum for 10 min, sections were incubated overnight with ERα and ERβ antibodies at 1:75 dilution in PBS at 4°C under a humid chamber. Sections were washed with PBS and incubated with secondary antibodies for 30 min. Immunostaining was done using avidin-biotin peroxidase method with diaminobenzidine (Zhongshan Goldenbridge Biotechnology Co., Ltd., Beijing) as the chromogen. This was followed by counterstaining with hematoxylin, thoroughly washed with tap water, and air-dried.

Positive controls with sections known to contain the protein as well as negative controls without the usage of the primary antibody were performed to ensure that specific immunoreactivity was analyzed. Expression of ERα and ERβ were observed in the cell nucleus. Expression levels of ERα and ERβ were quantified according to the percentage of positive cells from five randomly selected view fields with 100 cells counted per field. The results were judged by two independent pathologists as - (no positive staining, and < 10% positive cells), + (10%-60%), or ++ (> 60%).

Statistical analysis

Analyses were performed using the Statistical Package for the Social Sciences program (SPSS). Chi-square analysis was used to test for differences in genotype and allele frequencies of the polymorphism between endometrial cancer and control samples as well as between the stages and grades of cancer. The relative risk associated with a particular genotype or allele was estimated by calculating odds ratios (ORs), along with 95% confidence intervals (CIs).

Results

The polymorphism of CYP1B1 L432V in the 72 patients with endometrial cancer and 80 control subjects was analyzed by the PCR method. Table 1 shows the frequency of distribution of the genetic polymorphism of CYP1B1 L432V. Genotype-specific ORs were estimated with the assumption that the genotype frequencies in the controls were consistent with the Hardy-Weinberg equilibrium. The distributions of genotypes on codon 432 were significantly different between endometrial cancer patients and the control group (χ2 = 7.644, p = 0.022). Of the endometrial cancer patients, 16.7% showed 432C/G and 7.5% of the controls showed this genotype, while 36.1% of the endometrial cancer patients showed 432C/G and 23.8% of controls. The relative risks of 432G/G and 432C/G were calculated as 3.235 and 2.214, respectively, in comparison with the wild-type.

Table 2 shows that the frequencies of individuals carrying the G allele were 34.7% and 19.4% for endometrial cancer patients and controls, respectively. The allele frequency distribution on codon 432 were significantly different between the endometrial cancer patients and the controls (χ2 = 9.133, p = 0.003). When the adjusted ORs were calculated, patients with G allele revealed a 2.213-fold higher risk of endometrial cancer than those with C allele. The higher frequency of patients with G/G genotype or G allele indicates that a person carrying this genotype or allele has an increased risk for endometrial cancer.

The correlation of the L432V polymorphism of the CYP1B1 gene with ERα and ERβ expressions and the clinical pathological data of endometrial cancer tissue are shown in Table 3. The 432G/G showed a significant correlation with ERα and ERβ positive expressions. Of the samples, 83.3% and 84.6% of those with 432G/G and 432C/G were ERα positive, whereas 55.9% of the sam-
Table 3. — Correlation between the genotypes of L432V of the CYP1B1 gene and ERα and ERβ receptor expressions.

<table>
<thead>
<tr>
<th>Genotype of L432V of CYP1B1 gene</th>
<th>ERα Positive</th>
<th>ERα Negative</th>
<th>ERβ Positive</th>
<th>ERβ Negative</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>51 (70.8%)</td>
<td>19 (29.2%)</td>
<td>22 (16.7%)</td>
<td>10 (43.2%)</td>
<td>6.977</td>
<td>0.031*</td>
</tr>
<tr>
<td>CG</td>
<td>15 (22.2%)</td>
<td>21 (30.6%)</td>
<td>6 (4.6%)</td>
<td>5 (21.1%)</td>
<td>8.370</td>
<td>0.015*</td>
</tr>
<tr>
<td>GG</td>
<td>2 (2.9%)</td>
<td>6 (9.1%)</td>
<td>5 (3.7%)</td>
<td>4 (16.2%)</td>
<td>9.070</td>
<td>0.003*</td>
</tr>
</tbody>
</table>

*p < 0.05

In the present study, a significant difference in the genotypic distributions and allelic frequencies of the codon 432 region of CYP1B1 was found between endometrial cancer patients and healthy controls in a Datong population. The presence of a mutant G allele revealed a 2.213-fold higher risk of having endometrial cancer than allele C. The relative risk was calculated at 3.235-fold compared with wild-type C/C. The higher frequency of patients with G/G genotype or G allele indicates that a person carrying this genotype or allele has an increased risk for endometrial cancer. Mutant genotype 432G/G may increase the effects of exogenous or endogenous estrogen, increase the sensitivity of estrogen, or increase the catalysis of 4-hydroxy estrogen. These results are in agreement with studies done on ovarian and prostate cancers. Goodman et al. [5, 19] reported an association between these cancers and the Val^{402} of CYP1B1. Cecchin et al. [20-22], however, did not find any association of ovarian and colorectal cancer with codon 432.

The 432G/G also showed a significant correlation with ERα and ERβ positive expression, indicating that heterozygous or homozygous mutations of 432G increase the exposure of estrogen and genotoxic 4-hydroxy estrogen conversion. Thus, 432G appears to be of importance in the pathogenesis of endometrial cancer. Previous studies have shown that the 432G/G genotype has a positive correlation between ER and the risk for endometrial and breast cancers, although some studies have shown no association between this type of polymorphism and cancer risk [23-25].

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The correlation between the 432G/G genotype of CYP1B1 and the stages and grades of endometrial cancer were also analyzed. No association for cancer risk was found at any site. This lack of association with the stage and grade has also been shown to be true with other CYP gene polymorphisms in endometrial cancer, such as CYP1A1, CYP19, CYP17, and CYP2D6 [18, 26, 27].

The L432V polymorphism on the CYP1B1 gene is correlated with susceptibility to endometrial cancer, since polymorphisms are inherited. Thus, the 432G/G genotype may increase the effects of exogenous or endogenous estrogen, increase the sensitivity of estrogen, or increase the catalysis of 4-hydroxy estrogen. These findings suggest that the mutant genotype of CYP1B1 might be a risk factor for endometrial cancer.

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References

Association of CYP1B1 gene polymorphisms and the positive expression of estrogen α and estrogen β with endometrial cancer risk


Is postoperative CA125 level in patients with epithelial ovarian cancer reliable to guess the optimality of surgery?

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Summary

Introduction: Cytoreductive surgery is a pivotal component of primary treatment in patients with ovarian epithelial cancer (OEC) and several studies have shown better outcomes of optimal debulking. The aim of this prospective study was to determine if optimum versus suboptimal cytoreductive surgery predicts CA125 levels two weeks after surgery. Material and Methods: Sixty patients with epithelial ovarian cancer scheduled for cytoreductive surgery in Imam Khomeini Hospital, Tehran, Iran were enrolled in this study. Two groups of patients were to undergo optimal or suboptimal cytoreductive surgery. Optimal cytoreduction was defined as the largest volume of residual disease < 1 cm in maximal dimension. CA125 levels were measured in all patients preoperatively and at two, seven and 14 days after surgery. CA125 levels were converted to a log scale. Results: The distribution of staging, grading and types of tumors in each group were statistically equal but insignificant (chi square). The difference in mean of CA125 before and two weeks after surgery was statistically significant (paired t-test; p = 0.0001) but the grade, stage and type of tumors did not have any impact on CA125 regression. However, regression of CA125 two weeks after the operation did not differ statistically between the optimal and suboptimal cytoreduction groups (repeated measure ANOVA). Conclusion: Although, postoperative CA125 decreased significantly in two weeks after tumor cytoreduction in patients with epithelial ovarian cancer, its regression did not differ according to optimal or suboptimal groups.

Key words: Ovarian cancer; CA125; Cytoreductive surgery; Optimal; Iran.

Introduction

Ovarian cancer is the fourth cause of cancer-related death in women. Cytoreductive surgery represents a pivotal component of primary treatment [1]. Several studies have shown the better outcomes of optimal debulking and amount of residual tumor following cytoreductive surgery is inversely proportional to survival [1-3]. Even complete pathological responses to chemotherapy depends on optimal or suboptimal surgery and may vary, respectively, 50% to 20% [1, 4, 5]. CA125 is an antigen expressed by tissue derived from celomic epithelium (mesothelial cells of the pleura, pericardium, and peritoneum) and mullerian epithelium (tubal, endometrial, and endocervical). The surface epithelium of normal fetal and adult ovaries does not express CA125 unless an inclusion cyst, metaplasia, and or papillary excrescences are present [6]. The CA125 level is elevated (> 35 U/ml) in 90% of advanced-stage epithelial ovarian cancers, while less than 50% of patients with Stage I disease have abnormal levels [7]. A correlation has been reported between tumor biology and CA125 levels; tumors that tend to be poorly differentiated or present with wide metastatic disease have higher levels of serum CA125 [8].

The extent of residual tumor after primary cytoreductive surgery has been proven to be an important prognostic factor of survival [9]. Although a number of potential tumor markers have been identified in ovarian cancer, by far the greatest interest has been attracted by CA-125.

Surgical cytoreduction improves survival only if the patient is optimally cytoreduced. The definition of optimal cytoreduction has evolved over time and is currently residual disease measuring 1 cm [10]. Survival is superior when EOC is surgically debulked by a gynecological oncologist presumably because greater cytoreduction can be achieved by surgeons more experienced in resecting the disease [11, 12]. In general, patients with tumor regression present with a decline in CA125 levels. We expected this decrease in CA125 level would be prominent in patients undergoing optimal debulking in comparison with suboptimal surgery, so this study was designed to verify this hypothesis.

Material and Methods

This prospective study was carried out at Imam Khomeini Hospital, Tehran, Iran. Sixty epithelial ovarian cancer patients admitted for cytoreductive surgery were enrolled. Patients in this study were operated without any previous chemotherapy, and adjuvant chemotherapy was performed 14 days after surgery. Two groups of patients were defined as undergoing optimal or suboptimal cytoreductive surgery. Optimal cytoreduction was defined as the largest volume of residual disease < 1 cm in the maximal dimension. CA125 levels were measured in all patients preoperatively and at the 2nd, 7th and 14th days after surgery. All patients gave informed consent and the study was approved by Tehran University Ethical Committee. All blood samples were taken using conventional venipuncture with minimal stasis. Separation was performed by centrifugation for 15 min, and immediately thereafter serum was stored frozen at -80°C until analysis. All serum samples from one patient were assayed in the same run and by the same analyst.

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Statistics

CA125 levels were logarithmically transformed before the statistical analyses due to a large variation. Preoperative CA125 level and age of patients were analyzed using an independent t-test; categorical data such as grading, staging, type of tumors and vascular space involvement were analyzed by the chi square test or Fisher’s exact test, if needed. The regression of CA125 in both groups (optimal versus suboptimal cytoreductive surgery) and according to different time points (preoperatively, 2, 7 and 14 days after surgery) was analyzed by repeated measure ANOVA; a p value less than 0.05 was considered significant. All analyses were performed by SPSS-16.

Results

The mean ± SD of age in the optimal (n = 30) and suboptimal (n = 30) cytoreductive groups were respectively, 49.7 ± 9 and 49.5 ± 12 years (t-test; p = 0.91). Preoperative serum levels of CA125 were elevated (> 35.0 U/ml) in all patients. The mean of CA125 before surgery in the optimal group was 952 U/ml and for the suboptimal group 1784 U/ml (log scale was compared by t-test; p = 0.81).

Most of the ovarian tumors were papillary serous (33/55%) followed by serous (15/25%), endometroid (9/15%), poorly differentiated (2/3.3%), and mucinous (1/1.7%). Grade 2 tumors were reported in 28 patients (46.7%), grade 3 in 19 (31.7%) and grade 1 in 13 (21.7%) patients. Also, Stage IIIIC was reported in 41 patients (68.3%) in comparison with only IIA and IIB in two patients (3.4%); and finally, vascular space involvement was seen in 45 patients (75%).

The difference in CA125 level between the preoperative and 14th day after surgery was positive in all cases, except for one patient (1.7%) in the suboptimal group in which the value was negative. Thus, in spite of CA125 regression in this period of time for nearly all subjects, which the value was negative. Thus, in spite of CA125 regression in this period of time for nearly all subjects, except for one patient (1.7%) in the suboptimal group in which the value was negative. Thus, in spite of CA125 regression in this period of time for nearly all subjects, none reached less than 35 IU/ml.

Another form of analysis showed that four out of 30 patients in the optimal group and five out of 30 in the suboptimal group had more than 50% reduction in CA125 level, 14 days after surgery (chi² test, p = 0.71).

The comparison of age, tumor pathology characteristics and mean of log transformed CA125 levels (preoperative, 2, 7 and 14 days postoperation) between two groups of cytoreduction surgery (optimal vs suboptimal) are summarized in Table 1. As shown, the mean age and CA125 levels (preoperative, 2, 7 and 14 days postoperation) did not differ significantly according to the two groups of cytoreduction surgery (optimal vs suboptimal).

Also, the distribution of stage, grade and vascular space involvement were equivalent in both groups. However mucinous (1; 3.3%) and poorly differentiated tumors (2; 6.7%) were found only in the suboptimal group and endometroid tumors were prominently located in the optimal group (8; 26.7% vs 1; 3.3%) (Table 1).

Although the linear regression of CA125 two weeks after surgery was statistically significant relative to preoperative values (repeated measure ANOVA; p = 0.001), it did not differ statistically between optimal and suboptimal cytoreduction groups (repeated measure ANOVA). Finally, the grade and stage, and type of tumor lesions did not have any impact on CA125 regression as a whole.

Table 1 — Comparison of tumor and patient characteristics in the two types of cytoreductive surgery.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cytoreductive surgery</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Mean ± SD</td>
<td>Optimal</td>
<td>Suboptimal</td>
</tr>
<tr>
<td>(min-max)</td>
<td>(33-70)</td>
<td>(20-77)</td>
</tr>
<tr>
<td>CA125 (U/ml) Preoperative</td>
<td>2.73 ± 0.48</td>
<td>2.71 ± 0.56</td>
</tr>
<tr>
<td>2 days later</td>
<td>2.65 ± 0.48</td>
<td>2.63 ± 0.53</td>
</tr>
<tr>
<td>7 days later</td>
<td>2.59 ± 0.48</td>
<td>2.57 ± 0.53</td>
</tr>
<tr>
<td>14 days later</td>
<td>2.52 ± 0.49</td>
<td>2.51 ± 0.53</td>
</tr>
<tr>
<td>Stage II or III</td>
<td>27 (90%)</td>
<td>24 (80%)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (10%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>7 (23.3%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>15 (50%)</td>
<td>13 (43.3%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>8 (26.7%)</td>
<td>11 (36.7%)</td>
</tr>
<tr>
<td>Vascular space involvement</td>
<td>Positive</td>
<td>20 (66.7%)</td>
</tr>
<tr>
<td>Negative</td>
<td>10 (33.3%)</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>Types of tumor Serous</td>
<td>9 (30%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Papillary serous</td>
<td>13(43.3%)</td>
<td>20 (66.7%)</td>
</tr>
<tr>
<td>Endometroid</td>
<td>8(26.7%)</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>0</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>0</td>
<td>2 (6.7%)</td>
</tr>
</tbody>
</table>

Discussion

In this longitudinal study, postoperative CA125 levels decreased significantly in a short-term follow-up of women with epithelial ovarian cancer. Although statistical analysis did not prove any significant difference in CA125 regression in the two cytoreductive groups (optimal vs suboptimal) in a period of 14 days, it has been shown in different studies that optimal surgical debulking as an independent factor appears to improve the prognosis of patients with even Stage IV epithelial ovarian cancer (EOC) [13-16]. Since the original work by Griffiths [17] in 1975, numerous retrospective studies have reported the benefits of tumor cytoreduction for advanced ovarian carcinoma [18]. However, the Gynecologic Oncology Group (GOG) has demonstrated that tumor debulking improves overall survival only if optimal residual disease status can be attained. Pooled data of reports from numerous institutions suggest that optimal primary cytoreduction can be achieved in approximately 30-40% of patients with advanced ovarian carcinoma [19]. Therefore, the traditional approach to laparotomy and attempted tumor cytoreduction does not significantly benefit the majority of patients with advanced disease. In contrast, withholding attempts at cytoreduction may deprive a substantial number of patients from a procedure that could potentially double their median survival [19]. A structured review of 81 cohorts involving 6,885 patients reported that an average 42% of patients were declared optimally debulked using the standard definition at the time of the individual report; however, in “centers with a particular interest and expertise in cytoreductive surgery”, optimal debulking (OD) was achieved for 75% of patients [20]. The utility of preoperative computed tomography (CT) scans [21, 22] and serum CA125 to predict OD for patients with EOC has been examined. The performance
Estimated marginal means of MEASURE-1

Cytoreduction surgery
  - optimal
  - suboptimal

Figure 1. — The regression line of CA125 according to different time points for both surgery groups produced by repeated measure ANOVA.

of preoperative CA125 exhibited a sensitivity for predicting OD in patients with Stage III-IV EOC ranging from 55% to 78% and a specificity from 54% to 73% [23, 24]. Chi et al. [23] reported that the probability of OD was only one in five for those with CA125 greater than 500. CA125 is an antigen expressed by tissue derived from celomic epithelium (mesothelial cells of the pleura, pericardium, and peritoneum) and mullerian epithelium (tubal, endometrial, and endocervical). The surface epithelium of normal fetal and adult ovaries does not express CA125 unless an inclusion cyst, metaplasia, and or papillary excrescences are present [25]. CA125 level is elevated (> 35 U/ml) in 90% of advanced-stage EOC, while less than 50% of patients with Stage I disease have abnormal levels [26]. A correlation has been reported between tumor biology and CA125 levels; tumors that tend to be poorly differentiated or present with wide metastatic disease present with higher levels of serum CA125 [27].

Age of patients and postoperative pathologic results such as stage, grade and vascular space involvement were evenly distributed in both groups (optimal vs suboptimal). However mucinous and poorly differentiated types of tumors were found only in the suboptimal group; in contrast, endometroid tumors were more commonly reported in optimal debulking. However as verified by statistical analysis, none of the mentioned variables (age, stage, grade, vascular space involvement and tumor type) had any impact on overall CA125 regression 14 days after operation nor on each subtype of cytoreductive surgery, separately. Rustin et al. [28] used a method that defined treatment response on the basis of CA125 decrease; in the present study, only four out of 30 patients in the optimal group and five out of 30 in suboptimal group had more than 50% CA125 level decrease in 14 days. The suboptimal group seemed to have better treatment response but it was not proven by statistical analysis. However, it seems strange to believe this conflict because it has been shown that CA125 levels reflect volume of disease and the correlation between residual tumor and CA125 levels has been verified [29-35]. Albeit, it is worthy to say that CA125 remains elevated by tissue damage after surgery, potentially taking weeks to return to normal [13] Thus, further CA125 level measurement is required in longer durations of time to determine if there is any significant CA125 difference in two groups, as seen in Munstedt et al.’s [30] study where treatment response was defined by dividing CA125 value after chemotherapy by CA125 value at four weeks after surgery.

Finally, we were able to determine if optimal cytoreductive surgery predicts CA125 levels two weeks after operation, but no decrease in CA125 due to the effect of optimal debulking could be found in this study.

In conclusion, although, postoperative CA125 decreased significantly in two weeks after tumor cytoreduction in patients with epithelial ovarian cancer, its regression did not differ according to optimal or suboptimal groups.

Acknowledgement
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Is postoperative CA125 level in patients with epithelial ovarian cancer reliable to guess the optimality of surgery?


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Alveolar rhabdomyosarcoma originating from the uterine cervix

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Summary

Cervical alveolar rhabdomyosarcoma is a rare condition associated with poor prognosis. An 18-year-old patient presented with vaginal bleeding and a protruding mass from the vagina. Biopsy of the mass revealed alveolar rhabdomyosarcoma (ARMS), and radiological evaluation demonstrated that it originated from the uterine cervix. First, Wertheim’s operation was carried out followed by four cycles of vincristine, actinomycin-D, ifosfamide (VAI) chemotherapy. However, the disease relapsed within three months, and the patient died of disease progression. Despite combination treatment, we could not achieve a desirable survival advantage in ARMS. Future studies may unveil the genomic profile of this rare condition, leading to invention of targeted therapies, which is the emerging trend in the treatment of sarcomas.

Key words: Alveolar rhabdomyosarcoma; Cervix; Treatment.

Introduction

Rhabdomyosarcoma (RMS) is a common soft tissue tumor predominantly seen in children and adolescents. RMS has been classified into four subtypes: embryonal, alveolar, pleomorphic and botryoid. Alveolar RMS (ARMS) accounts for 20-30% of all RMS tumors, most of which occur in children and adolescents, often occurs in the skeletal muscle of the extremities. Although the major histologic appearance is muscle differentiation the tumor is believed to originate from incomplete myogenic differentiation in embryonal and fetal development. RMS can also occur in visceral organs. A rare case of alveolar RMS originating from the uterine cervix is presented.

Case Report

An 18-year-old nulliparous female patient was admitted to a state hospital in Izmir with vaginal bleeding and a protruding mass from the vagina in January 2006. Physical examination revealed a necrotic, red-purple colored mass 3 x 4 cm in dimension protruding from the vagina. Blood biochemistry and total blood count tests were normal. Abdominal magnetic resonance imaging (MRI) was performed for diagnosis which revealed a solid mass at the mid-pelvis appearing to originate from the uterine cervix and protruding from the vagina with necrotic components. The biopsy from the vaginal mass demonstrated ARMS. No evidence of distant metastasis was detected and Wertheim’s operation (total hysterectomy and pelvic-paraaortic lymph node dissection) was performed. Intraoperative observation showed that the mass originated from the uterine cervix, filled the vagina, and was enlarged to the pelvic region. There was a tumoral implant at the right parametrium 3 cm in dimension, and at the right obturator space 2 cm in dimension which were both excised. Peritoneal biopsy also showed tumoral infiltration. Postoperative pathological evaluation revealed a mass 11 cm in dimension that invaded the serosa of the uterine cervix with tumoral implants including cells with rhabdoid morphology and alveolar pattern. Immunocytochemical staining analysis showed that the tumor was positive for desmin and Myo D1 and negative for S100 and cytokeratin, thus making the diagnosis clear for ARMS (Figures 1-3).

Postoperatively, the patient was admitted to our university hospital for systemic chemotherapy. For evaluation of distant metastasis, an abdominal MRI, thorax computerized tomography (CT), bone marrow aspiration and biopsy, and bone scintigraphy were performed. There were no signs of distant metastatic disease. The patient received four cycles of vincristine (1.4 g/m² D1-5), actinomycin-D (1.4 g/m² D1-5), and ifosfamide (1800 mg/m² D1-5), since the patient was accepted as being in an intermediate risk group, according to the Intergroup Rhabdomyosarcoma Study Group. After termination of chemotherapy with no treatment related complications, a 50.4 Gy dose of radiotherapy was also performed to the pelvic region. During the follow-up period, the patient remained disease-free for only three months time. After that period, she presented with a huge intraabdominal mass that had grown very rapidly and which was accompanied by massive ascites. Unfortunately, she died within three days after hospitalization due to ascites infection and septicemia.

Discussion

ARMS of the cervix is a very rare condition in oncology. To the best our knowledge, only three patients have been reported in the literature [1-3]. The first case, reported by Emerich et al. in 1996, was a 45-year-old woman who had only 3.5 months survival although surgical resection and postoperative radiotherapy were performed [1]. Ng et al. and Case et al. also reported cervix RMS patients that achieved complete remission after surgery,
chemotherapy and radiotherapy at 36 months and 20 months follow-up, respectively [2, 3]. Although treatment strategies have improved survival in the last 30 years, the disease still has a very poor prognosis, especially in advanced stage. Our case also had a very short survival due to tumoral spread to the abdomen at the time of the diagnosis. Although she was treated by a combination of surgery, chemotherapy and radiotherapy, the disease-free survival period was very short with tumor relapse after three months time.

RMS is the most common soft tissue sarcoma seen in children and adolescents [4]. In recent years due to new treatment modalities survival rates have reached more than 70% [5]. The most common and also most favorable form of the disease is embryonal subtype with head-neck and genitourinary localization. Alveolar forms have a poorer outcome, often occur in skeletal muscle of the extremities, and genitourinary localization is very rare. Cytologically, alveolar RMS cells have large cells with Ewing-tumor like nuclei with centrally or peripherally placed nucleoli [6]. The differential diagnosis should be made with poorly differentiated adenocarcinoma, other types of sarcomas, melanoma and lymphoma.

As the case series have few numbers, the largest trials

Table 1. — IRSG postsurgical grouping classification.

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Localized disease, completely excised with no microscopic residual</td>
</tr>
<tr>
<td></td>
<td>A) Confined to site of origin, completely resected</td>
</tr>
<tr>
<td></td>
<td>B) Infiltrating beyond site of origin, completely resected</td>
</tr>
<tr>
<td>Group 2</td>
<td>Total gross resection</td>
</tr>
<tr>
<td></td>
<td>A) Gross resection with evidence of microscopic residual</td>
</tr>
<tr>
<td></td>
<td>B) Regional disease with involved lymph nodes, completely resected with no microscop residual</td>
</tr>
<tr>
<td>Group 3</td>
<td>Incomplete resection or biopsy with gross residual</td>
</tr>
<tr>
<td>Group 4</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

PM, Parameningeal; GUS, genitourinary system; N0, regional nodes not involved; N1, regional nodes involved by tumor; M0, no distant metastases; M1, distant metastases at diagnosis.

Table 2. — IRSG staging system.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites of primary tumor</th>
<th>Tumor size (cm)</th>
<th>Regional lymph nodes</th>
<th>Distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Orbit, non-PM head/neck; GUS nonbladder/prostate; biliary tract</td>
<td>Any size</td>
<td>N0, N1</td>
<td>M0</td>
</tr>
<tr>
<td>2</td>
<td>All other sites</td>
<td>≥ 5</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>3</td>
<td>All other sites</td>
<td>≤ 5</td>
<td>N1</td>
<td>M1</td>
</tr>
<tr>
<td>4</td>
<td>Any site</td>
<td>&gt; 5</td>
<td>N0 or N1</td>
<td>M1</td>
</tr>
</tbody>
</table>

Figure 1. — Myo D1 positivity in smooth muscle nucleus (arrow). Typical alveolar pattern of growth of the tumor. Tumoral implants including cells with rhabdoid morphology in fibrotic stroma are present.

Figure 2. — Desmin positivity in smooth muscle cytoplasm.

Figure 3. — Tumor cells with large eosinophilic cytoplasm and an eccentric settled nucleus is shown. The nucleus is pleomorphic with significant nucleoli.
have been performed by the Intergroup Rhabdomyosarcoma Study Group (IRSG). IRSG has suggested a postsurgical grouping classification and staging system (Tables 1 and 2) [7]. Raney et al. summarized the IRS-I to IV and suggested the optimal therapeutic strategies [8]. IRS-V combines the group, stage and histologic subtype to determine the risk profile and divides the patients into three risk groups (low-intermediate-high). To our knowledge from IRSG, the standard approach should include a multimodal therapy approach, containing surgery, chemotherapy and radiotherapy [7]. IRS-IV has reported that VAC (vincristine, actinomycin, cyclophosphamide), VAI (vincristin, actinomycin, ifosfamide) and VIE (vincristine, ifosfamide, etoposide) chemotherapies are equally effective in RMS patients and showed that embryonal subtypes are obtaining the best benefit from chemotherapy.

In our case, although the primary tumor was excised totally as peritoneal biopsy was positive for tumor, the patient regarded as Stage 1 and Group 2a (intermediate risk) received chemotherapy according to IRSG recommendations. However, due to the aggressive nature of the disease, despite the combination treatment, the patient died of disease in a very short period.

Thus, new treatment strategies are clearly needed to be defined because despite developments in treatment modalities in recent years, ARMS still has a very poor outcome. Also, future studies may unveil the genomic profile of the disease, leading to invention of targeted therapies, which is the emerging trend in the treatment of sarcomas.

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Metastatic gastric cancer mimicking an advanced cervical cancer: A case report

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Summary

Background: Metastasis to the uterine cervix from non-gynecologic neoplasms is rare. However, metastatic tumors sometimes precede the diagnosis of a primary tumor, and may lead to diagnosis of the primary tumor. Case: A 50-year-old woman was referred to us complaining of increasing right flank pain. Computed tomography scan demonstrated an enlarged uterus with right-sided hydroureter and hydrourerter. Cervical cytology revealed adenocarcinoma. She was considered to have a Stage IIIB cervical adenocarcinoma. Although no cervical lesion was seen colposcopically, histopathology from biopsies of the uterine cervix revealed poorly differentiated adenocarcinoma infiltrating around the normal endocervical glands. A metastasis from the gastrointestinal tract was suspected. The patient underwent gastroscopy and was found to have Borrmann type IV gastric cancer. Biopsies confirmed a poorly differentiated adenocarcinoma with signet ring cells. Conclusion: Physicians should bear in mind that metastatic tumors may precede the diagnosis of a primary tumor and could manifest by mimicking advanced cervical cancer.

Key words: Gastric cancer; Metastasis; Uterus.

Introduction

Metastasis to the uterus from extragenital malignancies is rare and is typically diagnosed in patients with known primary cancer or at autopsy [1]. However, metastatic tumors sometimes precede the diagnosis of a primary tumor and may lead to diagnosis of the primary tumor. In this paper, we present a case of gastric carcinoma that presented mimicking a FIGO (the International Federation of Gynecology and Obstetrics) Stage IIIB cervical cancer.

Case Report

A 50-year-old, gravida 2 para 2, Japanese woman with regular menstrual cycles noticed right flank pain. The pain gradually worsened over a week, and she became unable to lie down easily. Her past medical history included bilateral endometrial cysts, which had been managed by her primary gynecologist for over ten years. Routine cervical cytology taken three months earlier was normal. She consulted an orthopedic physician regarding her pain and was referred to our hospital for further investigation. After computed tomography scan revealed an enlarged uterus with right-sided hydroureter and hydrourerter, she was referred to our department for a presumed uterine tumor. On pelvic examination, the uterine cervix was enlarged with increased consistency and tenderness. Cervical cytology revealed clusters of adenocarcinoma cells. Her serum SCC were within normal limits. Although these findings led to the hospital for cancer pain with increased ascites and a pleural effusion. She received palliative chemotherapy with S-1 and supportive care, but she died of the disease two months after admission.

Discussion

Metastasis to the female genital tract from extragenital neoplasms is rare [2]. Mazur et al. analyzed 325 cases of metastasis to the female genital tract and reported that only 149 (45.8%) were of extragenital primary origin, with the ovaries and vagina being the most frequently affected sites (81%) regardless of the location of the primary [2]. The uterus is rarely a metastatic site, with some 200 cases reported to date [3, 4]. In particular, the uterine cervix is less affected than the uterine corpus and comprises only 20% of total uterine metastases [3]. Piura et al. reviewed 40 cases of metastases to the uterine cervix from extragenital cancers and reported that the most common site of the primary was the breast, followed by the
cancer. To summarize, physicians should bear in mind the possibility that metastatic tumors may manifest mimicking an advanced stage cervical cancer.

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Peptide YY producing strumal carcinoid tumor of the ovary

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Summary

\textbf{Background:} Primary ovarian carcinoid tumor is uncommon and represents less than 0.1\% of ovarian malignancies. The strumal carcinoid may be complicated by carcinoid syndrome induced by peptide YY (PYY). \textbf{Case report:} We describe a 45-year-old woman with a bilateral ovarian tumor diagnosed through periodical gynecological examination. She presented with severe constipation. Right ovarian cyst laparoscopically resected was diagnosed as a strumal carcinoid tumor; the left one was mature cystic teratoma. No metastatic findings were seen macroscopically on the ovarian surface and pelvic peritoneum. Constipation was drastically improved by resecting the tumor. The carcinoid tumor cells were positive for tumor-producing PYY by mRNA analysis. \textbf{Conclusion:} It is important to be aware of this entity in the pathological diagnosis of ovarian tumors, in the presence of any clinical indicator of carcinoid tumor/syndrome, as it carries a markedly better prognosis and clinical outcome in comparison with most other malignant ovarian tumors.

\textbf{Key words:} Ovarian strumal carcinoid; PYY; Carcinoid syndrome.

Introduction

Carcinoid tumors are rare slow-growing neoplasms that arise from the neuroendocrine cells and produce biogenic amines and various polypeptides [1]. However, carcinoids of the ovary are uncommon, especially primary ovarian carcinoids, which form approximately 0.3\% of all carcinoid tumors [2]. Women with carcinoid tumors may present with clinical carcinoid syndrome characterized by amine-related symptoms such as skin changes (facial flushing, telangiectasia), abdominal pain and constipation, and pulmonary and cardiovascular effects. Certain symptoms of carcinoid syndrome could be induced by a gastrointestinal hormone called as PYY (the peptide (P) having an N-terminal tyrosine (Y) and C-terminal tyrosine (Y)) that has a strong inhibitory effect on intestinal motility [3]. Additionally, PYY and its analogs may present with clinical carcinoid syndrome in various cancer cells in vitro and in vivo [4]. We examined a rare case of ovarian strumal carcinoid that was symptomatic for PYY expression.

Case Report

We present the case of a 45-year-old woman, gravida 0, para 0, with an ovarian tumor diagnosed through periodical gynecological inspection. She complained of no gastrointestinal symptoms including constipation or loose bowel movement. Magnetic resonance imaging demonstrated an 8-cm sized cystic tumor with fat saturation in the left ovary in which hairball was depicted. The right ovary had a 2-cm diameter solid tumor-like mass. The level of serum CA19-9 was elevated to 94.6 U/ml; CA125 and CEA levels were within normal limits. The patient was diagnosed with mature cystic teratoma and underwent laparoscopic bilateral ovarian cystectomy. The ovarian surface and pelvic peritoneum appeared to be macroscopically normal.

After aspiration of the tumor contents, ovarian cystectomy was performed, and the tumor was removed from the abdominal cavity using a plastic bag. Tumor spillage occurred, and the pelvic cavity was washed extensively with 3 l of saline. Constipation was drastically improved by resecting the tumor. The removed left ovarian tumor, measuring 9 cm in the greatest dimension, contained hair, teeth, and fat, but macroscopically the solid portion was unclear. No malignant component was microscopically observed. Pathologic examination of the right ovarian tumor showed a complex tumor containing a carcinoid component representing about two-thirds of the tumor mass admixed with abnormal thyroid tissue, consistent with an ovarian strumal carcinoid (Figure 1). Argyrophilic granules were demonstrated in the cytoplasm using the Grimelius staining methods. When examined by mRNA analysis according to the previously described protocol (shigeta, matsuda), the tumor cells expressed PYY as well as neurohormonal polypeptides including serotonin.

Two months after cystectomy, the patient was submitted to right salpingo-oophorectomy to look for residual tumor. The extensively sampled adnexa tissue was histologically uninvolved by the tumor. The patient was advised regular follow-up for one year at the time of her discharge.

Discussion

Primary carcinoids are subdivided into four categories: insular, trabecular, mucinous, and strumal. Primary strumal carcinoid of the ovary is very uncommon and complicated sometimes by carcinoid syndrome that is a result of various bioactive polypeptides produced by tumor [3, 5]. Ovarian stumal carcinoid is of low malignant potential and its prognosis is usually good in the majority of patients. The tumor extended beyond the ovary in only four reported cases: one of which was a patient with strumal carcinoid containing trabecular carcinoid, in whom the metastatic tumor resembled a well-differentiated thyroid follicular carcinoma [6]. The second patient was a case of strumal carcinoid containing...
largely trabecular and partially insular carcinoid, in whom the metastatic tumor was poorly differentiated adenocarcinoma [7]. Matsuda et al. [3] describe an interesting case with ovarian strumal carcinoid tumor who suffered from carcinoid syndrome severe constipation, which was relieved by tumor removal but recurred with recurrent hepatic disease. She suffered again from constipation. Another case was a 44-year-old woman who had metastasis in the contralateral ovary, myometrium and lungs [8].

Carcinoid syndrome is mediated by bioactive polypeptides produced from carcinoid tumor cells, which are of germ cell origin. The syndrome is less frequent in primary ovarian carcinoid than in that of the intestine. It was postulated that the syndrome typically occurs in the absence of extraovarian spread because the ovarian venous drainage, unlike intestinal origin, bypasses the liver which inactivates the substances responsible for the syndrome [3]. Our case was a strumal carcinoid composed of thyroid tissue and trabecular carcinoid, in which PYY mRNA was not detected. Constipation was drastically improved by resecting the tumor. This fact could provide evidence of the correlation between constipation and PYY. It is important to be aware of this entity in the pathological diagnosis of ovarian tumors, in the presence of any clinical indicator of carcinoid tumor/syndrome, as it carries a markedly better prognosis and clinical outcome in comparison with most other malignant ovarian tumors.

In conclusion, our case provides more convincing information to indicate that PYY protein, produced by ovarian carcinoid tumor of strumal component, may be associated with a favorable prognosis predictor.

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Advanced embryonal rhabdomyosarcoma of the uterine cervix: a case report

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Introduction

Embryonal rhabdomyosarcoma (RMS) is a tumor composed of embryonal rhabdomyoblasts, the origin of which is the stromal mesenchyme in the lamina propria. Its former name, “sarcoma botryoides”, reflects the gross appearance of the neoplasm as multiple “grape-like” polyps [1]. Primary embryonal RMS arising from the uterine cervix is a rare and extremely malignant entity. Mostly young women aged 12-26 years are affected [1, 2].

The most common symptom is vaginal bleeding, which in infants is often detected because of intermittent bloody discharge on the diaper. If large, the tumor may distend the lumen of the vagina and protrude through the introitus as soft, polypoid, grape-like masses.

Microscopically, embryonal RMS has a “cambium layer”, represented by a subepithelial condensation of tumor cells. The neoplastic cells are reactive for desmin, myo-D1, and myogenin [1].

Before the introduction of effective adjuvant chemotherapy, the prognosis of these lesions was poor. A combined modality approach to treating RMS using surgery, multidrug chemotherapy, and radiotherapy has significantly improved survival [3, 4]. With treatment, the overall survival rate nears 80% [5].

We have treated a very young woman suffering from advanced embryonal RMS using a combination of surgery, chemotherapy and radiation therapy with excellent results.

Case Report

A 16-year-old girl presented to a gynecologist with one-month history of abnormal vaginal bleeding and abdominal pain. Her past medical history was unremarkable. Physical examination revealed a decaying lobulate necrotic tumor, filling the vagina and whole pelvis. Pelvic computed tomography (CT) scan revealed an anechogenic tumorous mass originating from the uterus and filling the whole pelvis. Chest X-ray was normal.

Histology of the vaginal tumor biopsy showed rhabdomyosarcoma botryoides with micro foci of cartilage (Figure 1). Immunohistochemically tumor cells were positive for the skeletal muscle markers: sarcomeric actin, myoglobin, myo-D1 and desmin, which confirmed the diagnosis of embryonal RMS (Figure 2).

At laparotomy, it was clearly that the tumor originates from the cervical part of the uterus, with normal appearance of the uterine corpus. There were no signs of dissemination of disease in the abdominal cavity. Lymphatic glands were without palpable signs of disease. We performed total abdominal hysterectomy, upper vaginectomy and bilateral pelvic and paraaortic lymphadenectomy. The ovaries showed no signs of disease and were preserved.

The surgical resected specimen measured 13 x 17 x 8 cm, and was partially necrotic. Tumor was present within the cervical canal and infiltrated through the introitus as soft, polypoid, grape-like masses. Tumor infiltrated the cervical and uterine wall with multiple overgrowths beneath the serosa. The microscopic resected specimen showed embryonal RMS including cartilaginous neoplastic elements. Metastases were present in the vaginal cuff, obturator and iliac lymph nodes. The tumor was classified as group II C by the Intergroup Rhabdomyosarcoma Study Group (IRSG) clinical grouping classification (Table 1) [3].

After surgery, the patient received treatment with adjuvant chemotherapy consisting of vincristin, actinomycin D and cyclophosphamide (VAC regimen) every three weeks for six courses. After six courses of chemotherapy, she was treated with radiotherapy. She was followed up closely (every 2-3 months) after completing the therapy.

The patient was alive and well with no evidence of disease five years after the surgery.
Discussion

RMS is a highly malignant tumor arising from embryonal mesenchyma, and is the most common soft tissue sarcoma in childhood and in young adults accounting for 4-6% of all malignancies in this age group [2]. Embryonal RMS occurs primarily in three regions – the head and neck, the genitourinary tract, and the infantile vagina is the most common site, but this cancer may also occur in the uterine cervix. This neoplasm frequently has a vaginal location in children younger than four years, whereas cervical onset has a peak incidence in the first or second decade of life [6]. Some recently published studies suggested that, in contrast to embryonal RMS occurring in the vagina, cervical embryonal RMS has a favorable outlook [7].

The IRS group has reported a new classification of RMS recognizing three major histological subtypes: embryonal, alveolar, and undifferentiated. The botryoid type is a variant of embryonal RMS [1], which accounts for no more than 5-10% of all RMS. A distinct “cambium layer” beneath the epithelium is characteristic. Several cases, including ours, have shown metaplastic cartilaginous differentiation, which is a positive prognostic factor. Histopathologic factors that appear to correlate with an adverse prognosis include deep myometrial invasion, lymphatic invasion, and a focal alveolar pattern [8].

At the time of presentation, the embryonal subtypes are often localized with a favorable prognosis, in contrast to alveolar subtypes which present with distant metastasis and less favorable prognosis [8].

Pathologically the tumor may be misdiagnosed as malignant mixed müllerian tumor, because both conditions are characterized by malignant epithelial and supportive tissue. Absence of malignant epithelial tissue is the critical point for the differential diagnosis between carcinosarcoma and RMS [9]. Immunohistochemistry is extremely useful for confirming the diagnosis of RMS. Myogenin and myo-D1 are relatively new antibodies generated against intranuclear myogenic transcription factors and are considered to be relatively specific markers of skeletal muscle differentiation, although occasional myogenin-positive nuclei may be seen in reactive lymph nodes [9, 10]. These markers are more commonly positive in alveolar than embryonal RMS. They are considered the best available markers for confirmation of RMS.

In our case the tumor cells were positive for sarcomeric actin, myoglobin, myo-D1 and desmin, which confirmed the diagnosis of embryonal RMS.

The mainstay of primary therapy consists of local or radical surgery with or without adjuvant postoperative chemotherapy and radiotherapy [11, 12]. Prior to the introduction of multiple chemotherapeutic agents in the 1960s, surgery played a principal role in the treatment of patients with RMS. In the past, these lesions were treated with extensive surgery, including exenteration, with poor results. The addition of chemotherapeutics as an adjuvant
to surgery has markedly improved the overall prognosis for RMS. The IRS Group was formed under the auspices of the National Cancer Institute in 1972 to investigate the therapy and biology of RMS and undifferentiated sarcoma, thus the treatment of RMS has been extrapolated from this group, so that optimal management may be achieved. As a result, the five-year survival rates for patients in clinical groups I-IV reported by the IRSG were 83%, 70%, 52% and 25%, respectively [3]. For cervical sarcoma botryoides, Brand et al. [5] reported an overall survival of 80%. Approximately 75% of cervical RMS patients present with group I disease.

The surgical procedures range from tumorectomy, wide local excision, and trachelectomy up to radical hysterectomy and pelvic lymph node dissection in cases with more advanced disease or large or deeply infiltrating neoplasms [4, 13]. Patients with embryonal RMS with favorable prognostic parameters, such as localized disease without deep myometrial invasion, a single polyp and embryonal histologic subtype, can effectively be treated by surgery. In early disease, also with the aim of preserving the reproductive potential, a conservative surgical approach consisting of local excision of the neoplasm has been reported [4, 13, 14]. This type of treatment is reserved only for patients with Stage I disease (Table 1) and neoplasm confined to the cervix. Patients with unfavorable prognostic parameters seem to benefit from a multimodality approach including surgery, adjuvant chemotherapy and radiotherapy.

The most widely used chemotherapy regimen includes VAC. One important result of the IRSG Study II for group I patients (Table 1) was that cyclophosphamide did not contribute to the success of treatment, but significantly reduced treatment toxicity [12]. A report by Gordon and Montag suggested that between six and 12 VAC cycles would allow a reasonable probability for return of menstruation and reproductive function [15].

The most important prognostic factors appear to be extent of disease at diagnosis and site of primary tumor, with sites that produce symptoms earlier having a better prognosis [2, 12].

In the present case the necessity of complementary chemotherapy and radiotherapy was chosen according to the locally advanced disease infiltrating also the upper vaginal vault and both obturator and iliac lymph nodes. This case represents another example of a successful multimodality approach to treatment of advanced RMS with excellent results.

Conclusions

Patients with embryonal RMS with favorable prognostic parameters, such as localized disease without deep myometrial invasion, a single polyp and embryonal histologic subtype, can effectively be treated by surgery. Patients with unfavorable prognostic parameters seem to benefit from a multimodality approach including surgery, adjuvant chemotherapy and radiotherapy. The medical community should keep in mind that embryonal RMS of the uterine cervix, despite its malignancy and rarity, can be cured if adequate and timely treatment is given.

References


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Borderline mucinous tumor arising in a paratubal cyst: a case report

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Summary

Background: Paratubal borderline tumors (PBTs) are found incidentally at frozen section or permanent pathology, and are extremely rare. We describe the first case of a paratubal borderline mucinous tumor (PBMT). Case report. A 20-year-old woman was referred with a complex right adnexal mass on pelvic sonogram. She underwent laparoscopic paratubal cyst enucleation. We used an endobag for cyst extraction. Cyst rupture or tearing of the endobag in the laparoscopic field was absent. Frozen section analysis was reported as a borderline mucinous tumor of low malignant potential. Currently, she has had no evidence of disease recurrence after a laparoscopic fertility-sparing staging procedure. Conclusion. A proper preoperative differential diagnosis of an adnexal mass is difficult. Thus, laparoscopy is needed in large or symptomatic cysts. Although growth, torsion and malignancy are rare in paratubal cysts, the possibility of tumor seeding should be excluded with use of an endobag.

Key words: PBMT, Paratubal cyst, Laparoscopy.

Introduction

Tumors of low malignant potential (LMP) originating in the fallopian tube and paratubal cysts are found to be extremely rare. Paratubal cysts are unusually large enough to be clinically significant and may be incidental findings. Borderline ovarian tumors (BOTs) often occur in reproductive-age women, generally behaving in a benign fashion. However, they can exist with metastatic disease and recur. BOTs account for 10-15% of all ovarian tumors. However, after a review of the literature, borderline tumors arising in a paratubal cyst have been in a total of two previously reported cases, one being endometrioid [1] and one serous [2]. We report the first case of a paratubal borderline mucinous tumor (PBMT).

Case Report

A 20-year-old, nulliparous woman was referred with a one month history of a complex adnexal mass. Abdominal-pelvic CT scan revealed a 10 x 7.6 x 9.4 cm multi-lobulated cystic adnexal mass that contained an enhancing solid portion. On laparoscopic inspection, the 10 x 8 cm paratubal cyst was located in the ampullary and fimbrial region of the right fallopian tube (Figure 1). Firstly, we obtained fluid for peritoneal cytology by washing with normal saline in the cul de sac and both paracolic gutter. After such, she underwent laparoscopic right paratubal cyst enucleation without cyst rupture. We used an endobag for extraction of the removed cyst. Rupture of the cyst was performed in the endo-bag. Frozen section analysis indicated a borderline mucinous tumor of low malignant potential (LMP) with areas suspicious for invasion. On examination of other internal organs and after peritoneal inspection there were no suspicious areas of metastasis. The patient underwent fertility sparing comprehensive surgical staging including right salpingo-oophorectomy, partial omentectomy, appendectomy, and bilateral pelvic lymphadenectomy. The ovary and fallopian tube were grossly unremarkable. The specimen of tumor consisted of multiple fragments of cystic mass, measuring 9 x 7.5 cm. The inner surface showed 5.3 x 2 x 0.6 cm in size multiple papillary excrescences. The microscopic finding is shown in Figure 2. The epithelium lining the papillae was remarkable for stratification and tufting. There were focally significant nuclear atypia and a tiny focus of stromal invasion. The stroma underlying the proliferating epithelium was fibrotic and focally hyalinized. In the final pathologic report, paratubal tumor was classified as a borderline mucinous tumor (BMT) of endocervical-like subtype with microinvasion and intraepithelial carcinoma (IECa). She was assigned as Stage Ia. The patient underwent no further therapy and is currently free of disease 30 months after the initial surgery.

Discussion

Paratubal cysts represent approximately 10% of all adnexal masses and the reported incidence of malignancy is about 2-3% [3]. They most frequently occur in premenopausal patients. Although growth, torsion and malignancy are rare in paratubal cysts, laparoscopy can be needed in large or symptomatic cysts. Papillary projections on the cyst wall should be searched carefully, as in our case, for the possibility of cystadenoma, adenofibroma and borderline tumor. There have been a total of 16 previously reported cases of tumors of LMP of the fallopian tube and paratubal cysts in the literature since 1966, ten being serous, four mucinous, and two endometrioid type. While endometrioid and serous borderline tumors arising in a paratubal cyst have been reported [1, 2], our case is the first report in the literature of PBMT. Previously reported BMTs have been associ-
Borderline mucinous tumor arising in a paratubal cyst: a case report

The tumors occurred in the fallopian tube and had secreted mucinous material via the fimbrial end of the fallopian tube into the peritoneal cavity thus causing pseudomyxoma peritonei [4]. In this case, the tumor consisted of a cyst attached to the tube and independent of the lumen. Thus, it did not cause pseudomyxoma peritonei and may be better regarded as a paratubal lesion. BMTs have been subclassified into intestinal and endocervical-like subtypes. Pseudomyxoma peritonei is common in the intestinal type. Our case was the endocervical-like subtype. This type accounts for 5-15% of BMT. Single BMT may include IECa and microinvasion because of the heterogeneity of mucinous tumors. Our patient showed both IECa and microinvasion. Cancer progression rate of BMT is 1.6% and for tumors including IECa it is 6% [4]. There is no evidence-based recommendation for paratubal borderline tumors as yet, and clinical manifestation has been extrapolated from tumors of LMP of the ovary. Many young patients who have not completed childbearing can be safely treated with unilateral salpingooophorectomy after surgical staging for preserving fertility. In our case, the patient underwent laparoscopic cyst extraction without intraperitoneal rupture and fertility sparing staging surgery. Although the incidence of recurrence and cancer progression for borderline tumors are low, laparoscopic surgeons should be aware of the possibility of tumor seeding. Although laparoscopy for borderline tumors is controversial, laparoscopy of PBMT may be carefully performed without trocar site leakage or rupture of the cyst content by use of an endobag and skillful gynecologic oncology staff.

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Primary fallopian tube cancer in term pregnancy: a case report

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Summary

Purpose: This work aimed to study the features of primary fallopian tube carcinoma during pregnancy and to improve the understanding of clinical gynecologists. Methods: The clinical features of a case of primary fallopian tube carcinoma during pregnancy were analyzed. Results: The final diagnosis was Stage IA fallopian tube cancer after cesarean delivery. Conclusions: It is helpful to detect CA-125 level and employ B-mode ultrasound imaging. Patients should undergo routine celiac examinations before gynecological and obstetric procedures (including cesarean section and abdominal hysterectomy) are performed.

Key words: Fallopian tube cancer; Pregnancy; Case report.

Introduction

Primary fallopian tube carcinoma is a rare female reproductive malignant tumor, which accounts for 0.1%-1.8% reported gynecological malignancies [1]. Since primary fallopian tube cancer has atypical symptoms, the diagnosis is difficult with a high misdiagnosis rate and thus poor treatment. A case of primary fallopian tube carcinoma during pregnancy is reported together with a review of the literature.

Case Report

A 35-year-old patient, gravida 1, para 0, at 38 and four weeks of gestation was admitted to the Shenzhen Nanshan Hospital on October 26, 2009 due to vaginal bleeding with abnormal hypogastralgia for four hours. Her last menstrual period was on January 28, 2009 and the expected date of childbirth was November 5, 2009.

She had a history of morning sickness (nausea and vomiting) for 40 days after amenorrhea, which was alleviated after four months of gestation. During the gestational period, she was neither exposed to drugs nor radioactive substances. She had undergone regular obstetric examinations; her blood glucose level was 8.97 mmol/l, determined by oral glucose (50 g) tolerance tests performed at 24+ of gestation. On September 25, 2009 the oral glucose tolerance test (OGTT) showed that blood glucose levels were 10.77 mmol/l, 11.35 mmol/l, and 8.13 mmol/l, respectively at one, two and three hours after oral medication. She had gestational diabetes mellitus. She had been managed with diet control without drug therapy until the time of admission.

Routine medical examinations were performed after admission. The following results were obtained: body temperature 36.5°C; pulse rate, 90 beats/min; respiratory frequency 20 cycles/min; and blood pressure 137/74 mmHg. The general condition of the patient was good with no obvious cardiopulmonary abnormality. Obstetric examinations showed that the fundal height was 36 cm, abdominal perimeter was 98 cm, and the estimated fetal weight was 3,400 g. The position of the fetus was left occipito-anterior (LOA), the head appeared first with partial engagement, and the fetal heart rate was 138 beats/min. Vaginal examination showed that the head appeared first, and the cervix was undilated. The fetal membranes were not ruptured, amniotic fluid outflow was not observed, and vaginal pH was negative; the cervical canal disappeared partially. External pelvicmetry showed that the interspinous diameter was 24 cm, intercrural diameter 26 cm, external conjugate diameter 20 cm, and the bischial diameter was 9 cm. Auxiliary examinations showed negative results for human immunodeficiency virus (HIV), rapid plasma regain, and hepatitis B surface antigen. Therefore, at admission, the fetus was in the LOA position, and there was premature rupture of the fetal membranes.

On October 27, 2009 the patient underwent cesarean delivery under combined spinal-epidural anesthesia with a transverse incision of the lower uterine segment and left salpingectomy. The lower uterine segment was well developed and the amniotic fluid (800 ml) was clear. The patient delivered a baby boy weighing 3,750 g and the Apgar score was 10 at both 1 and 5 min. The placenta was completely stripped, and uterine examination indicated that the uterus was normal. The ampulla of the left fallopian tube was thickened with an allantoid-shaped mass 4 x 3 cm in size. The surface of the mass was smooth and intact without adhesions. The left ovary and the right adnexa were normal in appearance.

After the patient underwent left salpingectomy the surgical specimens were sent for pathological examination. The results of pathological examination performed after surgery (pathological report no. 200909535) showed well differentiated adenocarcinoma of the left fallopian tube without cancerous invasion to the serosa. Immunohistochemistry revealed that the tumor cells were progesterone receptor (PR)(+), estrogen receptor (ER)(-), CerB2 (-), p53 (-), and (CEA)(-). The diagnosis was confirmed by the pathology report of Sun Yat-Sen University. Thus, the final diagnosis was Stage IA fallopian tube cancer. After the patient was discharged, she was admitted to Beida Shenzhen Hospital where she underwent total hysterectomy plus bilateral salpingo-oophorectomy, omentum majus resection, appendectomy and pelvic lymph node dissection. She received chemotherapy consisting of the combination of taxol plus carboplatin (TP regimen). The serum CA-125 value at the last follow-up was within normal range.

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Discussion

Primary fallopian tube cancer (PFTC) is a rare cancer of the female reproductive system, accounting for 0.1-1.8% of female genital tract malignancies. The morbidity rate due to PFTC in the USA from 1998 to 2003 was reported to be 0.41/100,000 [1]. The peak onset age is 50-60 years, and PFTC occurs in two-thirds of patients after menopause. Reports show that morbidity due to PFTC tends to increase gradually, and increases markedly in patients in the middle and early stages of PFTC [2, 3]. The pathogenesis of PFTC remains unclear, but it may be associated with chronic salpingitis, infertility, tuberculous salpingitis, and endosalpingiosis. Annika, et al. [4] reported that parity plays a protective role against fallopian tube cancer (FTC) and that this protection was enhanced with increased parity. A cytogenetic study showed that p53, HER2/ne, and c-myc were overexpressed in patients with FTC. Further, the number of BRCA1 and BRCA2 mutations was greater in patients with PFTC than in normal subjects [1]. We have successfully treated a case of PFTC at term-pregnancy. To our knowledge, this is the first report on this condition.

The survival rate of patients in early stages of PFTC is greater than for those in late stages; therefore, early diagnosis of the condition is very important. The trio of abnormal vaginal discharge, hypogastralgia, and pelvic mass are the main signs of tubal carcinoma; however, these signs are seldom observed simultaneously. Imaging studies, especially vaginal B-mode ultrasound imaging facilitates the early diagnosis of PFTC. Following are the characteristics [5] of an acoustic image of FTC: 1) the annex region presents with an allantoid or irregular-shaped mass, and a cystic-solid-papillary appearance; 2) the ovarian morphology of the annex region is intact; 3) both the solid echo of the annex region and resistance index (RI) of the bloodstream in the papilla are low [5].

Monitoring serum CA-125 levels is essential for the detection of recurrence of PFTC. Continuous monitoring of serum CA-125 levels indicated that this value reached up to 145-535 U/ml, declined after the initial treatment, and increased in cases where PFTC relapsed. Therefore, serum CA-125 level is an important indicator in the diagnosis and monitoring of FTC. Some studies have also reported that increased serum CA-125 values occurred three to 11 months before the appearance of clinical symptoms, and thus early diagnosis was possible by detection of serum CA-125 [6]. Some studies have also reported [7] that the serum CA-125 level was not correlated with cancer grade in early stage FTC. However, nonspecific early diagnostic methods were used in the above-mentioned examination. In our case, pregnancy and premature rupture of fetal membranes obscured the symptoms of FTC; pregnant uterine hypertrophy covered the mass of the adnexa, and it was difficult to locate the cancer focus via imaging examination. Thus we conducted routine pelvic examinations on the patient to avoid reoperation for further investigation; the pelvic architecture was examined during cesarean delivery and frozen sections were prepared of the tissue samples collected from the adnexa during the same operation.

PFTC metastasizes via local diffusion and lymph node metastasis. It is mostly treated by surgery and chemotherapy and/or radiotherapy are administered as adjuvant therapies. The strategy for surgical treatment of PFTC includes cytoreductive surgery, including hysterectomy bilateral salpingo-oophorectomy, pelvic lymph node dissection, omentum majus resection, and appendectomy. Thus, the approach involves resection of all primary and metastatic carcinomas as far as possible, such that the residual cancer focus is reduced to less than 1 cm. A recent study [8] showed that 33% of the patients with Stage I/II FTC developed paraaortic or pelvic lymph node metastasis. Therefore, our patient underwent total hysterectomy plus bilateral salpingo-oophorectomy, omentum majus resection, appendectomy and pelvic lymph node dissection.

Chemotherapy is the major postoperative adjuvant therapy. A study by the Gynecologic Oncology Group (GOG) showed that combined chemotherapy with taxol plus carboplatin (TP regimen) for 60 months reduced the risk of progression by 28% and mortality by 34%. Moreover, follow-up studies for 6.5 years indicated that the TP regimen has superior long-term efficacy as compared to the CP regimen (cisplatin plus cyclophosphamide) [9]. These findings support the TP regimen as the preferred chemotherapy for PFTC. Our patient also underwent chemotherapy with the TP regimen. Findings reported by a previous study [10] showed that pelvic radiotherapy did not improve survival rate; its efficacy to treat the entire abdomen has not been determined, and extra-abdominal metastasis recurred and was commonly complicated by severe gastrointestinal complications. Thus radiotherapy is not the preferred postoperative adjuvant therapy but should be used for palliative care in relapse patients.

On the basis of the results from the above-mentioned case report, we recommend that PFTC should be suspected in pregnant women presenting with abnormal vaginal discharge and metrorrhagia, women in the puerperium (especially eutocia) who present with a pelvic mass detected by color Doppler ultrasound imaging, blood vessels (RI < 0.5) in the mass detected by color Doppler ultrasonography, and increased levels of serum CA-125. These women should undergo surgery and other treatments as early as possible. Patients should also undergo routine celiac examinations before gynecological and obstetric operations (including cesarean section and abdominal hysterotomy) are performed. If the fallopian tubes are observed to be thickened and hardened during the operation, FTC should be suspected after excluding inflammation of the fallopian tubes and salpingocytosis. Further, tissue samples should be obtained and frozen sections prepared for histological examination to avoid misdiagnosis. After the diagnosis is confirmed, patients should undergo immediate surgery and adjuvant chemotherapy, and be followed-up regularly.
Acknowledgement

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Prolonged survival after episiotomy recurrence of cervical cancer complicating pregnancy

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¹Department of Radiation Oncology, ²Division of Gynecologic Oncology, Indiana University School of Medicine, Indianapolis, IN (USA)

Summary

Background: We report a case of recurrent cervical cancer in an episiotomy scar and the late treatment-related sequelae. Case: Cervical cancer was diagnosed following a vaginal delivery, and was treated with surgery and radiotherapy. The patient developed a recurrence in her episiotomy scar, and was treated with chemoradiation. She remains without evidence of disease ten years later. Conclusion: Successful treatment of recurrent cervical cancer with chemoradiation is possible, but may be associated with significant normal tissue toxicity.

Key words: Episiotomy; Cervical cancer; Pregnancy complication; Surgery; Radiation therapy.

Introduction

Although the exact incidence and prevalence of cancer during pregnancy remains unknown, reliable estimates suggest that it is uncommon, occurring at a frequency of between one to two new cases in every 1,000 pregnancies [1]. More specifically, the incidence of cervical carcinoma during pregnancy is estimated to be 1.2 cases per 10,000 pregnancies [2]. However there have been only 17 cases of cervical cancer recurrence at the site of an episiotomy in the English language literature (Table 1). The majority of cases (14 of 17) recurred within five months of delivery; many were rapidly fatal. We discuss the long-term course of treatment for – and sequelae of – a woman with cervical adenosquamous carcinoma diagnosed at the time of delivery with subsequent recurrence at the episiotomy scar. The case highlights an exceptionally unique example of long-term survival following an episiotomy recurrence of cervical cancer that was treated with chemoradiation alone and without excision and the issues surrounding quality of life that such survival entails.

Case Report

A 35-year-old female, G3P3A3, received a diagnosis of squamous cell carcinoma (IBG2) of the cervix at the time of delivery at another medical treatment facility. Following an otherwise normal vaginal delivery, the patient underwent radical hysterectomy and postoperative cobalt radiotherapy. She received 50 Gy to the whole pelvis using opposed anteroposterior fields, with the placement of a midline block after 38 Gy. More detailed records of her initial treatment were not available. Five months following treatment, the patient was found to have a perineal recurrence of her cancer at the site of the episiotomy. An exploratory laparotomy, with pelvic lymph node dissection, at the time was negative. She received 45 Gy using small anteroposterior photon fields inferior to the area demarcated by her prior treatment tattoos and existing subcutaneous fibrosis. A 16.2 Gy electron boost was then delivered using the en face technique to perineal residual disease at that point, to a total dose of 61.2 Gy with five cycles of concurrent 5-fluorouracil and mitomycin. Within three months of completion of chemoradiation, the patient developed dyspareunia, proctitis, and a persistent, tender ulcer of the perineal body. Excision was negative for malignancy; however, the patient developed necrosis of the perineal body with persistent tenesmus and rectal bleeding. Over the ensuing years, she experienced dyspareunia and post-coital bleeding, and subsequent rectovaginal fibrosis.

Discussion

Cervical cancer complicating pregnancy is a rare event. Even more infrequent is cancer recurrence at the site of an episiotomy scar. Seventeen such cases have been reported to date, with patient ages ranging from 21 to 37 (Table 1). Survival times vary, but seem to improve notably with aggressive therapy of the recurrent lesion typically consisting of excision with chemoradiation or brachytherapy in combination with external beam radiation. We found only four reported cases where patients with episiotomy recurrences were treated using chemoradiation alone [7, 9, 11, 13]. In three of these, the patients died of disease within three years of recurrence. Our patient thus is an anomaly: she was treated using salvage chemoradiation alone without excision, and has survived more than 120 months after her recurrence.

To avoid a theoretical risk of dystocia and massive bleeding from the tumor mass, cesarean section as a route of delivery has been a prevailing recommendation for...
Amanie et al. [11] 30 A IIIA 1.5 years chemotherapy and radiotherapy 6 months
Heron et al. [12] 32 A IB1 8.7 years radiotherapy > 10 months
Baloglu et al. [13] 36 S IIIA 8 months radiotherapy and chemotherpay > 1 year
Neumann et al. [11] 35 AS IB2 5 weeks radiotherapy and chemotherpay 8 months
Hafeez et al. [10] 35 S IB 10 months radiotherapy and chemotherpay > 10 years

A = Adenocarcinoma, S = Squamous Carcinoma, AS = Adenosquamous Carcinoma.

Table 1.—Cases of episiotomy recurrences of cervical cancer from the literature.

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In conclusion, recurrence of cervical cancer at the site of an episiotomy scar is rare. Long-term prognosis varies greatly, with increased survival potentially favored by aggressive therapy, including chemoradiation. We report a case of long-term survival greater than ten years following chemoradiation. This case illustrates the importance of inspecting the perineal area of a patient diagnosed with cervical cancer during pregnancy, especially after vaginal delivery and when an episiotomy has been performed. In the event of cervical cancer diagnosed during pregnancy with unavoidable vaginal delivery and episiotomy, regular reexamination of the scar is prudent.

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<td>radiotherapy</td>
<td>&gt; 10 months</td>
</tr>
<tr>
<td>Baloglu et al. [13]</td>
<td>36</td>
<td>S</td>
<td>IIIA</td>
<td>8 months</td>
<td>radiotherapy and chemotherpay</td>
<td>&gt; 1 year</td>
</tr>
<tr>
<td>Neumann et al. [14]</td>
<td>35</td>
<td>AS</td>
<td>IB2</td>
<td>5 weeks</td>
<td>radiotherapy and chemotherpay</td>
<td>8 months</td>
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<tr>
<td>Hafeez et al. [10]</td>
<td>35</td>
<td>S</td>
<td>IB</td>
<td>10 months</td>
<td>radiotherapy and chemotherpay</td>
<td>&gt; 10 years</td>
</tr>
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A = Adenocarcinoma, S = Squamous Carcinoma, AS = Adenosquamous Carcinoma.

pregnancies complicated by cervical cancer since the 1960s [15]. However proof of such benefit is difficult to determine from the literature. It is not known whether delivery by cesarean section carries a risk for tumor implantation in the abdominal scar or for metastases to regional lymphatics, and at least one case suggests the possibility of cervical cancer recurrence in the scar of a previous cesarean section [16]. Furthermore, the prognosis for cervical cancer diagnosed during pregnancy remains in dispute, with Hopkins et al. reporting no decrement in survival of patients with Stage IB cervical cancer associated with pregnancy [17]. A case-control study in women diagnosed postpartum done in 2000, however, showed an increased risk of recurrent disease, with generally poorer outcome, especially after vaginal delivery, versus women diagnosed during pregnancy [18].

Chronic radiation effects to tissue at risk of scarring and thus poor vascularity may be significant. We have previously discussed this effect in treating skin cancers of the lower extremity in the elderly [19]. The result was similarly dramatic here in a perineal body biopsied several months after chemoradiation: necrosis and persistent rectovaginal communication distally requiring colostomy.

In conclusion, recurrence of cervical cancer at the site of an episiotomy scar is rare. Long-term prognosis varies greatly, with increased survival potentially favored by aggressive therapy, including chemoradiation. We report a case of long-term survival greater than ten years following chemoradiation. This case illustrates the importance of inspecting the perineal area of a patient diagnosed with cervical cancer during pregnancy, especially after vaginal delivery and when an episiotomy has been performed. In the event of cervical cancer diagnosed during pregnancy with unavoidable vaginal delivery and episiotomy, regular reexamination of the scar is prudent.

References
Prolonged survival after episiotomy recurrence of cervical cancer complicating pregnancy


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Aggressive ovarian psammocarcinoma: a case report

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Summary
Serous psammocarcinoma is a rare form of ovarian carcinoma characterized by massive psammoma body formation. We report a new case of aggressive ovarian psammocarcinoma with omental and peritoneal implants.

Key words: Psammocarcinoma; Ovary; Psammoma body.

Introduction
Psammocarcinoma is an unusual form of epithelial serous ovarian carcinoma characterized by the presence of psammoma bodies.

Histologically, it is characterized by massive psammoma body formation, destructive invasion of ovarian stroma, vascular invasion or intraperitoneal visceria in extraovarian tumors and moderate cytological atypia [1]. We report a new case of serous psammocarcinoma with clinical and pathological aspects.

Case Report
A 52-year-old woman (gravid 4, para 4) was admitted to a gynecology clinic for an adnexal mass which was suspected at first to be a dermoid cyst.

The patient underwent a minilaparotomy which revealed a voluminous abdominopelvic mass with multiple pelvic adherences. The biopsy of the mass revealed a psammocarcinoma of the ovary (Figure 1). She was then referred to our institution for treatment. Pelvic examination showed a sensitive voluminous abdominopelvic mass. Abdominal computed tomography scan revealed a heavily calcified abdominopelvic mass (= 10 cm) (Figure 2). The serum CA-125 level was elevated (79 UI/ml; normal: < 35 UI/ml).

Primary chemotherapy was planned. The patient received three courses of paclitaxel 175 mg/m² and carboplatin (5 AUC). Then she underwent exploratory laparotomy. Intraoperative findings showed the presence of an irregular mass adherent to the bladder, the small bowel, the sigmoid colon and Glisson’s capsule. The omentum and peritoneal surface were covered with tumor implants. The International Federation of Gynecology and Obstetrics (FIGO) stage was IV, and surgical debulking was impossible (Figures 3 and 4). The patient received three postoperative courses of paclitaxel (175 mg/m²) and carboplatin (5 AUC). The chest-abdominal and pelvic CT scan revealed a progression of the abdominopelvic mass and the CA-125 level was more elevated (1000 UI/ml).

Discussion
Psammocarcinoma is a rare form of low-grade serous carcinoma characterized by the presence of psammocarcinoma bodies. Thirty-seven cases have been published up to now. Gilks et al. [1] defined some criteria for diagnosis of psammocarcinomas:

– destructive invasion of ovarian stroma, vascular invasion, or in extra ovarian cases, invasion of intraperitoneal visceria;

– no more than moderate nuclear atypia;

– no areas of solid epithelial proliferation except for occasional solid nests with no more than 15 cells in diameter;

– 75% of papillae or nests associated with or completely replaced by psammoma bodies [1].

In our case, histopathology was compatible with Gilks et al’s criteria.

Psammoma bodies are commonly found in certain human cancers (e.g., thyroid, meningial, ovarian, gastrointestinal tumors, and gastric adenocarcinoma) [2].

The median age of clinical presentation of the disease is 54 years and FIGO stage is commonly Stage III (only one case was classified as IA) [3].

Psammocarcinoma can be asymptomatic or incidentally detected but in a lot of cases there is lower abdominal pain or swelling, a pelvic mass, nausea, vomiting, and then at last heavy menstrual bleeding [4, 6]. In our case it was a pelvic mass and pelvic pain.

Psammocarcinoma is an ovarian neoplasm with a more favorable prognosis than other serous carcinomas and is similar to serous borderline lesions of the ovary with no difference in rate of survival [2].

The mechanism of psammoma body formation in ovarian serous adenocarcinomas is the consequence of neoplastic and histiocytic cellular degeneration [5].

High CA-125 levels are usually detected in psammocarcinoma of ovary [6].

Treatment consists of total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, lymphadenectomy, appendicectomy, and maximal tumor debulking [7].

Sometimes, adjuvant chemotherapy or tamoxifen therapy in recurrent tumors has been planned [4]. There are no studies indicating the best treatment for this neoplasm [4].
Aggressive ovarian psammocarcinoma: a case report

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Vertical rectus abdominis myocutaneous flap for vaginal reconstruction after radical pelvic surgery for Stage II vaginal carcinoma

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Summary

Primary carcinomas of the vagina are uncommon, occurring only 2-3% of all gynecological malignancies. In women with early stage of disease, primary surgery, consisting of radical vaginectomy (plus hysterectomy in patients with tumors involving the upper vagina) and systematic dissection of lymphatic drainage of tumor, is a valid option. In these patients, a rectus abdominis myocutaneous (RAM) flap may be favorably used for vaginal reconstruction during radical pelvic surgery. Here we describe a case of Stage II vaginal carcinoma treated with radical pelvic surgery and vertical-RAM (V-RAM) flap reconstruction.

Key words: Vaginal carcinoma; Oncopelvic surgery; Reconstruction; V-RAM flap.

Introduction

Primary carcinomas of the vagina are uncommon, occurring in only 2-3% of all gynecological malignancies. Squamous cell carcinoma (SCC) is the most common histologic type (80-92%) [1]. In women with early stage of disease, primary surgery, consisting of radical vaginectomy (plus hysterectomy in patients with tumors involving the upper vagina) and systematic dissection of lymphatic drainage of tumor, is a valid option [2]. In these patients, a rectus abdominis myocutaneous (RAM) flap may be favorably used for vaginal reconstruction during radical pelvic surgery [3, 4]. A case of Stage II SCC of the vagina treated with radical pelvic surgery and vertical-RAM (V-RAM) flap reconstruction is described.

Case Report

A 52-year-old menopausal woman with the complaint of vaginal bleeding was referred to our oncology department. A warty, necrotized, exophytic mass of the vagina, originating from the right fornix and anterior vaginal wall and extending to the middle part of the anterior vaginal wall was found. Biopsy specimen of the vaginal mass showed squamous cell carcinoma (SCC) of the vagina. Preoperative magnetic resonance imaging (MRI) revealed a 4.5 x 3.5 x 3 cm mass originating from the right-anterior vaginal wall and involving the subvaginal tissue but not extending to the pelvic wall. She underwent radical vaginectomy and Wertheim hysterectomy, and bilateral pelvic lymphadenectomy. Then a V-RAM flap reconstruction was performed (Figure 1a-b-c). The histopathological finding demonstrated SCC of the vagina with clear margins and the absence of metastasis to the lymph nodes. The clinical-pathologic stage (FIGO) was Stage II. There were no major flap or donor area complications in the postoperative period. Favorable aesthetic and functional outcomes were observed after adjuvant radiotherapy in the six months follow-up (Figure 1d).

Discussion

Vaginal reconstruction after cancer resection is a difficult challenge because of the functional, anatomical and aesthetic importance of this region. Increased use of adjuvant radiotherapy and chemotherapy not only demands uncomplicated wound healing but also needs healthy, well-vascularized tissue. Successful management of vaginal reconstruction patients requires a multidisciplinary approach. The oncologist, gynecologist and reconstructive surgeon play an important role in the overall treatment plan. Sexual function and restoration of the pelvic floor can most reliably be achieved by planning and choosing the appropriate flap. Today there are various techniques to be used for vaginal reconstruction. More recently RAM flaps have become a reliable and advantageous procedure [3].

In conclusion, we believe the use of pedicled V-RAM flaps for vaginal reconstruction in radical oncopelvic surgery should be considered owing to the low specific morbidity and postoperative complication rate. This procedure may also reduce secondary re-interventions.
Vertical rectus abdominis myocutaneous flap for vaginal reconstruction after radical pelvic surgery for Stage II vaginal carcinoma

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Figure 1. — a) Perineal view of the patient after radical pelvic surgery, b-c) Steps in the creation of a VRAM flap, d) Perineal view of the patient six months after operation.
Successful salvage treatment of recurrent endometrial cancer with multiple lung and abdominal metastases

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Summary

The prognosis of recurrent endometrial carcinoma is generally poor except for isolated vaginal or pelvic relapse without previous radiation. Recurrences associated with infield failure or distant metastasis carry a poor prognosis [1-4]. We report a case of recurrent endometrial carcinoma treated with cytoreductive surgery, targeted radiation to residual lung metastasis defined by computed tomography (CT) and positron emission tomography (PET) and adjuvant chemo-hormone therapy followed by maintenance progestin therapy with a good outcome. This case implied that chemo-hormone therapy with targeted radiation should be evaluated in recurrent endometrial cancer with positive progesterone receptor for salvage treatment.

Key words: Recurrent endometrial cancer; Chemo-hormone therapy; Targeted radiation; Salvage treatment.

Introduction

The prognosis of recurrent endometrial carcinoma is generally poor except for isolated vaginal or pelvic relapse without previous radiation. Recurrences associated with infield failure or distant metastasis carry a poor prognosis [1-4]. We report a case of recurrent endometrial carcinoma treated with cytoreductive surgery, targeted radiation to residual lung metastasis defined by computed tomography (CT) and positron emission tomography (PET) and adjuvant chemo-hormone therapy followed by maintenance progestin therapy with a good outcome.

Case

A 62-year-old female patient with a history of endometrial cancer presented in July 2002 with left lower abdominal pain and small caliber stool for six months after staging surgery and adjuvant radiation in another hospital two years before. CT showed suspicious peritoneal and lung metastases (Figures 1A/B). There was no organic lesion on her low gastrointestinal series but stenosis of the canal was noted on her sigmoidoscopic study. Serum CA-125 was 97.5 U/ml. Bone scan was negative. There was no palpable neck or inguinal lymph node. Pelvic examination showed no obvious pelvic mass. Review histology slides from her initial surgery revealed well-differentiated endometrioid adenocarcinoma of the endometrium with cervical and ovarian metastasis. PET scan (Figure 2) revealed bilateral lung fields with pleura involved and tumor seedings over intraabdominal and presacral areas. CT-guided biopsy on lung and abdominal tumors showed metastatic adenocarcinoma with progesterone receptor+++ and negative estrogen receptor by immunohistochemical analysis.

Second debulking surgery was performed in which the pelvic seedings and omental tumors were resected. The cytoreductive surgery was suboptimal because of residual multiple subphrenic tumor seedings. Adjuvant chemotherapy with cisplatin (60 mg/m²) and epirubicin (60 mg/m² 3-weekly) and hormone therapy with megestrol acetate (160 mg daily) were initiated after surgery. Her serum CA-125 was 10 U/ml after four cycles of chemotherapy.

In the interval assessment of tumor response, chest high-resolution CT scan showed regression of previous lung lesions except a left hilar mass. Because of the pulmonary finding, we added radiotherapy of 36 Gy concurrently with chemotherapy.

Figure 1. — CT scans show carcinomatosis with (A) intraabdominal tumors and (B) multiple lung metastases.
Successful salvage treatment of recurrent endometrial cancer with multiple lung and abdominal metastases

The role of salvage cytoreductive surgery on recurrent endometrial cancer is undefined. In a case series of 20 patients undergoing surgical resection for recurrent endometrial cancer, the overall survival was significantly better in those without residual tumor than those with suboptimal debulking surgery, 53 months versus nine months [6]. Awtrey et al. [7] found that residual disease after second cytoreduction was the sole significant prognostic factor for progression-free and disease-specific survival. Bristow et al. [8] compared the survival of the patients treated with surgery (optimal and suboptimal) from those without surgery. They concluded that the amount of residual disease was the only independent predictor of progression-free and overall survival time.

Chemotherapy is considered the mainstay in the management of advanced and recurrent endometrial cancer. The response rate to combination chemotherapy is approximately 34-46%, [2-3, 9]. Targeted therapies for endometrial cancer obtained 0-15.1% response rates in a phase II study [3, 9]. Progestins are the most widely used hormone therapy in the treatment of recurrent or metastatic endometrial cancer [10-13]. The response rate is approximately 11-56%, and median time to progression 2.5-14 months in grade 1 or 2 tumors [11]. Chemotherapy plus sequential hormone therapy with megestrol acetate and tamoxifen achieved 30.8% complete and 46.2% partial response rates in a small phase II study (n = 13) [12]. However, the combination of hormone therapy and...
PET is now widely applied on the management of cancer patients. The role of PET in endometrial cancer is relatively less defined because of the lack of data in the literature [14]. Chao et al. [15] reported a prospective study of 49 endometrial cancer patients, including 26 for recurrence surveillance and seven after salvage therapy. They concluded that the clinical impact was positive in 73.1% for post-therapy surveillance, and 57.1% after salvage therapy. The value of PET for the current case was defining the extent of recurrences and monitoring response to salvage therapy.

This case indicates that multimodality therapy with cytoreduction surgery, chemo-hormone therapy and targeted radiation has successfully accomplished a long-term disease-free survival for a patient with recurrent endometrial cancer of extremely poor prognosis. Chemo-hormone therapy with targeted radiation should be evaluated in recurrent endometrial cancer with positive progesterone receptor for salvage treatment.

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Metastatic cervical adenocarcinoma mimicking retroperitoneal sarcoma of the psoas muscle on imaging

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Summary

Background: The incidence of bone metastasis is low in metastatic cervical cancer, especially in the case of adenocarcinoma. Incidental finding of a mass located in an unusual metastatic site in the absence of identifiable primary tumor often results in a difficult diagnostic problem. Case report: We report the case of a 59-year-old woman presenting left-sided foot drop as her initial symptom. At first, after performing lumbar spine magnetic resonance imaging (MRI), a huge paravertebral mass with ipsilateral psoas muscle involvement suggesting retroperitoneal sarcoma was identified. However, cervical punch biopsy and sono-guided paravertebral mass biopsy revealed cervical adenocarcinoma with lumbar spinal metastasis. Conclusion: Although rare, a neurological symptom such as foot drop, not vaginal symptoms, in a woman may be a first manifestation of metastatic cervical cancer, especially in spinal metastasis. Furthermore, any abnormal lesion should not be ignored because of the possibility of metastasis from the primary malignancy, especially in the current case of cervical adenocarcinoma, so a complete evaluation is always mandatory.

Key words: Cervical cancer; Adenocarcinoma; Retroperitoneal sarcoma; Spinal metastasis.

Introduction

Cervical cancer is the second most common malignancy in women worldwide [1]. Metastases from cervical cancer usually originate in the pelvic cavity for more distant sites. However, bone metastases are relatively infrequent, occurring in 3% to 4% of patients [2, 3]. Tumor spread to bone generally occurs by direct invasion or through lymphatic or venous channels of the pelvis, particularly those conduits that communicate with the paravertebral venous plexus [4]. Herein, we report the case of a patient who presented with a paravertebral soft tissue mass, suggesting retroperitoneal sarcoma originating from the psoas muscle, but was finally proven to be cervical adenocarcinoma with lumbar spinal metastasis.

Case Report

A 59-year-old woman, who was gravid 6, para 2, presented to the Emergency Department at Guro Hospital, College of Medicine of Korea University with complaints of left-sided foot drop. The patient had suffered from low back pain radiating to the left leg for two months, but her symptoms did not improve after conservative management. MRI scan of the lumbar spine at a local clinic revealed a large paravertebral mass at the L4-5 region. When the patient presented to our hospital, a neurologic examination was performed and revealed no other abnormalities. She then proceeded to a MRI scan of the lumbar spine and a 8 x 7 cm paravertebral mass abutting the L4-5 vertebrae with direct extension to the L4-5 body and left transverse process, suggesting retroperitoneal sarcoma such as leiomyosarcoma or dedifferentiated liposarcoma (Figure 1). Left L4-5 nerve root involvement was suspected, with left psoas and iliacus muscular involvement. In addition, a large heterogenous mass with enhancement at the uterus with a 2.5 cm-sized, enlarged right iliac lymph node was also observed. She was, then, referred to the Department of Obstetrics and Gynecology for evaluation of a possible uterine malignancy.

The patient’s menses had ceased at 55 years of age. She had no complaints of vaginal bleeding or low abdominal discomfort. She had never had a Pap smear. On pelvic examination, the cervix was small and no specific abnormalities were observed. A Pap smear and Hybrid Capture 2 test were performed, which revealed adenocarcinoma (endocervical type) and high-risk human papillomavirus (HPV), respectively. A colposcopic-guided biopsy was performed and confirmed adenocarcinoma (endocervical type; Figure 2). Serum CA-125 and CA 19-9 were elevated (2330 U/ml and 304.95 U/ml, respectively), whereas the squamous cell carcinoma (SCC) antigen was in the normal range. An endoscopic examination of the stomach and colon showed no evidence of metastasis and the chest X-ray was normal. Mammography and breast sonography were within normal limits.

Pelvic MRI showed an approximately 13 cm uterine mass, suggestive of a uterine myoma with an enhancing solid lesion in the uterine cervix (Figure 3A). In addition, there was an approximately 7 cm-sized mass in the paravertebral area with direct extension to the L4-5 vertebrae, which was previously shown by lumbar spine MRI, and enlarged lymph nodes in the right obturator fossa and the left paraaortic area suspicious of multiple lymph node metastases. On whole body PET-CT scan, a huge hypermetabolic mass-like lesion was seen adjacent to the left psoas muscle, suggesting metastasis (Figure 3B). Intravenous pyelography showed multiple renal stones in the left kidney, but there was no evidence of hydronephrosis. Finally, a sonographic-guided biopsy of the left paravertebral mass was performed and the mass was proven to be metastatic carcinoma.

The final pathologic diagnosis was eventually proven to be a cervical adenocarcinoma with L4-5 spinal metastasis. After radiation treatment, low back pain and foot drop were improved.
Discussion

Bone metastases occur in 1.8% to 6.6% (mean 4.6%) of patients with cervical carcinoma [2, 3, 5-7]. The spine is the most common site, with a reported incidence of 54.2% [2]. In another report, 50% of all vertebral metastases were to the lumbar spine, followed by the thoracic (41%) and sacral spine (9%) [3]. However, the relationship between the original histologic type of cervical cancer and bone metastasis revealed that 88% of cervical cancers with bone metastasis are squamous cell carcinomas, whereas adenocarcinomas consisted of a much smaller proportion (7.7%) [8]. In the current case, the histologic type was adenocarcinoma (endocervical type).

Spinal involvement usually occurs by direct extension of the tumor from a paraaortic lymph node mass, or hematogenously via the paravertebral venous plexus [2]. Metastasis to the thoracic and lumbar spine occurs through direct extension and lymphatic spread, whereas metastasis to more distant areas, including the cervical spine, is probably due to hematogenous spread [9].

In the current case, the patient’s initial complaint was not vaginal bleeding, which is the most common symptom of cervical cancer, but left-sided foot drop. The colposcopic examination also failed to reveal any abnormal finding. For this reason, we initially could not come up with an idea that the paravertebral mass originated from the uterine cervix. Instead, retroperitoneal sarcoma such as...
as leiomyosarcoma or liposarcoma originating from the psoas muscle was strongly suspected. It may cause a variety of neurologic symptoms and is often clinically undetectable [10]. The foot drop may be attributed to the involvement of the L4-5 spinal nerve root, which is the origin of the sciatic nerve that divides into the deep peroneal nerve leading to foot drop. Examples of neurologic symptoms related to spinal involvement in retroperitoneal sarcoma include paraplegia, numbness, loss of sensation, and motor disturbances depending on the specific sites of involvement [11]. Similarly, these neurologic symptoms may appear at a time subsequent to the diagnosis and primary treatment of cervical cancer. In contrast, the patient described herein presented with foot drop as the initial symptom of cervical cancer, making the diagnosis somewhat confusing.

Another reason for the delay in the diagnosis of metastatic cervical cancer may be attributed to the histologic type of the cancer. In the current case, the histologic type was adenocarcinoma and there was no exophytic mass visible on the cervix, which may account for the absence of abnormal vaginal bleeding.

We reported a case of cervical cancer with spinal metastasis incidentally diagnosed by virtue of sudden foot drop as an initial symptom of the disease. This case also highlights the fact that metastasis from cervical carcinoma can present as a retroperitoneal sarcoma. Therefore, it should be kept in mind that a symptom rarely seen in the gynecologic field, such as foot drop, can be the clue to find out the hidden gynecologic malignancy. Furthermore, any abnormal mass should not be ignored because of the possibility of metastasis from the primary malignancy, so a complete evaluation is always mandatory.

References


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CT-guided cryoablation of both breast cancer and lymph node axillary metastasis

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Summary

Breast conservation is a major goal of cancer treatment. Many different minimally invasive options have been considered such as cryoablation. This technique is the best visualized of all ablation techniques due to the phase change during ice formation. We describe a case of breast cancer with lymph node axillary metastasis treated by CT-guided cryoablation. Cryoablation may have unique benefits for cost-effective outpatient breast cancer therapy using only local anesthesia and/or mild sedation.

Key words: Cryoablation; Breast; Lymph node axillary metastases.

Introduction

Breast conservation is a major goal of cancer treatment, and local excision (i.e., lumpectomy) followed by radiation therapy is the current standard of care [1]. However, 35% of patients who undergo lumpectomy note serious breast asymmetry, and morbidity rates of 11% for bleeding and 3% for infections [2]. Therefore, many different minimally invasive options have been considered such as cryoablation. This technique is the best visualized of all ablation techniques due to the phase change during ice formation. The margins of low-density, solid ice are well seen with US, CT, and MR imaging [3, 4]. We herein report the case of a patient with breast cancer with lymph node axillary metastasis treated by CT-guided cryoablation.

Case Report

A 57-year-old Caucasian woman presented to our Breast Center with left breast cancer and metastasis (cT2, N1, M1, bone), negative for hormonal receptors, (HER2++, Ki67 30%). In 2006 the woman underwent medical treatment by chemotherapy with good clinical local response and no progression of disease. In May 2009, because of relapse of disease in the left breast and axillary lymph node (Figure 1a; 3a), we proposed a standard surgical treatment but the woman refused. Thus we performed CT-guided cryoablation of the left mass (3.2 cm) in the superior internal quadrant and of the omolateral axillary lymph node (2 cm).

For local anesthesia, 2-5 ml of 1% lidocaine was injected into the deeper tissues proximal to the mass along the expected course of the cryoprobe. Thereafter, two cryoprobes were percutaneously inserted through the skin opening, with CT-guidance, into the center of the breast mass and of the lymph node, respectively (Figure 2a-b). A tabletop argon gas-based cryoablation system (Galil Medical, Yokneam, Israel), which was designed to create probe temperatures of –180°C, was used to treat the lesions in an outpatient setting. The cryoablation procedure consisted of a double-freeze-thaw protocol. Cell destruction is caused by not only the freezing of the cell but also the thawing of the cell. A double-freeze-thaw cycle has been reported to increase the extent of cell damage and to ensure complete cell destruction at final freezing temperatures [5].

Complete ablation of the breast and lymph node lesions was obtained.

CT follow-up after one month (Figures 1b-3b) demonstrated the lack of enhancement of the breast lesion and lymph node lesion: this finding indicated complete destruction of the cancer. After eight months (Figures 1c-3c), the patient was free from local disease.

Discussion

A lumpectomy, while an important improvement over mastectomy, is still an invasive procedure, with potentially undesirable cosmetic results. For this reason, there has been interest in less invasive percutaneous ablation. Cryoablation is tissue destruction by using controlled freezing and has been investigated as an alternative to conventional surgery in the treatment of benign and malignant neoplasms [5-7].

To our knowledge, this case is very rare because the woman had metastasis and refused the standard surgery after relapse of disease. However, cryoablation permitted the destruction of the breast and axillary lesions. Today, the patient is free from local disease.

CT-guided cryoablation of both breast and lymph node metastasis in our case was a safe and feasible technique. The lack of complications is promising. Cosmetic outcome is very positive. The reduced morbidity and mortality compared with those of surgery and those of nonsurgical options in patients who are not candidates for surgical therapy are also advantages.
CT-guided cryoablation of both breast cancer and lymph node axillary metastasis

[Figures 1-3 shown]

Figure 1. — CT shows left breast cancer (a). CT of the left breast, performed after 1 month (b) and 8 months (c), showing lack of enhancement.

Figure 2. — Photo of the two cryoprobes percutaneously inserted through the skin opening (a). Two cryoprobes percutaneously inserted through the skin opening, with CT-guidance, into the center of the breast mass and lymph node (b).

Figure 3. — CT shows axillary lymph node metastasis (a). CT of the lymph node, performed after 1 month (b) and 8 months (c), showing lack of enhancement.

References


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Six-year follow-up without recurrence after a carcinosarcoma of the breast: case report

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Summary

Carcinosarcoma (CS) of the breast is a rare entity (less than 0.2% of breast malignancies), characterized by the presence of a biphasic pattern of malignant epithelial and mesenchymal elements, and with a high risk of loco-regional recurrence. The diagnosis of CS of the breast is difficult and needs detailed histological investigations to differentiate it from other malignant breast tumors. Expertise and evidence-based information on optimal treatment is very limited due to the low incidence and inconsistent classification. The principles of treatment modalities seem to be similar to others breast malignancies. CS has a different biologic behavior from others breast cancers, being very aggressive in keeping with its high-grade mesenchymal stroma. Still many questions remain about its origin and optimal treatment modalities for better outcome. We report the case of CS of the breast without local or regional recurrence after six years of follow-up in an 82-year-old woman.

Key words: Breast tumors; Carcinosarcoma; Follow-up.

Introduction

Carcinosarcoma (CS) of the breast is a rare entity, occurring in less than 0.2% of breast malignancies. CS is characterized by the presence of a biphasic pattern of malignant epithelial and mesenchymal elements. Overall CS appears to have a poor prognosis with a high risk of loco-regional recurrence [1], most likely due to the fact that these lesions tend to be poorly differentiated tumors [2, 3].

Case Report

An 82-year-old Caucasian woman was referred with a right breast tumor which had enlarged rapidly in the previous three weeks. The patient had a significant personal history of hypertension, hypercholesterolemia, and two arterial bypasses for limb ischemia. No personal or familial cancer history was detected. Physical examination showed an irregularly mass (25 x 30 mm) in the upper outer quadrant of the right breast with limited adhesion to the skin. Mammography and ultrasonography (US) demonstrated a high-density mass with irregular margins and five right axillary lymph nodes. A modified radical mastectomy with axillary lymphadenectomy was performed.

The tumor was irregular measuring 30 x 27 mm, showing solid and lobulated features. Histology revealed a tumor composed of both carcinomatous (10%) and sarcomatous (90%) features, with a distinct demarcation between the two components. The sarcomatous areas showed pleomorphism with significant pleomorphic spindle cells with giant hyperchromatic nuclei, some multinucleate. Marked mitosis was seen, 25 mitoses per 10 high-power fields (HPF) in the carcinomatous component and 12 mitoses per HPF in sarcomatous component. The 19 axillary lymph nodes isolated were negative. Immuno-histochemically, expression of cytokeratin and S-100 were diffusely positive in carcinomatous cells and negative for vimentin, while sarcomatous cells were only positive for vimentin. Estrogen and progesterone receptors and expression of the c-erbB2 were negative in both components. The diagnosis of CS of the breast was established, and the patient was classified pT2 N0 M0.

A pluridisciplinary medical staff including breast surgeon and medical oncologist decided on adjuvant chemotherapy, but due to the age and the Karnofsky score (50%) of the patient, no therapy was added to the surgical treatment. Six years after the diagnosis, clinical examination, mammography and US showed no local recurrence.

Discussion

CS of the breast is a rare tumor characterized by the presence of a biphasic pattern of malignant epithelial and mesenchymal elements. Most of the patients with CS are postmenopausal and white. The classical manifestation is a large mass with irregular margins in mammography [3]. The histogenesis of CS is controversial and has been debated and analyzed using a variety of approaches, including immunohistochemical analysis, ultrastructural studies, cell culture and transplantation to nude mice. A variety of terminology has been used to describe the various histological patterns that may be encountered. Wargotz and Norris [3] proposed a classification of the mixed epithelial mesenchymal tumors of the breast into three groups: matrix-producing carcinoma, spindle cell carcinoma, and CS. The term CS is reserved for when the demarcation between carcinomatous and sarcomatous components is distinct in all light microscopic fields. In 1998, Wada et al. [4] reported that immunohistochemical analysis supported the independent origin of the carcinomatous and sarcomatous components of the tumor. Although cytokeratin was only positive in the carcinomatous component, vimentin was strongly positive in the sarcomatous component of the tumor, but showed only patchy or very weak reactivity in carcinomatous compo-
Six-year follow-up without recurrence after a carcinosarcoma of the breast: case report

nent. They concluded that molecular analysis clearly showed that CS of the breast derived by divergent patterns of differentiation from a single totipotent stem cell.

Expertise and evidence-based information on optimal treatment is very limited due to the low incidence and inconsistent classification. The principles of treatment modalities seem to be similar to others breast malignancies. Treatment of choice is modified radical mastectomy with postoperative radiotherapy (locoregional control) and chemotherapy (metastatic spread control) [3, 5, 6]. The high risk of local recurrence should make oncologists consider whether breast-conserving surgery is the right option for patients, particularly with T2 and higher T stages [2, 3]. Although axillary node invasion is less common than in other metaplastic carcinomas of the same size, it frequently occurs in CS [2, 3, 6]. However, the number of invaded lymph nodes is often limited. In a recent retrospective study concerning all biphasic metaplastic sarcomatoid carcinomas of the breast in the Surveillance, Epidemiology and End-Results (SEER) database, Hennessy et al. [7] concluded that patients with these tumors may derive less benefit from conventional breast cancer chemotherapy. For Wargotz and Norris [3], postoperative radiotherapy and hormonal therapy do not seem to be effective in cases of CS, due to the low incidence of hormonal receptors in these tumors (around 10%). Overall carcinosarcomas appear to have a poor diagnosis related to the large tumor size, the advanced TNM stage, and most likely due to the fact that these lesions tend to be poorly differentiated tumors [6, 8, 9]. The recurrence rate is around 60% and tends to be regional in approximately one-third of the cases of CS [3, 6].

In conclusion, the diagnosis of carcinosarcoma of the breast is difficult and needs detailed histological investigations to differentiate it from other malignant breast tumors. CS has a different biologic behavior from others breast cancers, being very aggressive in keeping with its high-grade mesenchymal stroma. Still many questions remain about its origin and optimal treatment modalities for better outcome.

References


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Metastasis from breast cancer to an endometrial polyp; treatment options and follow-up.

Report of a case and review of the literature

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Summary

Introduction: The female genital tract is rarely involved by metastatic tumors. The most common anatomic locations are the ovaries and the vagina. A case is presented of metastatic breast carcinoma to the vulva and endometrial polyp, both exceptional.

Case Report: We report the case of an 83-year-old female who presented with vaginal bleeding. Lobular breast carcinoma was diagnosed earlier and during follow-up vulvar metastasis was detected. Hysteroscopic examination because of postmenopausal bleeding revealed an endometrial polyp which was resected. The morphology and immunohistochemistry of the polyp were consistent with lobular breast cancer: metastatic breast cancer to an endometrial polyp. After reviewing the literature 15 cases of metastatic breast carcinoma to endometrial polyps have been reported. The clinical presentation and course, risk factors, treatment and follow-up are discussed.

Conclusion: Metastasis of a breast carcinoma to the vulva and an endometrial polyp are extremely rare, but clinicians should be aware of both phenomena.

Key words: Breast cancer; Uterine metastasis; Endometrial polyp; Treatment; Follow-up.

Introduction

Metastases to the endometrium from extra-genital tumors are rare. The most common anatomic location for metastases to the female genital tract are the ovaries and the vagina. The primary tumor is most frequently located in the breast followed by the gastrointestinal tract, lung, kidney and skin (melanoma) [1, 2]. When an extra-genital tumor metastasizes to the uterus it is predominantly located in the myometrium, in a minority of cases the metastases is confined to the endometrium [1, 2]. We present a case of metastatic breast carcinoma to the vulva and endometrial polyp, and review the literature.

Case Report

An 83-year-old nulliparous female presented with postmenopausal uterine bleeding. She had been diagnosed with invasive lobular breast carcinoma five years before presentation. The breast cancer had been disseminated to the pleural and peritoneal cavity and was hormone receptor-positive and Her2/neu negative. She was then treated with first-line hormonal therapy with letrozol. During routine follow-up vulvar metastasis was detected which was surgically excised. The morphology and immunohistochemistry of the polyp were consistent with lobular breast cancer: metastatic breast cancer to an endometrial polyp.

Because of her postmenopausal bleeding transvaginal ultrasonography was performed and showed thickening of the endometrium and a polypoid lesion with mixed echo refringence.

Endometrial curettage revealed insufficient non-diagnostic material. Hysteroscopy showed an atrophic uterine cavity with an endometrial polyp which was resected diathermically.

Macroscopic examination showed a polyp with a diameter of 3.5 cm. Histologically the polyp consisted of cystic dilated glands lined by columnar epithelium without atypia, surrounded by a fibrovascular stroma. Focally the glands showed mucinous metaplasia and in some areas there was periglandular stroma condensation. Within the stroma there were several foci of monotonous epithelial cells arranged in small nests and cords (Figure 1). These cells were immunohistochemically positive for cytokeratin (AE1/3) and estrogen receptor (Figure 2). Morphology and immunohistochemistry were consistent with metastatic lobular breast carcinoma to an endometrial polyp.

The features of the polyp itself were characteristic, though not pathognomonic, for a tamoxifen-associated endometrial polyp.

After one year of follow-up the patient is in a good condition. There is no evidence of progressive disease.

Discussion

This is the first case of a metastatic breast cancer to the vulva and to an endometrial polyp in the same patient. Uterine metastases of extra-genital malignant tumors are rare. Breast cancers, especially lobular carcinomas are the most common primary tumor. The vulva is one of the more unusual sites of metastases from a breast carcinoma. Perrone et al. found only 16 cases in 72 years after reviewing the literature. For an accurate diagnosis and treatment, a differentiation should be made between primary and metastatic breast cancer of the vulva.
Metastasis from breast cancer to an endometrial polyp; treatment options and follow-up. Report of a case and review of the literature

Primary breast cancer of the vulva originates from ectopic breast tissue in the vulva, which develops along the mammary ridges [3]. In our case metastases from a primary breast cancer to the vulva was obvious because of the similarity in histological, immunohistochemical and receptor status. Furthermore, the diagnosis was supported by the absence of normal breast tissue in the specimen and a history of breast cancer.

Endometrial metastasis from a breast carcinoma is also uncommon. Kumar et al. found two of 63 cases (3.8%) with metastases to the endometrium, Mazur et al. seven cases in 149 patients (4.7%) [1, 2]. Polyps are the most common benign lesion in the endometrium, and metastasis to a polyp is exceptional. Because little is known about presentation, risk factors, clinical course, treatment and follow-up of metastasis to endometrial polyps we reviewed the literature.

A search was performed in May 2010 with the key words: breast carcinoma, metastasis and polyp. The search revealed 13 articles in which 15 patients with metastases from a breast carcinoma to an endometrial polyp are described [4-16]. The articles and patient characteristics, including our case, are described in Table 1. Eight patients had lobular breast cancer, seven had ductal adenocarcinoma and one patient an apocrine type. Ductal carcinoma accounts for approximately 70-75% of all breast cancers; lobular carcinoma for 5-20%. The breast cancer was primarily treated by surgery in 13 patients, and three patients were treated palliatively because of widespread dissemination (Manipadam et al., Aydin et al., and our case). Five patients received chemotherapy as adjuvant therapy, four radiotherapy and 12 patients (75%) hormonal therapy with tamoxifen. Tamoxifen, a nonsteroidal anti-estrogen, is used for adjuvant and palliative treatment and chemoprevention of breast cancer. Tamoxifen may also exert estrogenic effects on the endometrium and may result in a variety of proliferative lesions including primary or metastatic carcinomas. A causal association between tamoxifen and uterine metastasis from breast cancer has not been established. Vaginal bleeding or discharge was the first manifestation in 11 patients which led to further examination and diagnosis of the endometrial metastasis. In the remaining five patients the metastasis was diagnosed during routine examination. The time between the primary diagnosis and metastasis ranged between eight months and six or more years. The maximal diameter of the polyp ranged between 1.5 and 11.5 cm. Eight patients, with no signs of widespread dissemination, received a total abdominal hysterectomy with bilateral salpingo-oophorectomy. During follow-up two patients died (9 months and 4 years after diagnosis) because of disease progression. Two patients had no evidence of disease 11 and 26 months after surgery. Of the remaining four patients the follow-up was unknown. In the four patients with signs of widespread dissemination two patients received palliative treatment. One patient did not receive any treatment and our patient received a polyp resection as part of her treatment. Three patients had signs of disease progression during follow-up and one patient died within one year. Our patient has no signs of progressive disease after one year follow-up. The remaining four patients were treated with a polyp resection but the follow-up is unknown.

Although the number of patients is small, the results of the literature search show that treatment of an endometrial metastasis from breast carcinoma is dependent on signs of widespread dissemination. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed in patients without further evidence of disease.

If additional investigations revealed other sites of metastases no treatment or palliative treatment was given. The presence of uterine metastases usually indicates an advanced stage, but does not always imply widespread dissemination.
Table 1. — Summary of reported cases in the literature.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs.)</th>
<th>Histologic type primary tumor</th>
<th>Lymph node metastasis</th>
<th>Adjuvant therapy</th>
<th>Clinical symptom</th>
<th>Time elapsed between primary tumor and metastasis (months)</th>
<th>Maximal diameter polyp (cm)</th>
<th>Treatment procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sullivan et al. [4]</td>
<td>83</td>
<td>Ductal</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>72</td>
<td>11.5</td>
<td>TAH+BSO</td>
</tr>
<tr>
<td>Corely et al. [5]</td>
<td>58</td>
<td>Ductal</td>
<td>Yes</td>
<td>TAM</td>
<td>Vaginal bleeding</td>
<td>&gt; 36</td>
<td>NM</td>
<td>TAH+BSO</td>
</tr>
<tr>
<td>Aranda et al. [6]</td>
<td>76</td>
<td>Lobular</td>
<td>No</td>
<td>No</td>
<td>Vaginal bleeding</td>
<td>36</td>
<td>9</td>
<td>TAM+CT</td>
</tr>
<tr>
<td>Martinelli et al. [7]</td>
<td>71</td>
<td>Ductal</td>
<td>Yes</td>
<td>TAM</td>
<td>Vaginal bleeding</td>
<td>30</td>
<td>NM</td>
<td>Palliative RT/CT</td>
</tr>
<tr>
<td>Martinelli et al. [8]</td>
<td>78</td>
<td>Lobular</td>
<td>Yes</td>
<td>TAM</td>
<td>Vaginal bleeding</td>
<td>24</td>
<td>3.3</td>
<td>TAH+BSO</td>
</tr>
<tr>
<td>Martinez et al. [9]</td>
<td>58</td>
<td>Ductal</td>
<td>Yes</td>
<td>RT, CT</td>
<td>Vaginal bleeding</td>
<td>≥ 36</td>
<td>NM</td>
<td>TAH+BSO</td>
</tr>
<tr>
<td>Lambot et al. [10]</td>
<td>70</td>
<td>Apocrine</td>
<td>Yes</td>
<td>TAM, RT</td>
<td>Vaginal bleeding</td>
<td>48</td>
<td>1.5</td>
<td>TAH+BSO</td>
</tr>
<tr>
<td>Horn et al. [11]</td>
<td>73</td>
<td>Ductal</td>
<td>No</td>
<td>TAM, CT</td>
<td>No</td>
<td>56</td>
<td>8</td>
<td>TAH+BSO</td>
</tr>
<tr>
<td>Houghton et al. [12]</td>
<td>62</td>
<td>Lobular</td>
<td>Yes</td>
<td>TAM</td>
<td>Vaginal bleeding</td>
<td>48</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Houghton et al. [13]</td>
<td>92</td>
<td>Lobular</td>
<td>Unknown</td>
<td>TAM</td>
<td>Vaginal bleeding</td>
<td>60</td>
<td>3</td>
<td>Polyp resection</td>
</tr>
<tr>
<td>Al-brahim et al. [14]</td>
<td>53</td>
<td>Lobular</td>
<td>Yes</td>
<td>TAM</td>
<td>Vaginal bleeding</td>
<td>48</td>
<td>7</td>
<td>Polyp resection</td>
</tr>
<tr>
<td>Acikalin et al. [15]</td>
<td>58</td>
<td>Ductal</td>
<td>Yes</td>
<td>TAM, CT</td>
<td>No</td>
<td>48</td>
<td>5</td>
<td>TAH+BSO</td>
</tr>
<tr>
<td>Manipadum et al. [16]</td>
<td>70</td>
<td>Lobular</td>
<td>Yes</td>
<td>CT</td>
<td>Vaginal bleeding</td>
<td>NM</td>
<td>3</td>
<td>Polyp resection</td>
</tr>
<tr>
<td>Aydin et al. [17]</td>
<td>60</td>
<td>Ductal</td>
<td>Unknown</td>
<td>TAM, RT</td>
<td>Vaginal bleeding</td>
<td>8</td>
<td>6.5</td>
<td>CT, ANA</td>
</tr>
<tr>
<td>Our Case</td>
<td>83</td>
<td>Lobular</td>
<td>Yes</td>
<td>LET, TAM, FUL</td>
<td>Vaginal bleeding</td>
<td>60</td>
<td>3.5</td>
<td>Polyp resection</td>
</tr>
</tbody>
</table>


* Therapy started before the metastases to the endometrium was diagnosed.
* Palliative radiotherapy because of vaginal extension, unresectable. Because of disease progression palliative chemotherapy was started.
* 22 years earlier breast cancer to the right mammary, 19 years earlier left-sided breast cancer. 3 years after the left-sided breast cancer the patient presented with vaginal bleeding.
* No treatment was given because of widespread dissemination, with skull and spine metastasis.

**Conclusion**

Metastases from breast cancer to the genital tract are uncommon, with metastases to the vulva and endometrial polyp being very rare. Although metastasis to the endometrium is exceptional, it is clinically very important because it can be the first sign of widespread disease. Vaginal bleeding is often the first symptom, but patients can be asymptomatic. The relationship of metastases and tamoxifen treatment is unclear, but was found in 75% of the cases. Total hysterectomy with bilateral salpingo-oophorectomy is the treatment in patients without signs of widespread dissemination. Clinicians should be aware of the possibility of uterine metastatic involvement in women with uterine bleeding and a history of breast cancer.

**References**


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Diffuse intraabdominal fibrosis and inflammation mimicking peritoneal carcinomatosis recurred after surgery for borderline ovarian tumor misdiagnosed by $^{18}$F-fluorodeoxyglucose-positron emission tomography

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Summary
Background: $^{18}$F-fluorodeoxyglucose-positron emission tomography (FDG-PET) adds to conventional imaging in the detection and staging of peritoneal carcinomatosis. Case report: Herein we report a 27-year-old woman with multiple intraperitoneal masses detected by $^{18}$F-FDG-PET, suggesting peritoneal carcinomatosis. She had undergone laparoscopic unilateral oophorectomy for a left ovarian mucinous borderline tumor approximately five years before. Based on imaging and intraoperative findings, multiple intraabdominal masses strongly suggested peritoneal recurrence from a previous ovarian borderline tumor, but it finally proved to be inflammation and fibrosis on histopathologic examination. Conclusion: Although $^{18}$F-FDG-PET is well known to be a highly sensitive imaging tool for identification of peritoneal carcinomatosis, FDG uptake is not tumor-specific. Therefore, the possibility of a false-positive diagnosis due to benign conditions, such as inflammation, should always be taken into consideration.

Key words: Peritoneal carcinomatosis; $^{18}$F-fluorodeoxyglucose-positron emission tomography; Fibrosis; Inflammation.

Introduction
$^{18}$F-fluorodeoxyglucose-positron emission tomography (FDG-PET) is a useful technique for the detection and follow-up of a wide range of oncologic diseases, including peritoneal carcinomatosis. However, FDG-PET may produce false-positive results due to inflammatory lesions induced by surgery or irradiation [1].

Case Report
A 27-year-old woman was admitted for further evaluation of multiple intraperitoneal masses detected by an abdominopelvic computed tomography (CT) scan during regular post-operative follow-up. In March 2005, she had undergone laparoscopic unilateral oophorectomy for a left ovarian mucinous borderline tumor without malignant cells in the peritoneal fluid (Stage Ia). Adjuvant chemotherapy was not performed due to the early stage. The preoperative levels of CA-125 and CA-19-9 were 74.7 U/ml and < 2.0 U/ml, respectively. Although complete surgical staging had not been performed, there was no macroscopic evidence of metastatic lesions by laparoscopic exploration.

The CT scan showed multiple soft tissue masses in the fallopian ligament, perisplenic space, and omentum, as well as a small amount of ascites in the pelvic cavity (Figure 1). Additionally, a 3.8-cm enhancing soft tissue mass was visible on the rectal shelf, suggesting peritoneal carcinomatosis. Pelvic magnetic resonance imaging (MRI) revealed similar findings; however, the CA-125 and CA 19-9 levels were in the normal range.

$^{18}$F-FDG-PET was performed for two reasons: 1) to further clarify the discrepancy between the imaging modality and serum tumor marker levels, and 2) the rarity of recurrence in the form of peritoneal carcinomatosis after salpingo-oophorectomy for an early stage borderline ovarian tumor (Figure 2). However, the $^{18}$F-FDG-PET scan revealed multifocal, hypermetabolic FDG uptake in the perisplenic, perihepatic, omental, and rectal shelf areas, also suggesting peritoneal carcinomatosis.

A staging laparotomy was performed to confirm the diagnosis. The right ovary and fallopian tube were grossly normal in appearance, but an ovarian wedge biopsy was obtained to exclude the possibility of microscopic lesions. The left fallopian tube was adhered to the left pelvic side wall and a biopsy was also obtained. As previously shown in the imaging study, multiple, small, nodular masses were noted in the omentum, cul-de-sac, peritoneal surface, and small bowel. On histopathologic examination, including thorough immunohistochemical staining, the right ovary, left fallopian tube, omentum, and peritoneal mass had no tumor involvement. Multiple intraperitoneal masses were shown to be fibrosis with chronic inflammation and mesothelial hyperplasia (Figure 3). Following surgery, no further treatment was undertaken based on the histopathological results, and the postoperative course was uneventful.

Discussion
Borderline ovarian tumors are known to have a favorable survival outcome, even after recurrence. Most recurrences from borderline ovarian tumors depend on the initial tumor stage and the presence of invasive implants [2]. Indeed, recurrence in the form of peritoneal carcinomatosis after conservative surgery for a Stage Ia borderline mucinous ovarian tumor has not been reported. Nevertheless, we could not exclude the possibility of such a
recurrence due to the findings presented on CT, MRI, and 
$^{18}$F-FDG-PET. DeGaetano et al. [3] reported that $^{18}$F-
FDG-PET/CT is most suitable in patients with negative 
or uncertain conventional imaging data, such as CT or 
MRI. By contrast, they also mentioned the possibility of 
false-positive diagnoses caused by $^{18}$F-FDG-PET/CT, 
which are mainly related to bowel activity or focal-
retained activity in the ureters and bladder. In the current 
case, the differentiation between peritoneal carcinomatosis 
and benign inflammation was challenging because the 
findings of CT, MRI, and $^{18}$F-FDG-PET were all consis-
tent with peritoneal carcinomatosis. Moreover, the intra-
operative findings, such as multiple nodular masses in the 
small bowel, rectum, omentum, and spleen, strongly sug-
gested typical findings of peritoneal carcinomatosis.

Because the discrepancy between the histopathologic 
findings and imaging findings was so unpredictable, we 
reviewed the entire slide set of the previous left ovarian 
tumor, but it only showed a borderline mucinous tumor, 
not a true malignancy. Moreover, the right ovarian tissues

Figure 1. — Abdominopelvic CT images showing soft-tissue masses on the rectal shelf (A, arrow), omentum (B, arrow), perisplenic 
space (C, arrow) and falciform ligament (D, arrow).

Figure 2. — $^{18}$F-FDG-PET image shows increased uptake in the 
perisplenic, perihilar, omental, and rectal shelf area, suggesting peritoneal carcinomatosis.
Diffuse intraabdominal fibrosis and inflammation mimicking peritoneal carcinomatosis recurred after surgery for borderline ovarian etc. obtained from the current surgery were mostly corpus lutea with a small number of multinucleated giant cells and histiocytes, and also revealed no evidence of tumor. In the omentum, peritoneum, fallopian tube, and posterior cul-de-sac, fibrosis with lymphocytes, lymphoid aggregates, and mesothelial hyperplasia were demonstrated. Additionally, many CD68-positive histiocytes were intermixed with lymphocytes, suggesting reactive lesions. The possible reasons for the peritoneal fibrosis may be primary peritoneal fibrosis, lutenized thecoma with peritoneal fibrosis, or reactive changes due to previous surgery [4, 5].

The exact cause of diffuse intraabdominal fibrosis with inflammation in the present case is unclear. Although 18F-FDG-PET or PET/CT false-positive results may be attributed to the inflammation followed by surgery [1], it remains unclear whether the diffuse peritoneal fibrosis with inflammation mimicking peritoneal carcinomatosis in the present case was related to the previous surgery since it was performed > 4 years ago.

Herein we have presented a rare case that can be easily confused with peritoneal carcinomatosis by 18F-FDG-PET. The present case highlights the need for careful evaluation of suspicious peritoneal carcinomatosis demonstrated by 18F-FDG-PET because of the potential for false positivity. When the finding demonstrated by 18F-FDG-PET and serum tumor marker levels are discordant, even though peritoneal carcinomatosis is highly suspected, laparoscopic-targeted biopsy of highly suspicious lesions should be undertaken to prevent an unnecessary laparotomy.

References

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A case of bilateral ovarian synchronous tumors
(left ovarian serous papillary adenocarcinoma and right
ovarian malignant mixed Müllerian tumor)

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Summary
Synchronous bilateral ovarian cancer is extremely rare and there is no established guideline for management. A case of a 58-year-old multiparous woman with bilateral ovarian synchronous malignant tumors is presented. The clinical consideration and treatment of related cases are discussed.

Key words: Ovarian synchronous tumors; Serous papillary adenocarcinoma; Malignant mixed Müllerian tumor.

Introduction
Ovarian cancer involving both ovaries is common in advanced stage disease; however, the histopathologies are usually the same. In a case series with a small number of patients, synchronous ovarian and endometrial cancers were reported to occur in 1.4%-3.8% of female genital malignancies [1], but synchronous bilateral ovarian cancer is extremely rare. We report herein a case of synchronous bilateral ovarian cancer with a malignant mixed Müllerian tumor (MMMT) involving the right ovary and a serous papillary adenocarcinoma involving the left ovary.

Case Report
A 58-year-old multiparous woman was referred to our hospital with lower abdominal discomfort and a palpable mass. She was had been menopausal for three years. Physical and bimanual pelvic examination revealed a large mass occupying the entire pelvic cavity. A computed tomography (CT) scan of the pelvis revealed a 12 x 15 x 11 cm poorly demarcated, lobulated mass, likely originating from the ovaries bilaterally (Figure 1). The mass extended to the pelvic side wall and occupied the entire cul-de-sac, with possible direct invasion of adjacent organs, especially the serosa of the sigmoid colon. There were no other abnormal findings on the CT scan, including retroperitoneal lymphadenopathy. To exclude sigmoidal invasion, a sigmoidoscopy was performed, which was normal. CA125 was markedly elevated up to 1,059 U/ml. After preoperative evaluation, exploratory laparotomy was performed. Approximately 100 ml of red-colored, serous fluid was noted in the pelvic cavity and collected for cytologic evaluation, which revealed an adenocarcinoma one week later. The left ovary was enlarged (15 x 8 x 8 cm), with a 4 cm serous cyst and multiple, white, hard, cystic masses < 1 cm in diameter. The right ovary with the cystic mass measured 9 x 5 x 5 cm in size and occupied the entire cul-de-sac. The right ovary was sent to the Department of Histopathology for frozen section, which was reported as a malignancy. The pelvic lymph nodes were not enlarged.

Multiple nodular masses < 1 cm in diameter were noted on the surface of the diaphragm and the serosa of the small intestine. The large intestine was densely adherent to the peritoneum and both adnexa. The liver, spleen, stomach, and omentum were grossly free of adhesions. Primary cytoreductive surgery including total extracapsular hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and paraaortic lymph node dissection, infracolic omentectomy, and multiple biopsies was done.

Final pathologic examination demonstrated a moderately differentiated serous papillary adenocarcinoma (Figure 2-1) of the left ovary and a malignant mixed Müllerian tumor (MMMT) of the right ovary (Figure 2-2). Immunohistochemical staining was performed for further evaluation of the right ovary, and was positive for cytokeratin (Figure 2-3) and vimentin (Figure 2-4), negative for actin, desmin, and CD34, and weakly positive for S-100 protein. Therefore, the tumor of the right ovary was indirectly shown to be a carcinosarcoma. The uterus had atrophic endometrium and chronic cervicitis. Three weeks later the CA125 had normalized (33,53 U/ml). According to the surgical findings and pathologic results, the final diagnosis was a FIGO Stage IIIB, serous papillary adenocarcinoma of the left ovary and a FIGO Stage IIIB, MMMT of the right ovary. Postoperatively, the patient received five courses of chemotherapy consisting of paclitaxel (175 mg/m²) and carboplatin (500 mg-600 mg, according to an area under the curve [AUC]) = 4). Pelvic CT after completion of the fifth course of chemotherapy revealed a relapse. A secondary debulking procedure and permanent pathologic finding was consistent with a MMMT, and then the patient received two courses of chemotherapy with belotecan (0.5 mg/m²) as a second-line chemotherapy. Nevertheless she died of the disease seven months after the primary treatment.

Discussion
A synchronous tumor is defined as two or more primary tumors diagnosed simultaneously in a patient. In gynecologic malignancies, synchronous cancers involving the endometrium and ovary are infrequent, but a well recognized event [2], while synchronous tumors involving the bilateral ovaries are extremely rare and not well established. We managed a patient with bilateral ovarian tumors, who not only had synchronous malignancies, but...
A case of bilateral ovarian synchronous tumors (left ovarian serous papillary adenocarcinoma and right ovarian malignant etc).

Figure 1. — Pelvic CT scan showed that the mass extended to the pelvic side wall (Figure 1-1) and occupied the entire cul-de sac (Figure 1-2).

Figure 2. — Left ovary, moderately differentiated serous papillary adenocarcinoma (H&E x 100) (Figure 2-1), and right ovary, malignant mixed Müllerian tumor (H&E x100) (Figure 2-2). Immunohistochemical staining of the right ovary. The result was positive for cytokeratin (Figure 2-3) and vimentin (Figure 2-4).
with different pathologies (serous papillary adenocarcinoma of the left ovary and MMMT of the right ovary). MMMTs are very rare tumors and usually occur in the uterus. MMMTs represent <1% of ovarian malignancies. In 1864, Virchow classified neoplasms with carcinomatous and sarcomatous components as carcinosarcomas [3].

The origin of MMMTs are not clear, but they are presumably derived from pluripotent mesenchymal cells of the coelomic epithelium which differentiate into malignant epithelial and stromal elements [4-6]. Current evidence suggests that MMMTs usually arise from pre-existing carcinomas [7-10], and these tumors are regarded as dedifferentiated carcinomas of the ovary [9]. MMMTs are most prevalent in postmenopausal women, with a median age of 60 years [8]. Pelvic irradiation is presumed to play an important role in the pathogenesis of uterine MMMTs, but is not associated with ovarian MMMTs. The clinical presentation of ovarian MMMTs is similar to epithelial ovarian cancers. Unlike uterine MMMTs, which often metastasize to the lungs, the spread of ovarian MMMT is similar to that of primary epithelial ovarian carcinomas, which exhibit serosal and peritoneal seeding as early sites of metastasis [5, 11]. The tumor usually involves the ovary unilaterally; bilateral tumors occur in only 10% of the cases [12]. MMMTs arising from the ovary are staged surgically according to the criteria of the International Federation of Gynecology and Obstetrics [13]. Significant prognostic factors are stage, and for women with Stage III or IV disease, the feasibility of cytoreductive surgery [14]. Similarities in clinical presentation and tumor origin indicate that effective therapies for primary ovarian carcinomas should also be effective against ovarian MMMTs [9]. As in epithelial ovarian cancer, the initial therapeutic approach for patients with ovarian MMMT is meticulous debulking, including bilateral oophorectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, and pelvic and paraaortic lymph node dissection. However, surgery alone is seldom curative [3]. These tumors have highly malignant behavior, and adjuvant chemotherapy following surgery is usually recommended. There is little consensus on the optimal treatment regimen and duration of MMMTs due to the low incidence. A variety of chemotherapy regimens, including adjuvant adriamycin, dacarbazine, and cisplatin, have been reported to have response rates ranging from 27%-100% [15-18]. Furthermore, According to the chemotherapeutic approach mentioned above, a platinum-based taxane combination chemotherapy may be feasible in the case of synchronous epithelial ovarian cancer and MMMT of the ovary. However, despite optimal and aggressive treatment, including primary debulking surgery followed by chemotherapy, 70% of such patients die within one year of diagnosis [14, 16, 19]. The median survival of patients with MMMT of the ovary has been estimated to be 8-16 months [14, 19]. Synchronous ovarian malignancies are extremely rare. Clearly, additional research about the etiologic factors, mode of treatment, and prognosis of synchronous ovarian tumors is needed.

References


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Ovarian carcinoma presenting with axillary lymph node metastasis: a case report

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Summary

Ovarian cancer is usually limited to the abdomen and frequently remains confined. The occurrence of extraluminal metastases is unusual. In this report we describe a rare case of axillary involvement at initial presentation of ovarian cancer in a 48-year-old woman. The axillary mass was the only clinical abnormality. Cytological and histological findings, performed on axillary lymph nodes, showed the presence of psammoma bodies and specific immunohistochemical tumor markers (OC-125 and WT1), supporting the evidence of a metastatic axillary lymphadenopathy from ovarian cancer. Subsequently, chest and abdominopelvic computed tomography showed a right ovarian complex mass of 30 x 25 mm and biochemical tests showed high levels of CA125. Surgical therapy was performed. Histology confirmed the diagnosis, evidencing a poorly differentiated serous-papillary carcinoma of the right ovary. In conclusion, cytological and histological findings can play a crucial role in suggesting the correct origin of a metastatic adenocarcinoma when the clinical presentation is atypical.

Key words: Metastatic axillary Lymphadenopathy; Ovarian cancer; Psammoma bodies; Fine-needle aspiration biopsy.

Introduction

Ovarian cancer is the most important cause of death from gynecological malignancies in Western countries [1]. Because most women with ovarian cancer are asymptomatic or experience only non-specific symptoms, approximately 75% of patients are diagnosed with advanced disease. Usually, ovarian carcinoma spreads directly to the peritoneal cavity; distant metastases are infrequent and generally occur late during the course of disease [2, 3]. Metastases to extra-abdominal lymph nodes are uncommon with only isolated cases reported in the literature [4-8]. Identification of the origin of a metastatic lymphadenopathy may be very difficult, especially when it is the only clinical evidence of disease. When axillary lymph nodes are involved, the differential diagnosis includes several neoplasms, particularly breast cancer. A correct diagnosis is clearly of great clinical importance because the treatment and prognosis differ significantly.

Case Report

A 48-year-old woman was admitted to the Breast Unit of “Sapienza” University of Rome (Department of Surgery “Pietro Valdoni”) because she noted the development of a nodular mass in her right axilla. Clinical examination confirmed the presence of a palpable, mobile, painless mass suspected for lymphadenomely. No pathologic nodules were detected in the mammary gland bilaterally, or was the mass referred to other superficial lymph nodes. Anomalies of the thyroid gland were excluded; no skin lesions were evidenced. Chest and abdominal examination did not evidence any gross masses; the liver and spleen were not palpable. Instrumental examination of the breast, i.e., mammography plus ultrasound sonography (US) were negative. However, in the right axilla US revealed a well demarked hypoechoic nodule 25 x 20 mm in size, which was considered a lymph node undergoing structural changes. After fine-needle aspiration biopsy (FNAB), cytology revealed the presence of malignant cells with many psammoma bodies. Complete excision of the enlarged lymph node was performed for histopathological evaluation. At immunocytochemical examination the positive staining for antiovarian carcinoma antibody 125 (OC-125) and Wilms Tumor Gene (WT1) supported the diagnosis of lymph node metastasis from ovarian carcinoma. Chest and abdominopelvic computed tomography (CT) scanning showed a right ovarian complex mass 30 x 25 mm in size, consisting of cystic and solid regions. There was no evidence of disseminated intraabdominal disease, ascites or pelvic and paraortic lymph node involvement. Parenchymal metastases were not detected. Routine hematological and biochemical tests were found to be normal and serum CA125 level was 230 UI/ml (normal value < 35 UI/ml). The patient was treated by surgery plus simultaneous hyperthermic intraperitoneal chemotherapy (HIPEC). Intraoperative histological examination confirmed the diagnosis of an ovarian neoplasm. Surgical therapy included hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic and paraaortic lymphadenectomy and pelvic peritonectomy. The entire peritoneal surface was inspected and multiple peritoneal biopsies were performed in absence of gross extrapelvic disease. HIPEC was given with a closed technique, using cisplatin (dose = 75 mg/mq) at a temperature ranging from 42-43°C, for 60 min. Final histological findings showed a poorly differentiated papillary serous cystadenocarcinoma of the right ovary (G3; pT3c pN0 pM1; Stage IV). No complications were observed postoperatively. After hospital discharge, the patient was scheduled for systemic chemotherapy with carboplatin at a dose at an area under the curve (AUC) of six, plus paclitaxel, 175 mg/mq 3-hour IV infusion given every three weeks for six courses. The patient was followed-up every six months with clinical examination, serum markers (CEA, CA125, CA19.9) and chest and abdominopelvic CT. No recurrence was determined after 48 months of follow-up.
treatment may differ significantly. When axillary lymph nodes are involved, the differential diagnosis includes several neoplasms, especially breast and skin cancer. A complete physical examination may be useful to determine the cancer origin (breast mass, skin anomalies). Moreover, because neoplastic lymphadenomegaly may be the first evidence of metastatic dissemination of a preceding cancer disease, the oncologic anamnesis should be attentively considered. In the reported clinical case, with the exception of axillary lymphadenomegaly, the physical examination was not indicative of a neoplasm; clinical history resulted negative for oncologic disease, the patient was asymptomatic, and the instrumental investigation excluded breast cancer. The diagnosis was performed by cytological and pathologic findings (Figures 1 and 2). At cytological examination, the presence of psammoma bodies aroused the suspicion of adenocarcinoma of the ovary [10, 11]. Psammoma bodies are concentric lamellate calcified structures, usually associated with papillary neoplasms (thyroid, ovary) and meningioma. Although not pathognomonic, they are considered diagnostically helpful; one-third of serous cystadenocarcinomas of the ovary show psammoma bodies [12, 13]. The following immunohistochemical studies, performed on excised lymph nodes, showed staining of CA125 and WT1, two very sensitive markers for ovarian cancer. In contrast the marker for breast cancer cells (GCDFP-15) resulted negative [14]. Chest and abdominopelvic CT confirmed the presence of an ovarian neoplastic mass. Thus, our patient received a correct diagnosis and the appropriate therapy.

Conclusion

Axillary metastasis at the initial presentation of serous ovarian cancer is rare, but possible. This case underlines the need to consider ovarian carcinoma in the differential diagnosis of women with axillary lymphadenopathy, especially when mammography and mammary US examination exclude breast cancer. Because of the presence of
an atypical pattern (psammoma bodies, CA125, WT1), cytological and histological findings can be useful in indicating the correct diagnosis.

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Papillary serous adenocarcinoma of the uterine cervix: a case report

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Summary

Papillary serous adenocarcinoma of the endocervix (PSAE) is a rarely encountered neoplasm. The literature includes only a limited number of well documented case studies. The present study reports a case of papillary serous adenocarcinoma originating from the endocervix.

Key words: Papillary serous adenocarcinoma; Uterus, Cervix.

Introduction

Papillary serous adenocarcinoma of the endocervix (PSAE) is a rarely encountered neoplasm. The histological appearance of PSAE is similar to papillary adenocarcinomas in other locations, for example, in the ovary, endometrium and peritoneum. Although there have been brief references to PSAE in textbook chapters and compilations on cancers displaying glandular differentiation, the literature includes only a limited number of well documented case studies [1, 2].

The present study is a report of a case of papillary serous adenocarcinoma originating from the endocervix.

Case Report

A 75-year-old Caucasian patient, gravida 5, para 4, presented with symptoms of abdominal bloating, dyspnea, and difficulty in urinating that had started 1.5 months prior to her application to the clinic. The patient spoke of two instances of postmenopausal bleeding, one ten years before and the other one year previously.

In the pelvic examination, the cervix was of normal appearance. The uterus and ovaries could not be palpated due to acidity. In the ultrasound examination the uterus and ovaries were found to be of normal size. The patient’s serum CA-125 level was found to be >600 U/ml (normal interval < 35 U/ml), CA 15-3 was > 300 U/ml (normal interval < 25 U/ml), and CEA was 7.7 ng/dl (normal interval < 3.4 ng/dl). The result of the Pap smear indicated poorly differentiated adenocarcinoma. An endocervical curettage revealed PSAE. Computed tomography scan of the abdomen/pelvis showed minimal diffuse hepatomegaly and massive ascites. A consultation was carried out later with the gastroenterology department to trace the etiology of the malignancy. Paracentesis was performed on the patient for diagnostic purposes. The cytological examination revealed atypical cells, some of which showed signet ring cell papillary structures. The chest X-ray, colonoscopy, esophagogastroduodenoscopy in the preoperative work-up were unremarkable.

An exploratory laparotomy was performed. A large amount of acid was aspirated intraoperatively. Massive acidity and minimal diffuse hepatomegaly was observed intraoperatively. Numerous metastatic implants were observed in the surface of the liver, omentum and peritoneal surfaces. The uterus and ovaries were atrophic and of normal appearance. In addition to the peritoneal cytology, type II hysterectomy, bilateral salpingo-oophorectomy with lymph node dissection, omentectomy and appendectomy were performed. The patient was referred to the Oncology Department postoperatively for chemotherapy. The patient received chemotherapy with taxol/carboplatin and died one and a half years later.

Pathological findings

On examination of the radical hysterectomy specimen, its size and weight were found to be normal and no macroscopic neoplastic lesions were observed.

A small endometrial polyp and an intramural uterine leiomyoma were noted. The histological study revealed an area of the in situ tumor and a papillary serous adenocarcinoma originating in the endocervix (Figures 1 and 2). Pleomorphic and macronucleated atypical cells were observed in the endocervical glands.

In addition, papillae with vascular cores and dense calcification were present in the tumor areas. The tumoral growth was seen to have extended to within 2 mm of the inner endocervical wall. No lymphatic or vascular invasion was observed in the cervix. The fallopian tubes and appendix were normal. Two microscopic implants were observed on both ovarian surfaces as well as some metastatic implants on the omentum. The right pelvic lymph nodes also revealed metastases. Left pelvic and paraaortic lymph nodes were reactive. No psammoma bodies were noted. The surgical staging of the patient was found to be 3C.

Discussion

Adenocarcinoma of the uterine cervix comprises 5%-26% of invasive cervix carcinomas [1]. Papillary adenocarcinomas make up 10%-15% of all cervical adenocarcinomas and are of four types: well-differentiated villoglandular (endocervical or endometrioid), clear-cell and papil-
Papillary serous adenocarcinoma of the uterine cervix: a case report

These types of neoplasms originate from multipotential coelomic epithelium and its derivatives and usually have the potential for invasive growth, displaying a low prognosis [3]. PSAE is rare and there are only a limited number of well documented case studies on this condition.

The first case study was reported by Hendrickson et al. in 1982 [4]. Shintaku and Ueda [5] also reported a case of papillary serous adenocarcinoma of the cervix, appearing with deep invasion of the muscle layer of the cervix and vagina, vascular invasion and pelvic lymph node metastases [5]. Another case, this time of PSAE, can also be found in the literature, reported by Batistatou et al. [3], and displaying similarities in terms of histology to papillary serous adenocarcinoma of the endometrium, ovaries and fallopian tubes. Lurie et al. recorded a case of invasive PSAE in pregnancy [6].

The pathological appearance of PSAE is similar to papillary adenocarcinomas in other locations originating in the ovaries, fallopian tubes and the endometrium [5]. As in endometrial, peritoneal and ovarian papillary serous cancers, PSAE displays early metastasis as well as early and pronounced peritoneal disseminations [4].

The clinical behavior is more aggressive compared to other typical endocervical adenocarcinomas, with a high rate of regional metastasis in the lymph nodes as well as not infrequent cases of metastasis in more distant locations [2, 7].

In the original reports, PSAE was more frequently reported in the 4th and 5th decades [8]. In terms of clinical classification, while some patients have been observed to be in lower clinical stages, pathological assessment has shown pelvic and retroperitoneal lymph node metastases [8] in many patients. Case studies reporting patient follow-ups are very few. Zhou et al. reported 17 cases of PSAE [9]. The authors pointed out that PSAE is a heterogeneous entity, and that PSAE has a bimodal frequency distribution peaking at middle age and then increasing again at ages when serous adenocarcinomas peak. Such a bimodal distribution suggests that the etiologies of PSAEs seen in early and later stages of life are different [9]. It is accepted that advanced clinical and pathological stages and being under 65 years of age are risk factors for poor outcomes [10]. The age of our patient was 75.

In the present study, although the neoplasm originated from the endocervix, no tumoral growth appeared at gross inspection. High location of cancer in the endocervical canal may make preoperative diagnosis difficult. The pos-
sibility that the peritoneum was the primary site of the cancer was discarded because no peritoneal mass could be found during surgery and the main tumor had been diagnosed as situated between the endocervical mucosa and stroma [3].

As in many other reported PSAEs, no psammoma bodies were observed in the present case [3]. In cervix adenocarcinomas, an association has generally been found between high CA-125 and extracervical metastasis [11]. In the present case, CA-125 was high and a widely spread tumor was noted.

It should not be forgotten that PSAE cases might be familial to a certain extent. Patients with PSAE in their families should be closely monitored. Kaplan et al. have reported familial PSAE in the cervix, ovaries and fallopian tubes [10].

Due to the limited number of case studies, it is difficult to arrive at definitive conclusions about the biological behavior and treatment of PSAE. These tumors are generally aggressive and usually in advanced stages at the time of diagnosis. The usual course of treatment is primarily surgery and then effective courses of radiotherapy and/or chemotherapy [7, 9]. The present case study was of a 75-year-old patient with PSAE originating in the endocervix. As with the cases that have been reported previously, the disease had already displayed wide metastasis at the time of diagnosis and then progressed aggressively.

In conclusion, PSAEs are extremely rare tumors. Due to their rarity, optimal methods to treat these tumors have not yet been established and survival rates cannot be estimated due to lack of sufficient data. Every case of PSAE should be reported to ensure data accumulation.

References

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Rare case of an ovarian monodermal teratoma with functional ovarian stroma and extensive ovarian decidualization in a 74-year-old woman

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Summary
We present the clinicopathological findings of a rare case of a monodermal teratoma of the right ovary with functional ovarian stroma and extensive decidualization in a 74-year-old woman. The patient presented with vaginal bleeding. Ultrasound scan revealed a pelvic mass measuring 9.5 cm in the lower right abdomen. A right oophorectomy was performed. The tumor was cystic and multilocular filled with colloid material. Histological examination revealed follicles of thyroid type, and stromal clusters of fusiform or polygonal cells were found in the stroma. An extensive decidual reaction was observed. Morphological and immunohistochemical examination of the tumor revealed cystic struma ovarii with functional ovarian stroma and ectopic decidua. Total abdominal hysterectomy with oophorectomy was performed. A benign endometrial polyp, proliferative endometrium, two fibroids, and an ovarian cyst were observed.

Key words: Struma ovarii; Ovarian stroma; Decidua; Ovary.

Introduction
Mature teratomas represent 27-44% of all the ovarian tumors and are usually present during reproductive age, with a mean age at diagnosis of 32 years [1, 2]. Generally they are unilateral tumors and in 8-15% of the cases they are bilateral [1, 2]. Monodermal teratomas are rare tumors with the thyroid element as the main characteristic [1, 2]. Struma ovarii is found in 2.7% of all teratomas [1, 2]. It usually develops at the fifth decade of life [1], however some cases of struma ovarii in adolescents or in postmenopausal women have been reported in the literature [1, 3]. The clinical presentation is as an ovarian solid and cystic tumor and it rarely produces signs of hyperthyroidism. One third of the patients present with ascites or even Meigs syndrome [4, 5]. Decidualization is a normal finding during pregnancy, however it is not a common finding in postmenopausal women.

A rare case of an ovarian monodermal teratoma (struma ovarii) with functional ovarian stroma and extensive decidualization in a 74-year-old woman is presented.

Case Report
This is a case of a 74-year-old patient who presented to our department with vaginal bleeding of a month’s duration. Blood tests revealed normal levels of estrogen, progesterone, free T3 and freeT4. No remarkable personal or family history was reported and the patient had not received any hormonal therapy in the past.

Ultrasound scan revealed a tumor measuring 9.5 cm in diameter in the left ovary and an endometrial polyp measuring 0.7 cm. The patient underwent exploratory laparotomy and after frozen section biopsy of the left ovarian mass showing thyroid tissue, an abdominal hysterectomy with the right adnexa was performed.

The gross examination of the ovarian mass showed a partly solid, partly cystic, multilocular tumor measuring 9.5 cm in the greatest diameter filled with colloid-like material. The cystic wall measured 0.1-1 cm. After routine procession of the specimens, formalin-fixed paraffin sections were stained with hematoxylin-eosin, and additional sections from the ovarian tumor and ovarian stroma underwent immunohistochemical investigation by a streptavidin-biotin method (Ventana, Benchmark). Histological diagnosis was struma ovarii (Figure 1). The residual ovarian stroma revealed cells with acidophilic cytoplasm like luteal or Leydig cells. Locally nodules of fusiform cells were found, resembling theca cells (Figure 2) with hyperplastic changes in loose edematous stroma. In the ovarian cortex, clusters of large cells with eosinophilic cytoplasm and a distinctive nucleus were found (Figure 3) resembling decidua cells.

Immunohistochemical analysis of the tumor cells showed a positive immunoreaction to thyroglobulin and TTF-1 and a negative immunoreaction to AE1/AE3 excepting adenocarcinoma. The decidua-like cells showed a positive immunoreaction to vimentin (Figure 4) and negative immunoreaction to CD-68 excluding the cases of histiocytic infiltration. The immunophenotype was consistent with the decidual cells, inspite of the paradox of the patient’s age and absence of history of hormonal therapy of any kind. Furthermore, the stromal cells were positive for hormone receptors (ER, PgR) hCG and inhibin.

Histological examination of the uterus revealed an endometrial adenomatous polyp measuring 0.7 cm and two fibroids 0.5 and 2.5 cm in diameter. The endometrium was proliferative with mitotic activity and tubal metaplasia, despite the patient’s age. An ovarian cyst was observed in the right ovary. No other therapy was considered necessary and the patient is well and without any tumor recurrence 48 months after surgery.

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Discussion

In our case the ovarian neoplasm presented the features of a monodermal teratoma of struma ovarii type. Most interesting are the histopathologic findings of hormone-producing stromal cells with extensive decidualization of the ovary.

Monodermal teratoma, struma ovarii, presents in the fifth decade of life as an abdominal mass in one-third of the cases with ascites, and rarely as Meigs syndrome, or with signs of thyrotoxicosis [1, 3-5]. Usually, it is a unilateral brownish tumor measuring 0.5-10 cm [1, 2]. Cystic struma ovarii is a multilocular cystic tumor measuring up to 20 cm, filled with colloid-like liquid that may lead to the diagnosis [1, 2]. Microscopic examination of cystic struma ovarii shows a thin fibroid wall with thyroid type follicles. Immunohistochemistry is positive for thyroglobulin and TTF-1 [6]. Those immunohistochemical findings aid in the differential diagnosis from Sertoli-Leydig tumors [6]. Histologic examination of struma ovarii may reveal various types of thyroid pathology, from normal or hyperplastic thyroid cells to adenoma or even carcinoma, usually of papillary type with the characteristic ground glass nuclei [7-9].

The differential diagnosis of functional ovarian stromal cells includes ovarian stromal reaction to mucin neoplasms, Brenner tumors, other monodermal teratomas, dermoid cysts, dysgerminomas and less commonly epithelial ovarian carcinomas or metastatic ovarian tumors [7-11]. Pregnancy is the main cause of ovarian decidualization. Less common causes are progesterone treatment, trophoblastic disease and hormone producing tumors of the ovaries or the adrenal glands. Rare causes are pelvic irradiation or as an idiopathic finding in pre- or postmenopausal women. However, it should be mentioned that ectopic decidua is a random histologic finding [12].

Conclusion

In our case a rare combination of monodermal teratoma of cystic struma ovarii and of functional ovarian stroma with decidualization was observed. The could be explained either as idiopathic or due to progesterone-producing stromal cells, as the patient did not report any other hormone-producing tumor or hormone treatment. The treatment of choice is total abdominal hysterectomy with bilateral oophorectomy.

References

Rare case of an ovarian monodermal teratoma with functional stroma and extensive ovarian decidualization in a 74-year-old woman


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