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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.

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Second-line chemotherapy for carboplatin/paclitaxel-refractory ovarian cancer: are multi-agent chemotherapies of little value truly?

T. Ota, N. Takeshima, K. Takizawa

Department of Gynecology, Cancer Institute Hospital, Tokyo (Japan)

Summary

Purpose: We examined whether second-line multi-agent chemotherapies are of any value for carboplatin/paclitaxel (TC)-refractory ovarian cancer. Methods: Subjects included 60 patients with ovarian, peritoneal, or tubal carcinoma who received second-line platinum-based combination chemotherapy. Thirty-nine were treated with irinotecan/cisplatin or nedaplatin and 21 with docetaxel/cisplatin shortly after TC failure. Patients were divided between those who were refractory to initial platinum-based chemotherapy (n = 29, Group A) and those who were platinum-sensitive (n = 31, Group B). Efficacy and safety of the combination chemotherapies were compared between the two groups. Results: Response to the combination chemotherapy was 10.3% in Group A and 41.9% in Group B. Median time to disease progression was 4.02 months and 7.21 months, respectively (p = 0.006), and median survival time was 7.89 months and 9.23 months, respectively (p = 0.003). There was no difference in response between the two regimens. Grade 3-4 hematologic toxicities were more frequent with the docetaxel regimen. Conclusion: The choice between agents for second-line chemotherapy for TC-refractory ovarian cancer should be based on whether the cancer was previously platinum-sensitive. With a history of such response, multi-agent chemotherapies are worth considering after TC failure. With no previous response, the expected efficacy of second-line multi-agent chemotherapy is low, suggesting the use of monochemotherapy.

Key words: Second line; Combined chemotherapy.

Introduction

Today, standard first-line chemotherapy for treatment of ovarian carcinoma involves both paclitaxel and platinum [1-4]. Long-term survival for women with advanced-stage ovarian carcinoma is only 30%, even among those who have had optimal cytoreduction and front-line combination chemotherapy [1, 3, 5, 6]. Several reports have suggested that patients with ovarian cancer who initially respond to platinum-based treatment and in whom the disease recurs may respond to retreatment with platinum-based agents. Patients with recurrent ovarian carcinoma are considered to fall into one of two groups for which the prognoses differ. Patients in whom the disease progresses during primary therapy or after a treatment-free interval of < 6 months are considered platinum-refractory; those in whom the disease relapses or the disease progresses after a treatment-free interval of > 6 months are considered platinum-sensitive. Platinum-sensitive patients are more likely to respond to subsequent chemotherapy; the probability of a second response increases up to 60% [7-12], and as a result, the prognosis is more favorable [9, 11, 13-15]. In addition, several studies have shown that the response rate improves with longer platinum-free periods, thus providing evidence that nonplatinum-based compounds may be efficacious in a subgroup of platinum-sensitive patients [9, 16-18].

Platinum-sensitive patients receiving platinum-based combination chemotherapy vs single-agent chemotherapy also show prolonged survival and progression-free survival intervals [19-21], but platinum-based combination regimens are not always successful as second-line treatment in platinum-sensitive patients. In such cases, single-agent chemotherapy may be appropriate.

We conducted a study to examine the efficacy and safety of second-line chemotherapy in patients with ovarian cancer, asking whether multi-agent chemotherapies are always useless in patients for whom first-line carboplatin/paclitaxel (TC) chemotherapy has failed.

Patients and Methods

Subjects of our study included 60 patients with ovarian, peritoneal, or tubal carcinoma who were treated by second-line platinum-based combination chemotherapy at the Cancer Institute Hospital, Tokyo, Japan, between June 2005 and December 2008. All patients had received a combination of platinum and taxane combined chemotherapy as first-line chemotherapy. Disease stages were determined according to the International Federation of Gynecology and Obstetrics criteria.

Thirty-nine of the 60 patients were treated with irinotecan (CPT-11) plus cisplatin (CDDP) or nedaplatin (NDP), and 21 were treated with docetaxel (DTX) plus cisplatin (DP). The patients were divided into two groups: those in whom the disease progressed during the initial platinum-based chemotherapy, in whom the disease remained stable, or in whom the disease relapsed within six months after completion of the platinum-based chemotherapy (platinum-refractory group, Group A; n = 29) and those in whom a progression-free interval of > 6 months was seen after completion of the platinum-based chemotherapy (platinum-sensitive group, Group B; n = 31). The two patient groups are shown in Figure 1.
Follow-up examinations were done every month. All follow-up examinations included pelvic examination, transvaginal ultrasonography, tumor marker CA125 antigen assay, and identification of late complications. Every six months, we obtained a computed tomography scan of the abdomen and a chest X-ray film. For each patient, survival was calculated from the date therapy was started to the date of the last follow-up examination. Survival curves were drawn according to the Kaplan-Meier method. Differences in patient characteristics, progression-free survival time, overall survival time, and toxic events were evaluated by exploratory global chi-square test; p values < 0.05 were considered statistically significant.

**Treatment schedule**

For the CPT-11/CDDP regimen, patients received 60 mg/m² of irinotecan on days 1, 8, and 15, and 60 mg/m² of CDDP on day 1. Cycles were repeated every 28 days. For the CPT-11/NDP regimen, patients received 60 mg/m² of CPT-11 on days 1 and 8, and 80 mg/m² of NDP on day 1. Cycles were repeated every 28 days. For the DP regimen, patients received 60 mg/m² of docetaxel and 60 mg/m² of CDDP on day 1. Cycles were repeated every 21 days. Cycles were repeated in the absence of progressive disease or unacceptable toxicity.

**Evaluation of response and safety**

Tumor response was evaluated according to the RECIST guidelines. Complete response was defined as the complete disappearance of all evident disease for at least four weeks. Partial response was defined as a > 30% decrease in the product of perpendicular diameters for each measurable lesion without the appearance of a new lesion or increase in evaluable lesions or markers for at least four weeks. Progressive disease was defined as a > 20% increase in the product of perpendicular diameters of any measurable lesion or the appearance of any new disease. Stable disease was defined as disease for which none of these criteria were met. A progression-free interval was defined as the period of time from the day the study drug was administered until disease progression was observed. Survival was defined as the period from the first day of study drug administration to the day of death or last follow-up examination.

**Results**

**Study population**

Patient characteristics are shown per group in Table 1. Mean age of the patients was 57.4 years (range, 39-78 years). Overall, the numbers of patients with ovarian carcinoma, tubal carcinoma, and peritoneal carcinoma were 55, 3, and 2, respectively. The numbers of patients with serous adenocarcinoma and clear cell adenocarcinoma,
Second-line chemotherapy for carboplatin/paclitaxel-refractory ovarian cancer: are multi-agent chemotherapies of little value truly?

Table 1. — Patient characteristics per study group.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 29)</th>
<th>Group B (n = 31)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean: 55.9)</td>
<td>(mean: 58.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>27</td>
<td>28</td>
<td>.6958</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>2</td>
<td>1</td>
<td>.5115</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>--</td>
<td>2</td>
<td>.1000</td>
</tr>
<tr>
<td>Serous</td>
<td>18</td>
<td>24</td>
<td>.1936</td>
</tr>
<tr>
<td>Clear cell</td>
<td>8</td>
<td>4</td>
<td>.1528</td>
</tr>
<tr>
<td>Mixed</td>
<td>2</td>
<td>2</td>
<td>.9450</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
<td>.9617</td>
</tr>
<tr>
<td>No. of chemotherapy courses</td>
<td>1-7</td>
<td>1-8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mean: 3.0)</td>
<td>(mean: 4.3)</td>
<td></td>
</tr>
</tbody>
</table>

*p values were calculated by chi-square test for population.

In Group B patients given CPT-11, the complete response rate was 14.3%, and the partial response rate was 28.6%. In Group A patients given DTX, the complete response rate and partial response rate were 0.0% and 15.0%.

Table 2. — Responses to treatment per study group.

<table>
<thead>
<tr>
<th></th>
<th>Group A (n = 29)</th>
<th>Group B (n = 31)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>(10.3)</td>
<td>(41.9)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>23 (79.3)</td>
<td>13 (41.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(mean: 3.0)</td>
<td>(mean: 4.3)</td>
<td></td>
</tr>
</tbody>
</table>

*p values were calculated by chi-square test for population.

Table 3. — Chemotherapy-related adverse events (grade 3-4 toxicity).

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Group A</th>
<th>Group B</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukopenia</td>
<td>14</td>
<td>16</td>
<td>.7961</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>22</td>
<td>.6502</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1</td>
<td>2</td>
<td>.5898</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1</td>
<td>--</td>
<td>.2250</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>--</td>
<td>.2250</td>
</tr>
</tbody>
</table>

*p values were calculated by chi-square test for population.

were 42, and 12, respectively. The remaining six patients comprised four with mixed-epithelial carcinoma, one with transitional carcinoma, and one with squamous cell carcinoma. Thirty-three of the 60 patients had been subjected to one chemotherapy regimen previously, 24 patients had been subjected to two regimens, and the remaining three patients had been subjected to more than three regimens. There was no significant difference in patient characteristics between the two groups, except with respect to the number of patients who had undergone more than three chemotherapy regimens. Overall, patients were subjected to 1-8 courses (mean, 3.65 courses) of second-line combination chemotherapy.

Response to treatment

Responses to treatment are shown per group in Table 2. The response rate in Group A was 10.3% (partial response, n = 3). In Group B, the response rate was 41.9% (partial response, n = 5; complete response, n = 8). In Group A patients given CPT-11, the complete response rate was 0.0%, and the partial response rate was 15.0%.

Adverse events

Chemotherapy-related adverse events are shown per group in Table 3. There were no statistical differences in the incidence of adverse events between the two groups.

Discussion

Recurrent epithelial ovarian carcinoma is usually incurable. It has been shown that, upon relapse, the probability of a response to re-treatment with platinum-based chemotherapy depends on the platinum-free interval [9]. Retrospective studies of platinum-based second-line therapies have led to the identification of two subgroups of patients with recurrent ovarian cancer: those with platinum-refractory disease and those with platinum-sensitive disease [9, 11].

There has been no report that combination chemotherapy provides an advantage over single-agent chemotherapy in patients with platinum-refractory disease [22, 23]. In the present study, only 10.3% of platinum-refractory cases responded to second-line combination-chemotherapy. Generally, single-agent chemotherapies have been used in such patients in an effort to minimize toxicity and preserve a patient’s quality of life. Several randomized trials have compared outcomes of single agents in this patient population. In general, these studies showed no statistical difference, and no clear benefit of any one agent has been established [24-27].

There have been several reports that platinum-based combination chemotherapy, in comparison to single-
agent therapy, prolongs overall survival and progression-free survival in platinum-sensitive patients [13, 19-21, 28]. In addition, there have been several reports comparing combination chemotherapies among platinum-sensitive patients. In the International Collaborative Ovarian Neoplasm 4 (ICON 4) and Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Ovarian Cancer -2.2 randomized trial, more than 800 platinum-sensitive patients with recurrent ovarian carcinoma were randomly assigned to paclitaxel plus platinum or conventional platinum-based chemotherapy. The paclitaxel plus platinum combination improved overall survival and progression-free survival among patients with relapsed platinum-sensitive ovarian cancer [20]. Phisterer et al. studied 356 platinum-sensitive patients with recurrent ovarian carcinoma who were randomly assigned to gemcitabine plus carboplatin or carboplatin treatment. They reported that gemcitabine plus carboplatin improved the progression-free survival of these patients [15]. So, for platinum-sensitive patients with recurrent disease, platinum with taxanes is recommended as first-line combination chemotherapy. Moreover, in the S-P’s Caelyx in Platinum-Sensitive Ovarian Cancer study conducted by the Gynecologic Cancer Intergroup, over 900 platinum-sensitive patients with recurrent ovarian carcinoma were randomly assigned to treatment with liposomal doxorubicin plus carboplatin or paclitaxel plus carboplatin. The liposomal doxorubicin plus carboplatin combination chemotherapy proved favorable in terms of progression-free survival and quality of life [29].

However, when platinum-sensitive patients receive the first-line combination chemotherapy for treatment of recurrent diseases but a second response is observed, there has not been any debate regarding the next chemotherapy option. It is thought that monochemotherapy is appropriate for such patients, as in platinum-refractory patients. It is noteworthy, however, that 41.9% of our platinum-sensitive patients (Group B) responded to second-line combination chemotherapy. These patients show a high sensitivity to chemotherapy in general, so they respond to the subsequent combination chemotherapy.

Generally, patients who have already received the paclitaxel-platinum combination as primary treatment are at risk of severe cumulative neurotoxicity if this combination is used for relapse [30]. Phisterer et al. treated platinum-sensitive patients with carboplatin or gemcitabine plus carboplatin. Grade 3-4 hematologic toxicities were significantly more frequent in the combination arm; neutropenia was the predominant toxicity, but the toxicity profile was considered acceptable [13]. Martin et al. treated platinum-sensitive patients with carboplatin or paclitaxel plus carboplatin and found no significant between-group difference in grade 3-4 hematologic toxicities, but mucositis, myalgia/arthritis, and peripheral neuropathy were more frequent in the combination arm [28]. In the present study, neutropenia was the major hematologic toxicity associated with both treatments. Hematologic toxicity was more severe with the DTX regimen than with the CPT-11 regimen, but there were no differences in complications between Group A and Group B. The regimen used in the present study was also found to be safe and well tolerated, and adverse events were mild to moderate in the majority of patients.

In conclusion, it is likely that the second-line combination chemotherapy for TC-refractory ovarian cancer differs in effectiveness between platinum-sensitive and platinum-refractory patients, depending on whether cancer was previously sensitive to chemotherapy. If there is a history of response to chemotherapy, multi-agent chemotherapy is worth considering even after TC failure. When there is no history of previous success in chemotherapy, the efficacy of multi-agent chemotherapy as second-line chemotherapy is expected to be low, suggesting the use of monochemotherapy.

References

Second-line chemotherapy for carboplatin/paclitaxel-refractory ovarian cancer: are multi-agent chemotherapies of little value truly? 475


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Robotic surgery for endometrial cancer: comparison of perioperative outcomes and recurrence with laparoscopy, vaginal/laparoscopy and laparotomy

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Summary

Introduction: Comparison of perioperative outcomes and recurrence in patients undergoing primary surgical treatment for endometrial cancer by robotics, laparoscopy, vaginal/laparoscopy, or laparotomy approaches. Methods: Prospective analysis of 67 patients undergoing robotic surgery for endometrial cancer between March 2004 and December 2007. Comparison was made with similar patients operated between November 1999 and December 2006 by laparoscopy (37 cases), laparotomy (99 cases) and vaginal/laparoscopy approach (vaginal hysterectomy, bilateral adnexectomy/laparoscopic lymphadenectomy) (47 cases) and matched by age, body mass index (BMI), histological type and International Federation of Gynecologists and Obstetricians (FIGO) staging. Results: Mean operating times for patients undergoing robotic, laparoscopic, vaginal/laparoscopy or laparotomy approach were 181.9, 189.5, 202.7 and 162.7 min, respectively ($p = 0.006$); mean blood loss was 141.4, 300.8, 300.0 and 472.6 ml, respectively ($p < 0.001$); mean number of nodes was 24.7, 27.1, 28.6, and 30.9, respectively ($p = 0.008$); mean length of hospital stay was 1.9, 3.4, 3.5 and 5.6 days, respectively ($p < 0.001$). There were no significant differences in intra- or postoperative complications among the four groups. The conversion rate was 2.9% for robotics and 10.8% for the laparoscopy group (0.001). There were no differences relative to recurrence rates among the four groups: 9%, 14%, 11% and 15% for robotics, laparoscopy, vaginal/laparoscopy, and laparotomy, respectively. Conclusion: Robotics, laparoscopy and vaginal/laparoscopy techniques are preferable to laparotomy for suitable patients with endometrial cancer. Robotics is preferable to laparoscopy due to a shorter hospital stay and lower conversion rate and preferable to vaginal/laparoscopy due to a reduced hospitalization.

Key words: Endometrial cancer; Robotics; Laparoscopy.

Introduction

Several studies, including our experience, have shown a reduction in blood loss, complications, hospital stay, and recovery time without compromising recurrence and survival outcomes in patients with endometrial cancer treated by laparoscopy as compared to laparotomy [1-3]. There is no doubt that in expert hands laparoscopy is preferable to laparotomy for the surgical treatment of endometrial cancer.

We designed a study to evaluate the results of robotic surgery for the primary treatment of endometrial cancer patients amenable to surgery and to compare them to matched patients treated by laparoscopy, laparotomy or a vaginal/laparoscopy (vaginal hysterectomy, bilateral salpingooophorectomy and laparoscopic lymphadenectomy) approach [4-7].

Materials and Methods

During the period of March 2004 to December, 2007, a total of 597 patients underwent robotic surgery for gynecologic conditions at Mayo Clinic Arizona. Included among them were 67 patients who underwent a robotic approach for the primary surgical treatment of endometrial cancer. The patients were matched by age, body mass index (BMI), histological type of malignancy and International Federation of Gynecologists and Obstetricians (FIGO) staging, to similar groups of patients undergoing treatment by laparoscopy (N = 37), laparotomy (N = 99) or a combined vaginal/laparoscopy approach (vaginal hysterectomy, bilateral salpingooophorectomy/laparoscopic lymphadenectomy) (N = 47) at the same institution and during the period of November 1999 to August 2006.

The study received approval by the Institutional Review Board. Perioperative data for robotic patients were collected prospectively. Demographic data, previous medical conditions, previous abdominal or pelvic operations, pathology, postoperative course and follow-up were retrieved from patient records.

Operating time for all four groups was defined from the beginning of skin incision to completion of skin closure. Docking time was counted as the time to advance the robotic column to the operating table, to attach the robotic arms to the robotic trocars, and to introduce the laparoscope and robotic instruments. Console time was defined as the surgeon’s time sitting at the console and performing the operation. Because undocking times (time to remove the laparoscope and robotic instruments and to detach the robotic arms from the trocars) were less than one minute, they were not recorded separately. Blood loss was calculated by the difference in the total amounts of suctioned and irrigation fluids.

The standard or daVinci S robotic systems (Intuitive Surgical, Inc.; Sunnyvale, CA) were used depending on availability. A total of three robotic arms and three robotic instruments were used for almost all operations and placed as previously described. A fourth robotic arm was used only in selected patients. One additional trocar was used for the assistant. Trocar placement is similar to the one used for robotic radical hysterectomy and has been previously described [8].
Robotic surgery for endometrial cancer: comparison of perioperative outcomes and recurrence with laparoscopy, vaginal etc. 477

Our technique of robotic hysterectomy has been published elsewhere and a video is available on line [9]. Vaginal hysterectomy was performed following the standard technique. Our technique of vaginal salpingo-oophorectomy has been previously reported and it allowed the removal of both adnexa vaginally in 98% of patients [10].

Limiting factors for robotics, laparoscopy, or vaginal/laparoscopy routes were uterine size and patient preference. Limiting factors for robotics were the availability of the robotic system, and patient and/or surgeon preference. Patients undergoing any of the four surgical techniques were not consecutive.

Statistics

For each continuously scaled measurement, comparisons between the groups were evaluated using the F-test from a one-way analysis of variance (ANOVA) model. Pairwise comparisons between groups were assessed using Tukey’s studentized range test, thereby controlling the type I experiment-wise error rate. Categorical measures were compared using Fisher’s exact test. All calculated p values are two sided and p values < 0.05 were considered statistically significant. All computations were performed using SAS software version 9 (SAS Institute, Inc., Cary, NC).

Results

Patient demographics and pathology results are summarized in Table 1. There were no significant differences among the four groups in terms of age, BMI, FIGO stage, histology type, grade, preoperative hemoglobin and uterine weight.

Perioperative outcomes, recurrence rate, and proportion of adjuvant therapy for the four groups of patients are summarized in Table 2. No differences in operating times were observed among the four groups of patients, however, the vaginal/laparoscopy group had a significantly longer (p < 0.05) operating time when compared to laparotomy. The blood loss was significantly lower (p < 0.05) both groups had a

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Robotic (N = 67)</th>
<th>Laparoscopy (N = 37)</th>
<th>Vaginal/laparoscopy (N = 47)</th>
<th>Laparotomy (N = 99)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>64.6 (11.9)</td>
<td>69.3 (9.4)</td>
<td>68.5 (10.9)</td>
<td>65.2 (11.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI</td>
<td>Mean (SD)</td>
<td>30.77 (10.0)</td>
<td>27.32 (7.6)</td>
<td>26.91 (5.0)</td>
<td>30.5 (9.1)</td>
</tr>
<tr>
<td>FIGO Stage N (%)</td>
<td>NS†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>16 (24)</td>
<td>9 (24)</td>
<td>8 (17)</td>
<td>16 (16)</td>
<td></td>
</tr>
<tr>
<td>IB</td>
<td>30 (45)</td>
<td>14 (38)</td>
<td>26 (55)</td>
<td>37 (37)</td>
<td></td>
</tr>
<tr>
<td>IC</td>
<td>9 (13)</td>
<td>4 (11)</td>
<td>6 (13)</td>
<td>12 (8)</td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>3 (4)</td>
<td>2 (5)</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>2 (3)</td>
<td>1 (3)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>5 (7)</td>
<td>3 (8)</td>
<td>4 (9)</td>
<td>13 (15)</td>
<td></td>
</tr>
<tr>
<td>IVa</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>0 (0)</td>
<td>3 (8)</td>
<td>1 (2)</td>
<td>11 (11)</td>
<td></td>
</tr>
<tr>
<td>Histology N (%)</td>
<td>NS†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrioid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>adenocarcinoma</td>
<td>57 (85)</td>
<td>35 (95)</td>
<td>42 (89)</td>
<td>85 (85)</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>4 (6)</td>
<td>2 (5)</td>
<td>4 (9)</td>
<td>9 (9)</td>
<td></td>
</tr>
<tr>
<td>MMT</td>
<td>5 (7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Grade &gt; 2 (%)</td>
<td>17 (25)</td>
<td>28 (76)</td>
<td>28 (60)</td>
<td>30 (30)</td>
<td>NS†</td>
</tr>
<tr>
<td>Preop Hgb (g/dl)</td>
<td>Mean (SD)</td>
<td>13.5 (1.2)</td>
<td>13.7 (1.49)</td>
<td>15.00</td>
<td>12.8 (2.05)</td>
</tr>
<tr>
<td>Uterine weight (g)</td>
<td>Mean (SD)</td>
<td>145.0 (94.0)</td>
<td>123 (48.1)</td>
<td>150.4 (42.6)</td>
<td>225.6 (317.0)</td>
</tr>
</tbody>
</table>

†NS: non-significant.

There was a trend towards an overall higher postoperative complication rate (< 6 weeks) in the laparotomy group, however the difference was not statistically significant (p = 0.12). Complications in the robotic group consisted of single instances of bladder injury, venous thrombosis (DVT), vaginal dehiscence, and vesico-vaginal fistula, and two instances of trocar site hernias. In the laparoscopy group, there were single instances of ileus, DVT, vaginal dehiscence, and peritonitis. In the vaginal/laparoscopy group, two patients experienced an ileus and one had a DVT. In the laparotomy group, four patients experienced an ileus, two had wound infections, and there were single instances of myocardial infarction (MI), pulmonary embolism (PE), DVT, and wound dehiscence. The transfusion rate was significantly higher in the laparotomy group compared to the other three groups (p = 0.04). There were no major late postoperative complications (> 6 weeks) in any of the four groups. A higher proportion of laparotomy patients required postoperative blood transfusion as compared to the other three groups (p = 0.04).

Table 1. — Patient demographics and pathology results for the four groups of patients.
The conversion rate was significantly lower ($p < 0.001$) for the robotic group (2.9%) as compared to the laparoscopy group (10.8%). In the robotic group, one patient had excessive bleeding due to advanced disease and another had an external iliac vein injury. In the laparoscopy group, two patients were converted due to bleeding and one patient with an intraoperative diagnosis of serous papillary carcinoma on the hysterectomy specimen was converted for surgical staging.

There were no differences relative to the proportion of patients receiving adjuvant therapy or experiencing a recurrence in any of the four groups. There was no difference in recurrence rate when only surgical Stage I patients were addressed.

**Discussion**

In the present study, robotics and laparoscopy resulted in similar operating times as laparotomy but were associated with reduced blood loss and shorter hospital stay. These results are consistent with other studies demonstrating the patient benefits of robotics and laparoscopy as compared to laparotomy for endometrial cancer.
Robotics is associated with reduced blood loss, even with longer operating times, and a shorter hospital stay as compared to laparotomy [11-14]. We, and others, have observed a shorter hospital stay for robotic patients compared to laparoscopy, while most have noted a comparable number of hospital days [11, 12, 16, 17].

The benefits of robotics over laparoscopy are more apparent when evaluating obese or morbidly obese patients. Robotic patients experience a shorter operative time, reduced blood loss, a shorter hospital stay and an increased number of lymph nodes as compared to laparoscopic patients [16]. In our experience with simple hysterectomy, the operating time did not increase with patient’s BMI indicating a major benefit of robotics for obese patients [9].

The overall number of nodes was similar for the four groups of patients, as it was for the number of aortic nodes. The number of pelvic nodes was higher for the laparotomy group, a difference we did not observe in our robotics series of patients with cervical cancer [8]. Some have reported comparable numbers of nodes with robotics and laparotomy, while others obtained a higher number with robotics [11-14]. In regards to the number of nodes using robotics vs laparoscopy, they are similar, although some have reported a higher nodal yield with robotics [11, 16, 17].

We observed similar intra- and postoperative complications among the four groups of patients. Others have noted reduced postoperative complications with robotics as compared to laparotomy but no difference with laparoscopy [11-14, 16, 17]. The conversion rate was lower for robotics vs laparoscopy, 2.9% vs 10.8%, respectively, while no difference was noted by others [12].

Recurrence rates for all patients and for surgical Stage I patients were similar for the four groups of patients. Previous data have shown no difference in survival or recurrence between laparoscopy and laparotomy for endometrial cancer [1-3].

A summary of robotic perioperative outcomes for endometrial cancer is presented in Table 3 [11-14, 16, 17]. A review of comparison studies between robotics, laparoscopy and laparotomy for endometrial cancer is provided in Table 4 [11, 12]. A comparison of robotics with laparotomy and robotics with laparoscopy is shown in Tables 5, and 6, respectively [13, 14, 16, 17].

The use of laparoscopy for patients with endometrial cancer has been shown to result in a shorter recovery time and improved quality of life without a negative impact on surgical outcome [18]. There has been a slow acceptance of the use of laparoscopy for gynecological and colorectal malignancies despite generalized availability of laparoscopic technology in developed countries and favorable evidence from comparison studies [1-3, 19-21].

The difficulties with training, the counter intuitive movements of rigid laparoscopic instruments, and consequently a long learning curve, might be potential factors [7, 20-23]. Robotics has a higher user acceptance rate.

Table 5. — Comparison of reported perioperative outcomes of robotics and laparotomy for endometrial cancer patients.

<table>
<thead>
<tr>
<th></th>
<th>Robotics</th>
<th>Laparotomy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR time, min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veljovich et al.*</td>
<td>302</td>
<td>139</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DeNardis et al.**</td>
<td>177</td>
<td>79</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>EBL, ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veljovich et al.*</td>
<td>98</td>
<td>197</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DeNardis et al.**</td>
<td>105</td>
<td>251</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LNs (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veljovich et al.*</td>
<td>18</td>
<td>13</td>
<td>NS</td>
</tr>
<tr>
<td>DeNardis et al.**</td>
<td>19</td>
<td>18</td>
<td>NS</td>
</tr>
<tr>
<td>Hosp stay, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veljovich et al.*</td>
<td>1.8</td>
<td>5.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>DeNardis et al.**</td>
<td>1.0</td>
<td>3.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Complications, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Veljovich et al.*</td>
<td>8</td>
<td>20.6</td>
<td>NS</td>
</tr>
<tr>
<td>DeNardis et al.**</td>
<td>4</td>
<td>20.8</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

OR = operating time; EBL = estimated blood loss; LNs = lymph nodes; * Robotic = 25; Laparotomy = 131; ** Robotic = 56; Laparotomy = 106.

Table 6. — Comparison of reported perioperative outcomes of robotics and laparoscopy for endometrial cancer patients.

<table>
<thead>
<tr>
<th></th>
<th>Robotics</th>
<th>Laparoscopy</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR time, min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gehrig et al.*</td>
<td>189</td>
<td>215</td>
<td>.0004</td>
</tr>
<tr>
<td>Seamon et al.**</td>
<td>242</td>
<td>287</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>EBL, ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gehrig et al.*</td>
<td>50</td>
<td>150</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Seamon et al.**</td>
<td>88</td>
<td>200</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LNs (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gehrig et al.*</td>
<td>34</td>
<td>22</td>
<td>.0017</td>
</tr>
<tr>
<td>Seamon et al.**</td>
<td>31</td>
<td>35</td>
<td>NS</td>
</tr>
<tr>
<td>Hosp stay, days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gehrig et al.*</td>
<td>1.02</td>
<td>1.27</td>
<td>NS</td>
</tr>
<tr>
<td>Seamon et al.**</td>
<td>1.0</td>
<td>2.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Complications, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gehrig et al.*</td>
<td>12</td>
<td>21</td>
<td>NS</td>
</tr>
<tr>
<td>Seamon et al.**</td>
<td>13</td>
<td>14</td>
<td>NS</td>
</tr>
</tbody>
</table>

OR = operating time; EBL = estimated blood loss; LNs = lymph nodes; * Robotic = 49; Laparoscopy = 32; ** Robotic = 105; Laparoscopy = 76.

patients [1-3, 11-14]. We elected to evaluate the vaginal/laparotomy group because vaginal hysterectomy was found preferable to other routes in a Cochrane review including 27 randomized controlled trials [15]. Laparoscopic lymphadenectomy was avoided in patients not at risk for nodal metastases (2), and the proportion of patients was similar for all groups. Although the vaginal/laparoscopy group had similar perioperative benefits as the robotic and laparoscopic groups the operating time was longer significantly longer, likely due to the additional time to switch from the vaginal to the laparoscopic approach.

Robotic operating times have been reported to be shorter or similar as compared to laparoscopy [11, 12, 16, 17], possibly due to the level of expertise of the operating surgeons in both techniques and the involvement of trainees in the performance of the operations. Contrary to our results, most studies have reported longer operating times with robotics as compared to laparotomy [11-14].

Again, the extent of experience with robotics and the participation of trainees are potential factors.
than laparoscopy due to its advantages over laparoscopy resulting in a short learning curve [5, 6, 24]. Consequently, gynecologic oncologists have switched from laparotomy to robotics without a laparoscopic interlude, resulting in a reduction of the number of laparotomies and obvious patient benefits [13, 14]. However, the availability, accessibility, and the associated cost of the da Vinci robotic system are major negative factors at the present.

In summary, robotics, laparoscopy and vaginal/laparoscopy techniques are preferable to laparotomy for suitable patients with endometrial cancer. Robotics is preferable to laparoscopy due to a shorter hospital stay and lower conversion rate. Robotics is preferable to the vaginal/laparoscopy due to a shorter hospital stay. Although a prospective randomized trial is desirable, the present evidence strongly supports the use of robotics for endometrial cancer patients.

References


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Young adults awareness of HPV and vaccine acceptance after introduction of the HPV vaccine in the Dutch national vaccination program

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Summary

Purpose: To investigate the effect of implementation of the HPV vaccine on HPV knowledge and HPV vaccine acceptance.
Methods: From June until December 2009 in Nijmegen, the Netherlands, 698 male and female students aged 18-25 years were recruited and interviewed about HPV, cervical carcinoma and HPV vaccine acceptance.
Results: Of all participants 46.6% had never heard of HPV. Women and students from the medical faculty were significantly more aware of HPV. Acceptance of a “catch-up” HPV vaccination in women was 51% and in men 27%. Acceptance of the HPV vaccination for 12-year old girls was 79%.
Conclusion: After implementation of the HPV vaccine in the national vaccination program, > 50% of the students lack knowledge on HPV. Acceptance of a “catch-up” HPV vaccination was low. However, the acceptance of HPV vaccination for 12-year-old girls was high. Vaccine implementation strategies, focusing on 12-16 year old girls, might have caused this difference. Young adults need to be informed that the HPV vaccine may still be efficient when they are sexually active, but HPV 16 and 18 negative.

Key words: Young adults; Students; Human papillomavirus; Knowledge; Vaccine acceptance.

Introduction

Nearly 500,000 new cases of cervical carcinoma are being diagnosed worldwide annually. For the development of cervical carcinoma, a persistent infection with human papillomavirus (HPV) is a necessary factor [1, 2]. This virus is one of the most common sexually transmitted infections in the world, but is also highly transmissible as 90% of infected women resolve the infection spontaneously [2, 3]. Approximately 40 genotypes infect the genital mucosa, and at least 15 genotypes are defined as oncogenic. Of these oncogenic genotypes, HPV 16 and 18, are responsible for approximately 70% of cervical cancers [4, 5].

Two prophylactic HPV vaccines have been developed. The bivalent vaccine Cervarix (GloaxoSmithKline Biologicals, Rixensart, Belgium) targeting against HPV 16 and 18 [6, 7], and the quadrivalent vaccine Gardasil (Merck and Co., Inc., Whitehouse Station, N.J., USA) targeting against HPV16 and 18 and the non-oncogenic genotypes HPV 6 and 11 causing genital warts. Both vaccines have shown to be highly efficacious and well tolerated [6, 8-11].

In 2007, the US Advisory Committee on Immunization Practices (ACIP) recommended routine vaccination of females aged 11-12 years with three doses of quadrivalent HPV vaccine. Vaccination is also recommended for females aged 13-26 years who have not been previously vaccinated or who have not completed the full series [Centres for Disease Control and Prevention, MMWR, March 23, 2007; 56(RR02):1]. Additionally, in 2009, the Food and Drug Administration (FDA) licensed bivalent human papillomavirus vaccine (HPV2; Cervarix, Gloaxo-SmithKline) for use in females aged 10-25 years [Centres for Disease Control and Prevention, MMWR, May 28, 2010; 59:626] [12]. Although it is preferable to vaccinate before one becomes sexually active, studies have shown that in 15-26-year-old sexually active women the vaccines are still effective if they are negative for HPV 16 and HPV 18 prior to vaccination [7, 13]. In order to achieve success in the prevention of cervical cancer, public acceptance of the vaccine and the willingness of the target population to participate are paramount.

Some studies reported that the following factors influence the intention to get vaccinated with the HPV vaccine: perceived risk of HPV infection and cervical carcinoma, age, financial aspects, recommendation by medical professional, opinion of family members, perception that vaccination will induce unprotected sexual intercourse, safety of the vaccine, and knowledge about HPV and cervical carcinoma [14-24].

Knowledge about HPV and its vaccine is mainly gathered through media, healthcare workers and the personal social network of the women who are the target for vaccination [16, 23]. Studies showed that knowledge of HPV and the HPV vaccines was positively associated with intention to be vaccinated [15-17, 23]. However, despite a generally low awareness and knowledge about HPV, studies reported HPV vaccine acceptance with a wide range of 50-88% [14, 16, 18, 20, 25, 26]. Nonetheless the vaccine acceptance may potentially be improved with education [14, 25, 26].
Knowledge of human papillomavirus (HPV), risk factors for cervical carcinoma and Pap smears by gender.

<table>
<thead>
<tr>
<th>Knowledge items</th>
<th>Men (n = 336) N (%)</th>
<th>Women (n = 362) N (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had heard of HPV</td>
<td>130 (38.7)</td>
<td>194 (53.6)</td>
<td><strong>&lt; 0.01</strong></td>
</tr>
<tr>
<td>Had heard of cervical carcinoma</td>
<td>333 (99.1)</td>
<td>362 (100)</td>
<td>0.11</td>
</tr>
<tr>
<td>If heard of cervical carcinoma, named risk factors*:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early sexarche</td>
<td>105 (31.5)</td>
<td>144 (39.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Promiscuity</td>
<td>143 (42.9)</td>
<td>200 (55.2)</td>
<td><strong>&lt; 0.01</strong></td>
</tr>
<tr>
<td>No condom use</td>
<td>124 (37.2)</td>
<td>178 (49.2)</td>
<td><strong>&lt; 0.01</strong></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>67 (20.1)</td>
<td>65 (18.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td>28 (8.4)</td>
<td>46 (12.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Smoking</td>
<td>124 (37.2)</td>
<td>117 (32.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>Heredity</td>
<td>209 (62.8)</td>
<td>246 (68.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Age</td>
<td>127 (38.1)</td>
<td>141 (39.0)</td>
<td>0.88</td>
</tr>
<tr>
<td>Knowledge of cervical carcinoma (score 0-8) (mean) (SD)</td>
<td>3.6 (1.2)</td>
<td>3.7 (1.3)</td>
<td>0.65</td>
</tr>
<tr>
<td>Knew that from the age of 30 years, women in the Netherlands get a Pap smear</td>
<td>105 (31.2)</td>
<td>166 (45.9)</td>
<td><strong>&lt; 0.01</strong></td>
</tr>
<tr>
<td>Knew Pap smears diagnose cervical carcinoma and pre-malignancies</td>
<td>176 (52.4)</td>
<td>245 (67.7)</td>
<td><strong>&lt; 0.01</strong></td>
</tr>
<tr>
<td>Knew an abnormal Pap smear is not always due to cervical carcinoma</td>
<td>175 (52.1)</td>
<td>260 (71.8)</td>
<td><strong>&lt; 0.01</strong></td>
</tr>
<tr>
<td>Will get a Pap smear in the futurec</td>
<td>–</td>
<td>326 (90.1)</td>
<td></td>
</tr>
</tbody>
</table>

*p value: differences between groups of education using the chi-square test.
* More answers possible; † Using one-way analysis of variance; ‡ Women only

Before the implementation of the HPV vaccine in the national Immunization program (NIP) and its associated extensive attention in the Dutch media, knowledge of HPV and cervical cancer, and acceptance of HPV vaccination among young adults in the Netherlands was assessed by our group [27]. Despite low awareness of HPV (17.7%) in this group of young adults, a small majority (56%) would get vaccinated if the HPV vaccine was offered [27]. The objective of the present study was to investigate the potential effect of the implementation of the HPV vaccine on the knowledge of HPV and the HPV vaccine acceptance of Dutch students aged 18-25 years. These results might give insight into the acceptability of the HPV vaccine on the knowledge of HPV and the HPV national Immunization program (NIP) and its associated vaccination. The majority of the questions were multiple-choice, and contained a ‘don’t know’ option. For the analysis of knowledge a score was computed using a correcting for guessing technique. This means that one point was scored for a correct answer and one point was subtracted for an incorrect answer. All questionnaires were processed anonymously.

To test statistically significant differences between men and women the Fisher’s exact test and the t-test were used. To evaluate possible differences between the three education groups, the chi-square and one-way analysis of variance were used.

Potential factors influencing HPV vaccine acceptance were assessed with simple and multivariable logistic regression.

Materials and Methods

Before the implementation of the HPV vaccine in the national Immunization program (NIP) our study group found a vaccine acceptance of 56.0% for the whole group and 48.0% and 61.0% for men and women, respectively. The calculated power to detect a 10% increase or decrease of vaccine acceptance with a 95% confidence interval is 320 participants of each gender.

Seven hundred and thirty students in Nijmegen, the Netherlands, were asked from June until December 2009 to participate in this cross-sectional survey. These students were randomly approached at the faculties and college during lunch breaks and classes. Of these 730 students, 698 (96%) volunteered; 336 were male and 362 were female. There were 260 students of the medical faculty, 221 students of the non-medical faculty, and 217 students of the non-university college. The most common reason to refuse participation was time related. The inclusion criteria were: age between 18 and 25 years, and sufficient knowledge of the Dutch language to answer the questionnaire.

The students were asked to individually fill out a questionnaire under the supervision of the researcher. The participants did not receive background information preceding the questionnaire. In order to obtain comparable data, an identical questionnaire from the previous survey was used [26]. However, the questions about the HPV vaccine were no longer hypothetical. The questionnaire took about five minutes to fill out, and contained questions about demography and sexual behaviour, vaccine acceptance, knowledge of HPV, cervical carcinoma, and the national cervical screening program. The majority of the questions were multiple-choice, and contained a ‘don’t know’ option. For the analysis of knowledge a score was computed using a correcting for guessing technique. This means that one point was scored for a correct answer and one point was subtracted for an incorrect answer. All questionnaires were processed anonymously.

To test statistically significant differences between men and women the Fisher’s exact test and the t-test were used. To evaluate possible differences between the three education groups, the chi-square and one-way analysis of variance were used.

Results

Of the 698 participants, 51.9% (n = 362) were women and 48.1% (n = 336) were men. The mean age was 20.5 years [standard deviation (SD) 1.9]. The mean age differed significantly (p < 0.01) between the education groups; 21.3 years for medical students, 20.6 years for non-medical university students, and 19.4 years for college students, respectively. Of all participants, 92.3% were born in the Netherlands, 82.2% (n = 574) considered themselves to be sexually active, and 64.1% of them were currently in a relationship. The reported mean age of first sexual intercourse was 16.7 years (SD 1.7) (n = 545), which did not differ significantly between men and women. The mean number of sexual partners was 3.4 (SD 3.4) (n = 555); women had a higher number of sexual partners than men (p < 0.01), 4.0 (SD 3.0) and 2.9 (SD 2.0), respectively. Only 1.9% of the participants reported that they ever had a sexually transmitted disease.
Table 2. — Knowledge of human papillomavirus (HPV), risk factors for cervical carcinoma and Pap smears by education.

<table>
<thead>
<tr>
<th>Knowledge items</th>
<th>Medical faculty (n = 260) N (%)</th>
<th>Non-medical faculty (n = 221) N (%)</th>
<th>College (n = 217) N (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had heard of HPV</td>
<td>225 (86.5)</td>
<td>58 (26.2)</td>
<td>41 (18.9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Had heard of cervical carcinoma</td>
<td>260 (100)</td>
<td>220 (99.5)</td>
<td>215 (99.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>If heard of cervical carcinoma, named risk factors*</td>
<td>145 (55.8)</td>
<td>45 (20.5)</td>
<td>59 (27.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Early sexarche</td>
<td>203 (78.1)</td>
<td>63 (28.6)</td>
<td>77 (35.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Promiscuity</td>
<td>182 (70.0)</td>
<td>54 (24.5)</td>
<td>66 (30.7)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>No condom use</td>
<td>28 (10.8)</td>
<td>52 (23.6)</td>
<td>52 (24.2)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>33 (12.7)</td>
<td>19 (8.6)</td>
<td>22 (10.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td>119 (45.8)</td>
<td>51 (23.2)</td>
<td>71 (33.0)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>170 (65.4)</td>
<td>153 (69.5)</td>
<td>132 (61.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>Heredity</td>
<td>132 (50.8)</td>
<td>90 (40.9)</td>
<td>46 (21.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Age</td>
<td>4.0 (1.3)</td>
<td>3.2 (1.1)</td>
<td>3.7 (1.1)</td>
<td>0.05b</td>
</tr>
<tr>
<td>Knowledge of cervical carcinoma (score 0-8) (mean) (SD)</td>
<td>118 (45.4)</td>
<td>68 (30.8)</td>
<td>85 (39.2)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Knew that from the age of 30 years, women in the Netherlands get a Pap smear</td>
<td>180 (69.2)</td>
<td>116 (52.5)</td>
<td>125 (57.6)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Knew Pap smears diagnose cervical carcinoma and pre-malignancies</td>
<td>231 (88.8)</td>
<td>107 (48.4)</td>
<td>97 (44.7)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Will get a Pap smear in the future*</td>
<td>231 (88.8)</td>
<td>107 (48.4)</td>
<td>97 (44.7)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>(n = 139)</td>
<td>(n = 11)</td>
<td>(n = 112)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 95.0)</td>
<td>98 (88.3)</td>
<td>96 (85.7)</td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

* More answers possible; † Using one-way analysis of variance; ‡ Women only.

Of the total study population, 46.4% (n = 324) of students were aware of HPV. If they were aware of HPV, 87.0% (n = 282) knew that HPV is sexually transmitted, and 79.6% (n = 258) thought that condom use is fully protective against an HPV infection. Nearly half of the participants (47.5%, n = 154) knew that the lifetime risk of acquiring a genital HPV infection was > 50%, and 74.4% (n = 241) were aware that an HPV infection often passes asymptotically. Of all participants, 83.4% (n = 582) had heard of genital warts, of whom only 32.1% (n = 187) knew that HPV infection causes genital warts.

Almost all students (99.6%, n = 695) had heard of cervical carcinoma, of whom 50.9% (n = 354) knew there is a causal relationship with HPV. The mean knowledge score of cervical cancer was rather low: 3.6, out of a maximum possible score of 8. ‘Heredity’ was most (65.5%) falsely indicated as a risk factor for cervical carcinoma.

Table 1 presents the knowledge on HPV, risk factors for cervical carcinoma and Pap smears by gender. Women were significantly more aware of HPV than men; 53.6% vs 38.7% (p < 0.01). Additionally, they knew more often that an HPV infection may cause cervical cancer, and that an HPV infection often passes asymptomatic; 55.5% vs 45.9% (p = 0.01), and 79.9% vs 66.2% (p = 0.01), respectively (data not shown). Men and women scored comparably on knowledge of cervical carcinoma, but women knew significantly more often about Pap smears. Of the women 45.9%, compared to 31.2% of the men, knew that cervical cancer screening in the Netherlands starts at the age of 30 years. They also knew more often that not only cervical carcinoma, but also pre-malignancies, cause abnormal cytology results. Of all women, 90.1% intended to have a Pap smear in the future.

The knowledge of HPV, risk factors for cervical carcinoma and Pap smears is presented in Table 2. Of all students, medical students were significantly most often aware of HPV (86.5%), followed by students from the non-medical faculty (26.2%), and college students (18.9%). Medical students also had a significantly higher score on cervical carcinoma knowledge; with a score of 4.0 among medical students, 3.7 among college students, and students from the non-medical faculty scored 3.2. Although medical students had the highest mean score on cervical carcinoma knowledge, only 30.0% knew that condom use does not fully protect against HPV transmission, and 50.8% indicated ‘age’ as a risk factor for cervical cancer. Furthermore, medical students had a significantly higher knowledge of Pap smears, and the females of the medical students were also more willing to get a Pap smear in the future (95.0%).

In general, of all 698 participants 39.4% were willing to receive HPV vaccination if offered at their current age, with a significant difference between men (26.7%), and women (51.1%). The majority of the students (79.2%) agreed on vaccinating 12-year-old girls with the HPV vaccine, and this did not differ significantly between men and women. As shown in Table 3, in multivariate analysis gender and type of education were independent variables influencing the willingness of these young adults to get vaccinated with the HPV vaccine at their current age. Women were more favourable toward the vaccine and medical students were less prone to get vaccinated compared to college students. There were no factors identified of significant influence towards the national vaccination of 12-year-old girls.
Discussion

In the present study, 46.4% of the young adults were aware of HPV. Whereas, in our study performed in 2005, before the implementation of the HPV vaccine in the National Immunization Program (NIP), only 17.7% of the young adults were aware of HPV [27]. However, these results are in agreement with other studies that also showed an increase in knowledge of cervical cancer and HPV after the introduction of HPV vaccines [20, 25, 28].

Despite improved awareness of HPV, the willingness of all students to get vaccinated at their present age was only 39%, which is lower than the 56% acceptance in our previous study. On the other hand, the acceptance rate of the young adults agreeing on vaccinating 12-year-old girls was high (79%). Therefore we may conclude that young adults do accept the HPV vaccine, but not at their current age. We did not ask about the arguments of these young adults on vaccine acceptance, but the difference of vaccine acceptance between themselves and 12-year-old girls might be due to the implementation strategies of the vaccine. Vaccination with Cervarix was implemented in the Netherlands into the National Immunization Program (NIP), starting with catch-up HPV vaccination for girls aged 13-16 years, followed by vaccination of 12-year-old girls. This may have led to the misperception that the vaccine is not efficient for young adults. Although it is preferable to vaccinate before one becomes sexually active, young adolescents should be informed that the vaccines are still effective in 15-26-year-old, sexually active, HPV 16 and HPV 18 negative women [7, 13].

The vaccine acceptance rate of 79% for vaccinating 12-year-old girls is comparable with studies performed in Australia and Sweden [29, 30]. Before the implementation of the HPV vaccine in the NIP, our study group also performed a study concerning vaccine acceptance among parents [30]. In that study a good parental acceptance rate of 88% was found for HPV vaccination of 10-12-year-old girls. The 79% acceptance of the vaccine for 12-year-old girls despite lower knowledge among the students may be caused by a general vaccine acceptance or once implemented in the National Vaccination Program [21, 31, 32]. This difference between HPV knowledge and vaccine acceptance was reported by other studies as well [14, 16, 18, 20, 25, 26]. Education, however, is still considered to be a potential method to improve HPV vaccine acceptance [14, 16, 17, 25, 26].

Women were significantly more aware about HPV and had a higher knowledge score on cervical carcinoma and Pap smears than men. This was confirmed by several other studies [28, 29, 33]. The vaccine acceptance among female students at their current age is also significantly higher than among male students, 51% vs 27%, respectively. The male vaccine acceptance found in our study is comparable to the acceptance rate of 33% found by Ferris et al. [34]. Factors positively influencing vaccine acceptance in men were high general education, high-risk behaviour, and knowledge about HPV and safety and efficacy of its vaccine [34, 35]. Although expected otherwise, informing male students about the benefits of the vaccine for reducing cervical cancer risk in women did not increase interest [36]. Excluding boys from vaccination might send the wrong message that girls and women alone are responsible for acquiring an HPV infection. Because infected men serve as vectors sharing HPV with females, vaccination of men may create herd immunity and provide protection for women. However, protective efficacy has not yet been fully established in men and cost-effective-

<table>
<thead>
<tr>
<th>Table 3. — Odds ratios and adjusted odds ratios for the acceptance of human papillomavirus (HPV) vaccination.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potential factors influencing HPV vaccine acceptance</td>
</tr>
<tr>
<td>Gender:</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Education:</td>
</tr>
<tr>
<td>Medical University</td>
</tr>
<tr>
<td>Non-medical University</td>
</tr>
<tr>
<td>College</td>
</tr>
<tr>
<td>Age (years):</td>
</tr>
<tr>
<td>Had heard of HPV:</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Knowledge of HPV</td>
</tr>
<tr>
<td>Knowledge of cervical cancer screening programme</td>
</tr>
<tr>
<td>Sexual active:</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Sexarche</td>
</tr>
<tr>
<td>Number of sexual partners</td>
</tr>
</tbody>
</table>

Using logistic regression. CI, confidence interval. Ref, reference. Adj. OR, adjusted odds ratio, adjusted for the other variable in the model.
ness of including both boys and girls in national HPV immunization programs has to be proven [37].

We did not inform participants about any potential costs related to the vaccine. Previously it was shown that the actual vaccine uptake might be much lower when people have to pay for the vaccine [16, 17, 19]. In the Netherlands young adults are not the target of the NIP, which provides the vaccine for free, and the health insurance companies do not cover their costs. Therefore the actual HPV vaccine acceptance in our population of young adults may even be lower. On the other hand, they might expect there will be costs since they are not the target of the NIP. In 2005 there was no information yet about the NIP implementing the vaccine and to which age groups it would be offered to. At that time students might have assumed it to be free, and this may also be an explanation for the difference in acceptance of the vaccine.

Conclusion

Young adults seem to be more aware about HPV, but their knowledge is still low. Young adults have a high acceptance for vaccinating young girls with the HPV vaccine, but a lower acceptance for getting the vaccine themselves at their current age. A possible explanation for this might be that they do not know that the HPV vaccine is still effective at their current age. Therefore they should be informed about the efficacy of the vaccine in young adults, especially when they are HPV 16 and HPV 18 negative. In order to make HPV vaccination a success, more information needs to be provided about HPV, cervical carcinoma, and safety and efficacy of the HPV vaccine.

References


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Total colectomy in primary ovarian cytoreduction

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Summary

Objective: To review the indications, procedure, and complications associated with total colectomy with ileorectal anastomosis in women undergoing primary debulking of ovarian cancer. Methods: Charts were reviewed to determine all patients undergoing total colectomy with ileorectal anastomosis during primary debulking of ovarian, peritoneal, or fallopian tube cancer. Charts were also reviewed for perioperative morbidity and mortality, as well as rates of fecal incontinence. Results: Nine patients underwent the above procedures during primary debulking of ovarian cancer. The mean age was 61 years with a mean BMI of 31 kg/m². The average postoperative hospital stay was 11 days with an average estimated blood loss of 700 ml. There was no perioperative mortality. Although all patients had greatly increased frequency of stools, no patients had incontinence of stool after eight weeks. Conclusions: Radical surgery, including total colectomy, can be performed in select patients with primary ovarian cancer. Acceptable morbidity, mortality, and rectal continence can be obtained.

Key words: Ovarian cancer; Cytoreduction; Colectomy.

Introduction

How much surgery is too much surgery for the primary debulking of ovarian cancer? The paradigm has shifted in the management of ovarian cancer over the last one to two decades. While the goal has stayed the same: maximizing both quantity and quality of life, the means to attain this has shifted. Many authors have elegantly demonstrated that to lengthen life the goal of surgery must now be complete cytoreduction and not just optimal cytoreduction. In fact, the term optimal itself is misleading in that optimal cytoreduction, leaving residual tumor \( \leq 1 \) cm in maximal dimension, is not really optimal. An optimal surgery would truly be leaving no grossly palpable or visible disease.

Eisenkopf, Bristow, Chi and others have demonstrated that aggressive surgical cytoreduction is necessary to achieve longer survival and can be safely performed in select patients [1-6]. Although not all patients are medically fit to undergo radical debulking, in those patients who are able, radical debulking can be performed with acceptable morbidity and mortality. Often this will involve resection of portions of either the small or large intestine in order to obtain complete removal of disease [7-11]. Previously, Wheless demonstrated that permanent colostomies can be avoided even after large resections for pelvic malignancies by the use of automatic staplers [12]. When patients have adequate nutritional levels as documented by albumin or prealbumin, these extensive surgeries can be performed with low anastomotic leak rates [13, 14]. In contrast, Jaeger et al., demonstrated that performing bowel resection and not at least optimally cytoreducing patients has no survival benefit [15].

The purpose of this paper was to examine a series of women with primary ovarian cancer undergoing total colectomy with ileorectal anastomosis (IRA) at their initial debulking surgery.

Methods

Information was collected from outpatient charts and inpatient records from patients with the diagnosis of epithelial ovarian carcinoma from 2004-2006. The information was collected on an institutional review board approved protocol. Only patients with Stage IIIC and IV disease were included. All non-epithelial and low-malignant potential ovarian cancer patients were eliminated. All patients who had previously undergone neoadjuvant chemotherapy were eliminated. All patients having undergone previous exploration for ovarian cancer were eliminated unless they were transferred in for immediate (< 30 days) re-exploitation without interval chemotherapy. Patients with poor performance status were generally not seen as surgical candidates. Information was verified against hospital records. Cytoreduction was defined as follows: suboptimal - > 1 cm residual disease, optimal - \( \leq 1 \) cm residual disease, complete - no visible or palpable residual disease.

Total colectomy with IRA was performed if it emerged during the procedure that more than two anastomoses in the colon (including distal ileum) would be necessary to obtain complete removal of disease (Figure 1) or if blood supply to the colon would be inadequate or questionable after resection of multiple metastases. The bowel lumen was transected with a Autosuture GIA linear stapler (Autosuture, Covidien, Norwalk, CT) and the most common load used was a 60 mm load with 3.8 mm staples. The bowel mesentery was separated with Auto- suture Endo-GIA Universal (Autosuture, Covidien, Norwalk, CT) with 45 mm loads with 2.0 mm staples. Ileal-rectal anasto- moses were performed in one of two ways. The most common way was the creation of an ileal J-pouch by approximating the two antimesenteric borders and using the Autosuture GIA linear stapler to form a J-pouch. The Autosuture CEEA (Autosuture, Covidien, Norwalk, CT) with a 28 mm or 31 mm load was then used to perform a functional end-to-end anastomosis of the ileal J-pouch to the rectum (Figure 2). Alternatively, at the surgeon’s discretion, a side-to-side, functional end-to-end anastomosis was performed without the creation of a J-pouch if adequate
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All anastamoses were sprayed with Tisseel fibrin sealant (Baxter Healthcare, Deerfield, IL) to aid in healing [16].

All patients with normal renal function were treated with subcutaneous fondaparinux prophylactically. If renal function was impaired, enoxaparin was used. After the re-establishment of bowel function after surgery, all patients initially were treated with low potency narcotics (loperamide). Doses were raised or lowered as required to achieve lowest dose necessary to maintain normal function. If stronger medications were needed either paregoric or tincture of opium was used. Patients were also placed on bulking agents.

Statistics were performed utilizing SPSS 9.0 (SPSS, Chicago, IL). Categorical variables were studied using chi square or log rank. Ordinal data was analyzed using Student’s t-test or Wilcoxon rank-sum depending on whether or not the data were parametric. Two-tailed analyses were performed.

Results

One hundred and fourteen patients were found with newly diagnosed ovarian cancer with 108 undergoing primary surgical cytoreduction. Optimal or complete cytoreduction was obtained in 107 of 108 patients [14]. The average age of the patients undergoing the procedure in question was 61 years (mean 63 years, range 50-79) with a mean preoperative CA 125 of 407 IU/ml (median 189 IU/ml, range 34-2438). The mean BMI was 31 kg/m² with a median of 32 kg/m² (range 27-35).

Nine women underwent a total colectomy during their primary debulking surgery for Stage IIIc or IV epithelial ovarian carcinoma (8.3%). Five other patients underwent less extensive bowel resection. All nine patients had complete cytoreduction of disease. Mean estimated blood loss was 700 ml with a median of 600 ml (range 200-1250 ml). Three patients received intraoperative transfusions of 2-4 units of packed red blood cells. Six of nine patients received intraoperative or postoperative fresh frozen plasma for an INR of greater than or equal to 1.4 [17]. Concomitant extensive upper abdominal procedures were performed in seven of the nine patients (Table 1). In the two in whom other radical procedures were not needed, diaphragm peeling and/or ablation removed disease without requiring diaphragm resection.

Table 1. — Concomitant extensive upper abdominal procedures.

<table>
<thead>
<tr>
<th>Radical procedure</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Splenectomy with or without</td>
<td>5</td>
</tr>
<tr>
<td>distal pancreatectomy</td>
<td></td>
</tr>
<tr>
<td>Liver resection</td>
<td>2</td>
</tr>
<tr>
<td>Partial gastrectomy</td>
<td>2</td>
</tr>
<tr>
<td>Diaphragm resection</td>
<td>3</td>
</tr>
</tbody>
</table>

The mean postoperative stay was 11 days (median 10, range 6-19). One patient developed a staple line leak from the gastrectomy site which healed without surgical intervention. Another patient developed a vesicovaginal fistula which did not heal with simple urinary catheter diversion. She required an outpatient transvaginal fistula repair and delay of chemotherapy by one week. Postoperative infections were encountered in two patients (bacteremia in one patient, pyelonephritis in one patient).

All patients had rectal continence by eight weeks postoperatively using loperamide (2 tablets by mouth daily). The average patient had more than one bowel movement during hospit
daily (mean 2 daily, median 2 daily, range 1–4) which was an increase over their reported preoperative number (3 times/week) (p = 0.04).

Discussion

The goal of primary debulking of ovarian cancer is the complete removal of visible or palpable disease [18–21]. Often, this will entail bowel resection in order to achieve complete removal of all disease. Many authors have discussed the need for bowel resection as well as the morbidity and mortality associated with the procedure. Recently, Bristow and colleagues published on their series of patients undergoing transverse colectomies for ovarian cancer [6]. In their series of patients, transverse colectomies could be done with acceptable morbidity and mortality to achieve optimal cytoreduction. In their series, despite often multiple anastomoses, low rates of anastomatic leaks were encountered. However, no mention of patients’ nutritional status or pre- or postoperative need for parenteral feeding was documented.

Hoffman and colleagues have further documented their aggressive approach to cytoreduction [22]. Their approach involves en bloc resection of the left upper quadrant as opposed to a piecemeal approach. They concluded that in highly selected patients such extensive surgery is a reasonable method for obtaining optimal cytoreduction. How do we as gynecologic oncologists determine who these highly selected patients are? Silver and Zghieb recently demonstrated that extended left colon resections were feasible in ovarian cancer patients [23]. They noted that patients undergoing extended left colectomies could even tolerate intraperitoneal chemotherapy.

Despite aggressive surgical intervention and adjuvant platinum-based chemotherapy, some patients recur quickly with platinum-resistant disease. This is one of the arguments used by those who do not believe in aggressive, radical debulking of primary disease. Jaeger and colleagues showed that there was no benefit of bowel resection if only suboptimal cytoreduction was obtained [15]. Unfortunately, no gynecologic oncologist can accurately predict at the time of primary cytoreduction which patients will have platinum-refractory disease and which will have platinum-sensitive disease with a long disease-free interval. If it could be predicted, it would be beneficial to withhold radical procedures in patients in whom they would not increase the disease-free interval. The only way to do this currently is to withhold radical procedures at initial cytoreduction and apply them to those undergoing secondary cytoreductive efforts after long disease-free intervals. However, some groups have shown that increasing level of cytoreduction increases sensitivity to platinum [24]. Another approach would be to perform neoadjuvant chemotherapy in all bulky disease patients. This would decrease the need for radical procedures needed.

None of the patients in the current study had fecal incontinence after eight weeks. The rate of daily bowel movements was similar to that shown in the colorectal literature [25]. However, this level of bowel movements, after a surgery for a benign condition, was seen as distressing as compared to a preoperative level of two to three per week. This same level of bowel movements was not seen as a problem by the women undergoing extensive cytoreductive surgery for ovarian cancer in this study. Since none of the patients had total or near-total proctectomies in this study, the decision on whether or not to use a J-pouch was based on the surgeon’s opinion of the length of the residual rectum (i.e., the longer the segment left, the less the need for a J-pouch).

Often patients are encountered that are truly not good surgical candidates for cytoreductive surgery [26]. Whether it is poor performance status, poor health status, or poor nutritional status, some patients are at too high a risk to undergo cytoreductive surgery [12, 13]. The Mayo group has shown that with a low albumin there is a higher risk for anastomotic leakage due to the decreased healing potential [13]. Other groups have shown that multiple perioperative complications significantly increase when poor nutrition, as documented by low prealbumin, is present preoperatively [14].

Tisseel fibrin sealant, is a fibrin-based sealant approved for use as a tissue sealant and hemostatic agent. For several years, this medication has been used to help in wound healing, fistula closure, and strengthening anastomoses [27]. Prior to detailed studies, this sealant was being used to increase healing of bowel anastomoses. During the last decade, experimental and clinical evidence has been presented and published which supports this supposition [28–31]. Because of the high-risk nature of the gynecologic oncology patient population, this medication was used on all of the bowel anastomoses. Just because a procedure can be done, does not mean a procedure should be done. Bristow et al. have shown that ovarian cancer patients can tolerate multiple gastrointestinal anastomoses [6]. This fact alone may decrease the need for such extensive procedures below the low rate of 8.3% shown even in this study. Since they have shown that multiple anastomoses in the same patient are well tolerated, performing a colectomy to avoid multiple anastomoses may be avoided. Thus, patients with multiple anastomoses and not colectomies will be seen. Still, rarely will there be patients that have such extensive disease that a colectomy may be warranted to achieve optimal cytoreduction. Surgical experience and individualization of patient care comes into play. It should be part of the armamentarium of the gynecologic oncologist so that we can give our patients the best chance at survival from this dreaded disease.

References


Association between Arg399Gln polymorphism of X-ray repair cross-complementing 1 (XRCC1) gene and sporadic endometrial cancer in the Polish population

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²Laboratory of Molecular Genetics, Department of Pathology, Institute of Polish Mother’s Memorial Hospital, Lodz
³Department of Pathomorphology, Medical University of Lodz, Lodz (Poland)

Summary

Background: Endometrial cancer is one of the most common malignant neoplasms which appear in the uterine body. X-ray repair cross-complementing 1 (XRCC1) protein can be involved in the repair of DNA lesions, which are known to contribute to endometrial cancer. Material and Methods: The genotype analysis of XRCC1 Arg399Gln gene polymorphisms for 456 endometrial cancer patients and 300 controls of cancer-free subjects in the Polish population were performed using the PCR-based restriction fragment length polymorphism (PCR-RFLP). Results: The association between endometrial cancer occurrence and the Gln/Gln genotype of the Arg399Gln polymorphism (odds ratio, OR 2.28; 95% confidence interval, CI 2.02-2.54) was found. The Gln/Gln genotype of XRCC1 increased the risk of type I endometrial cancer occurrence (OR = 2.42, 95% CI = 2.12-2.72). No statistically significant association was found between gene polymorphisms and endometrial cancer risk factors such as BMI, HRT, uterine bleeding, endometrial ultrasound transvaginal, diabetes and hypertension. Conclusion: The results support the hypothesis that the Arg399Gln polymorphism of the XRCC1 gene may be associated with the incidence of sporadic endometrial cancer in Polish women.

Key words: XRCC1; Endometrial cancer; Gene polymorphism.

Introduction

Endometrial cancer is the most common malignancy of the female genital tract. Annually 150,000 new cases of this cancer are noted worldwide. Every year in the age group 65-75 years, 65 new cases of endometrial cancer are diagnosed among every 100,000 women [1].

Uterine cancer is the fourth cancer site for incidence cases among women in Poland. The number of deaths caused by uterine corpus cancer amounts to 814 (12th cause of death among women). Morbidity is 7.1% and mortality 2% for uterine corpus cancer [2].

The number of morbidity cases rises dramatically beginning with the age of 45; thereafter it stabilizes to the level of 600-700 new cases in subsequent 5-year age groups and after the age of 70 it quickly diminishes. Increase in the number of deaths with age is similar to the one observed for morbidity.

Endometrial cells are constantly under oxidative stress during menstrual cycles [3]. The stress is generated in the metabolic reactions of estrogens, producing reactive oxygen species (ROS), which can cause damage to biomolecules, including DNA. ROS may induce mutations in proto-oncogenes and tumor suppressor genes, as well as in other genes important for induction, promotion and progression of cancer, thus accelerating malignant transformation [4].

Oxidative damage to the DNA bases are mainly removed by the base excision repair (BER) pathway. BER is the repair mechanism for small lesions such as single-strand breaks, non-bulky adducts, oxidative damage, alklylation, or methylation [5]. X-ray repair cross-complementing 1 (XRCC1) and the human oxoguanine glycosylase 1 (hOGG1) and genes are key genes in the BER pathway.

XRCC1 is a multidomain protein that repairs single-strand breaks in DNA. Two major single nucleotide polymorphisms (SNPs) of the XRCC1 gene have been identified at codon 194 (C → T substitution at position 26304, exon 6, Arg to Trp) and 399 (G → A substitution at position 28152, exon 10, Arg to Gln). Genetic polymorphisms of DNA repair genes have been reported to lead to amino acid substitution in various cancers. There were some reports about the relation between XRCC1 polymorphisms and risk for several cancers: breast, prostate, laryngeal and bladder cancer [6-14].

Little is known about XRCC1 polymorphism in endometrial cancer risk. In the available literature not many researchers have investigated an association of XRCC1 polymorphism and endometrial carcinoma [15-17].

In the present work we performed a hospital based case control study using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay to genotype polymorphism of gene XRCC1 Arg399Gln in relation to endometrial cancer susceptibility.
Materials and Methods

Endometrial cancer patients

Four hundred and fifty-six patients with histologically proven diagnoses of endometrial cancer were included in the study (Table 1). Paraffin-embedded tumor tissues were obtained from postmenopausal women with endometrial carcinoma treated at the Department of Menopausal Diseases, Institute of Polish Mother’s Memorial Hospital between 2002 and 2009. All tumors were staged according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO). DNA from normal endometrial tissue (n = 300) served as a control. Detailed information on demographic factors, menstrual and reproductive history, hormone use, prior disease history, physical activity, tobacco and alcohol use, diet, weight history, and family history of cancer was collected for all participants. Body weight, height, and circumferences of the waist and hips were measured according to a standardized protocol at the time of interview. Menopause was defined as cessation of the menstrual period for at least 12 months before the reference date (diagnosis date for the cases and interview date for the controls), excluding lapses caused by pregnancy, breastfeeding, or estrogen hormone use. Body mass index (BMI, weight in kilograms/height in meters²) and waist-to-hip circumference ratio (WHR) was calculated using measured anthropometrics.

DNA isolation

DNA was extracted from material using the commercially available QIAamp Kit (Qiagen GmbH, Hilden, Germany) for DNA purification according to the manufacturer’s instructions.

Determination of XRCC1 genotype

Genotypic analysis of the XRCC1 polymorphism was determined by the PCR-based restriction fragment length polymorphism (PCR-RFLP) method. Polymorphism Arg399Gln of the XRCC1 gene was determined by PCR-RFLP, using primers 5’-TTTGCTTCTCTCTGTTCA-3’ and 5’-TCCTCCAGCCTTTTCTGATA-3’. The PCR was carried out in a GeneAmp PCR system 9700 (Applied Biosystems) thermal cycler. The 25 µl PCR mixture contained about 100 ng of DNA, 12.5 pmol of each primer, 0.2 mmol/l of dNTPs, 2 mmol/l of MgCl₂ and 1 U of Taq DNA polymerase. The PCR cycle conditions were 94°C for 30 sec, 62°C for 30 sec then 72°C for 30 sec, repeated for 35 cycles. The PCR products were digested overnight with 10 U of MspI at 37°C.

The wild-type Arg allele for codon 194 is identified by the presence of a 313 bp band (indicative of the absence of the MspI cutting site). For codon 399, the presence of two bands of 375 and 240 bp, respectively, identifies the wild-type Arg allele and 240 bp, respectively, identifies the wild-type Arg allele, while the uncut 615 bp band identifies the mutant Gln allele (indicative of the absence of the MspI cutting site).

Statistical analysis

For each polymorphism, deviation of the genotype frequencies in the controls from those expected under Hardy-Weinberg equilibrium was assessed using the standard χ² square test. Genotype frequencies in cases and controls were compared by χ²-tests. The genotypic-specific risks were estimated as odds ratios (ORs) with associated 95% confidence intervals (CIs) by unconditional logistic regression; p values < 0.05 were considered to be significant.

### Table 1. — Characteristic of endometrial cancer (n=456) patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>64</td>
</tr>
<tr>
<td>Range</td>
<td>52-83</td>
</tr>
<tr>
<td>BMI (body mass index) (kg/m²)</td>
<td></td>
</tr>
<tr>
<td>&lt; 24.9</td>
<td>96 (21%)</td>
</tr>
<tr>
<td>25-29.9</td>
<td>147 (32%)</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>213 (47%)</td>
</tr>
<tr>
<td>Number of pregnancies</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>144 (32%)</td>
</tr>
<tr>
<td>2-3</td>
<td>312 (68%)</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>0</td>
</tr>
<tr>
<td>Use of hormone replacement therapy - HRT</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>288 (63%)</td>
</tr>
<tr>
<td>No</td>
<td>168 (37%)</td>
</tr>
<tr>
<td>Staging</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>249 (54%)</td>
</tr>
<tr>
<td>II</td>
<td>102 (22%)</td>
</tr>
<tr>
<td>III</td>
<td>105 (23%)</td>
</tr>
<tr>
<td>Grading</td>
<td></td>
</tr>
<tr>
<td>G1</td>
<td>249 (55%)</td>
</tr>
<tr>
<td>G2</td>
<td>180 (39%)</td>
</tr>
<tr>
<td>G3</td>
<td>27 (6%)</td>
</tr>
<tr>
<td>Menopause status</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>456</td>
</tr>
<tr>
<td>Yes</td>
<td>300 (65%)</td>
</tr>
<tr>
<td>No</td>
<td>156 (35%)</td>
</tr>
<tr>
<td>Endometrial transvaginal sonography - TVS</td>
<td></td>
</tr>
<tr>
<td>&gt; 5 mm</td>
<td>345 (75%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>84 (18%)</td>
</tr>
<tr>
<td>No</td>
<td>362 (82%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>240 (53%)</td>
</tr>
</tbody>
</table>

### Table 2. — Allele and genotype frequencies and odds ratio (OR) of Arg399Gln polymorphisms of the XRCC1 gene in patients with endometrial cancer (n = 456) and controls (n = 300).

<table>
<thead>
<tr>
<th>Allele</th>
<th>Number of cases</th>
<th>Controls</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg</td>
<td>39 (16%)</td>
<td>33 (29%)</td>
<td>0.48 [0.24-0.94] 0.051</td>
</tr>
<tr>
<td>Gln</td>
<td>257 (74%)</td>
<td>277 (71%)</td>
<td>1.34 [0.77-2.3] 0.292</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>171 (68%)</td>
<td>123 (44%)</td>
<td>2.42 [2.12-2.72] 0.013</td>
</tr>
</tbody>
</table>

Data in boldface are statistically significant.

### Table 3. — Dependency of genotypes and frequencies of the alleles of the XRCC1 gene Arg399Gln polymorphism on tumor grade in patients with endometrial cancer.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Grade I (%)</th>
<th>Grade II+III (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg/Arg</td>
<td>39 (16%)</td>
<td>33 (29%)</td>
<td>0.48 [0.24-0.94] 0.051</td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>257 (74%)</td>
<td>277 (71%)</td>
<td>1.34 [0.77-2.3] 0.292</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>171 (68%)</td>
<td>123 (44%)</td>
<td>2.42 [2.12-2.72] 0.013</td>
</tr>
</tbody>
</table>

p < 0.05. χ² square test.

Data in boldface are statistically significant.
Table 4. — Distribution of genotypes and frequencies of the alleles of XRCC1 gene Arg399Gln polymorphisms and endometrial cancer risk factors.

<table>
<thead>
<tr>
<th>BMI</th>
<th>&lt; 24.99 kg/m² (n = 96)</th>
<th>25-29.99 kg/m² (n = 147)</th>
<th>&gt; 30 kg/m² (n = 213)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number</td>
<td>frequency</td>
<td>number</td>
<td>frequency</td>
<td>number</td>
</tr>
<tr>
<td>Arg/Arg</td>
<td>24</td>
<td>0.25</td>
<td>45</td>
<td>0.31</td>
<td>36</td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>15</td>
<td>0.16</td>
<td>21</td>
<td>0.14</td>
<td>39</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>57</td>
<td>0.60</td>
<td>81</td>
<td>0.55</td>
<td>138</td>
</tr>
<tr>
<td>Arg</td>
<td>63</td>
<td>0.32</td>
<td>111</td>
<td>0.38</td>
<td>111</td>
</tr>
<tr>
<td>Gln</td>
<td>129</td>
<td>0.68</td>
<td>183</td>
<td>0.62</td>
<td>315</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>3.68*</td>
<td></td>
<td>2.15*</td>
<td>3.43*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormone replacement therapy - HRT</th>
<th>yes (n = 240)</th>
<th>no (n = 216)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg/Arg</td>
<td>84</td>
<td>0.29</td>
<td>36</td>
<td>0.21</td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>108</td>
<td>0.37</td>
<td>30</td>
<td>0.18</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>96</td>
<td>0.33</td>
<td>102</td>
<td>0.61</td>
</tr>
<tr>
<td>Arg</td>
<td>276</td>
<td>0.48</td>
<td>102</td>
<td>0.30</td>
</tr>
<tr>
<td>Gln</td>
<td>300</td>
<td>0.52</td>
<td>234</td>
<td>0.70</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>0.001*</td>
<td>2.74*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uterine bleeding</th>
<th>Metrorrhagia (+) (n = 156)</th>
<th>Metrorrhagia (-) (n = 300)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg/Arg</td>
<td>42</td>
<td>0.18</td>
<td>63</td>
<td>0.21</td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>63</td>
<td>0.05</td>
<td>63</td>
<td>0.21</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>51</td>
<td>0.77</td>
<td>174</td>
<td>0.58</td>
</tr>
<tr>
<td>Arg</td>
<td>147</td>
<td>0.47</td>
<td>189</td>
<td>0.32</td>
</tr>
<tr>
<td>Gln</td>
<td>165</td>
<td>0.53</td>
<td>411</td>
<td>0.68</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>0.051*</td>
<td>9.68*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TVS</th>
<th>&lt; 5 mm (n = 111)</th>
<th>&gt; 5 mm (n = 345)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg/Arg</td>
<td>30</td>
<td>0.27</td>
<td>66</td>
<td>0.19</td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>33</td>
<td>0.29</td>
<td>60</td>
<td>0.17</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>48</td>
<td>0.43</td>
<td>219</td>
<td>0.63</td>
</tr>
<tr>
<td>Arg</td>
<td>93</td>
<td>0.42</td>
<td>192</td>
<td>0.28</td>
</tr>
<tr>
<td>Gln</td>
<td>129</td>
<td>0.58</td>
<td>498</td>
<td>0.72</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>0.001*</td>
<td>0.169*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>yes (n = 240)</th>
<th>no (n = 216)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg/Arg</td>
<td>42</td>
<td>0.18</td>
<td>33</td>
<td>0.15</td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>30</td>
<td>0.13</td>
<td>45</td>
<td>0.21</td>
</tr>
<tr>
<td>Gln/Gln</td>
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<td>0.70</td>
<td>138</td>
<td>0.64</td>
</tr>
<tr>
<td>Arg</td>
<td>114</td>
<td>0.24</td>
<td>111</td>
<td>0.26</td>
</tr>
<tr>
<td>Gln</td>
<td>366</td>
<td>0.76</td>
<td>321</td>
<td>0.74</td>
</tr>
<tr>
<td>$\chi^2$</td>
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<td>1.350*</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Diabetes mellitus</th>
<th>yes (n = 84)</th>
<th>no (n = 372)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arg/Arg</td>
<td>15</td>
<td>0.18</td>
<td>57</td>
<td>0.15</td>
</tr>
<tr>
<td>Arg/Gln</td>
<td>18</td>
<td>0.18</td>
<td>72</td>
<td>0.19</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>51</td>
<td>0.60</td>
<td>243</td>
<td>0.65</td>
</tr>
<tr>
<td>Arg</td>
<td>48</td>
<td>0.29</td>
<td>186</td>
<td>0.25</td>
</tr>
<tr>
<td>Gln</td>
<td>120</td>
<td>0.71</td>
<td>558</td>
<td>0.75</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>2.082*</td>
<td>3.280*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$p > 0.05$ as compared with Hardy-Weinberg distribution.

Results

Table 2 shows genotype distribution of XRCC1 (Arg399Gln) polymorphism between endometrial cancer patients and controls. It can be seen from the table that there were significant differences ($p < 0.05$) between the two investigated groups. The women with endometrial cancer showed an incidence of 16, 20 and 64%, respectively, for the Arg/Arg, Arg/Gln, and Gln/Gln genotypes of the XRCC1 gene, whereas the control group showed 24, 48, and 28% for the same genotypes. In patients the observed frequencies of the Arg/Arg, Arg/Gln and Gln/Gln genotypes differed significantly ($p < 0.05$) from the distribution expected from the Hardy-Weinberg equilibrium. The Gln/Gln genotype frequency was statistically significant with an OR of 2.28 and 95% CI of (2.02-2.54) (Table 2).

Because we were interested in the association between the distribution of genotypes and frequencies of alleles of investigated polymorphisms on the tumor stage evaluated according to FIGO criteria, these data were also analyzed (Table 3). The histological grade was evaluated in all cases (n = 456); 249 cases were grade 1, 180 cases were grade 2 and 27 cases were grade 3. Grade 2 and 3 were
grouped together for the purposes of statistical analysis. The homozygous Gln/Gln genotype was also associated with type I endometrial cancer (OR = 2.42, 95% CI = 2.12-2.72).

No statistically significant differences were observed in the alleles or in the genotype frequencies of the XRCC1 gene polymorphisms between risk factors of endometrial cancer such as BMI, HRT, uterine bleeding, endometrial transvaginal sonography (TVS), diabetes and hypertension and the women with endometrial cancer (Table 4).

Discussion

In this study, we aimed to verify a possible association between DNA repair gene XRCC1 Arg399Gln polymorphisms with histological characteristics and risk factors such as BMI, HRT, uterine bleeding, endometrial TVS, diabetes and hypertension in women with endometrial cancer.

The XRCC1-Arg399Gln gene polymorphism has been studied as a risk factor for various cancers. It was suggested that SNPs in the XRCC1 gene may alter the ability of XRCC1 to repair damaged DNA, especially SNPs at codon 399.

XRCC1-Arg399Gln has been associated with increased risks for lung cancer [18, 19], head and neck cancer [20] and possibly stomach cancer [21]. In contrast, no increased risk was observed for bladder cancer [22], esophageal cancer [23] and non-melanoma skin cancer [24].

We showed previously that the XRCC1-Arg399Gln polymorphism was not an independent marker in breast cancer [25] Similar results came from other laboratories [26-28]. In the literature little is known about XRCC1 Arg399Gln polymorphisms in endometrial cancer risk.

Only De Ruyck et al. showed that SNPs in XRCC1 with a combination of different polymorphisms in DNA repair genes (XRCC3 and hOGG1) are associated with an enhanced clinical radiosensitivity in endometrial cancer patients treated with late radiotherapy (RT) [15, 16].

We found an association between endometrial cancer and Arg399Gln polymorphisms in this study population. Our results obtained for the Arg399Gln polymorphism of the XRCC1 gene indicated that the Gln/Gln genotype was associated with an increased risk for the development of endometrial cancer compared with the Arg/Gln and Gln/Gln genotype. The 399Gln allele also increased the risk of endometrial cancer (OR = 1.42, 95% CI = 1.16 to 1.68) compared with the Arg allele, but no statistical difference was found (p = 0.100).

We also analyzed the distribution of genotypes and frequency of alleles in groups of patients with endometrial cancer according to different cancer staging by FIGO classification (Table 3). The homozygous Gln/Gln genotype was associated with type I endometrial cancer (OR = 2.42, 95% CI = 2.12-2.72, p < 0.05).

The present data confirm our previous suggestion that Arg399Gln polymorphisms of the XRCC1 gene have a phenotypic effect, manifested in changes in the extent of DNA damage [25].

These results suggest that homozygous Gln/Gln genotype of XRCC1 may be a risk factor for postmenopausal and type I endometrial cancer in a Polish population. Further studies, conducted on a larger group, are required to clarify this point.

Taken together our findings contribute to a better current understanding of the pathogenesis of endometrial carcinoma and the function of the SNP DNA repair gene polymorphism in this type of neoplasm.

These findings could be helpful for clinicians in the assessment and counselling of patients affected by these cancers or for scientists to consider new potential therapeutic agents for the treatment of these tumors.

References

Association between Arg399Gln polymorphism of X-ray repair cross-complementing 1 (XRCC1) gene and sporadic endometrial etc.


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PTEN, tau-AP-3, thymidylate synthase immunohistochemistry scoring expression in patients with uterine leiomyomas, uterine smooth muscle tumors of uncertain malignancy potential and uterine leiomyosarcomas

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1Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung, 2China Medical University, Taichung, 3Institute of Medicine, Chung Shan Medical University, Taichung, 4Department of Obstetrics and Gynecology, Clinic of Fu Jen Catholic University, Taipei, 5Department of Pathology, China Medical University Hospital, Taichung, 6College of Medicine, China Medical University, Taichung (Taiwan)

Summary

Uterine smooth muscle tumors are frequently classified as benign and malignant. However, an assortment of mitotic counts and nuclear atypia can be indecisive between uncertain malignant potential, and malignant uterine smooth muscle tumors. We applied three immunohistochemical parameters to distinguish between cases of benign, malignant, and those with uncertain malignant histology.

Key words: Allred immunohistochemistry scoring; Immunohistochemistry; Uterine smooth muscle tumors.

Introduction

Neoplasms of uterine smooth muscle can be classified into benign, malignant, and tumors of uncertain malignant potential (STUMP). The diagnosis of benign, uncertain malignant potential, and malignant uterine smooth muscle tumors depends on mitotic counts, nuclear atypia, and other morphologic features [1]. However, differentiating between STUMP and uterine leiomyosarcoma as well as assessing malignant potential can be problematic, especially when difficulty in recognizing mitotic figures occurs or when clumped and degenerative nuclei are misinterpreted as mitotic figures [2]. In this study, we used three immunohistochemical parameters to distinguish between cases of benign, malignant and those with uncertain malignant histology.

Immunohistochemistry (IHC) is a technique used to identify specific types of cells within a given sample and has been used since the 1940s [3]. Immunohistochemical staining is widely used in the diagnosis of abnormal cells such as in cancerous tumors.

The principle behind IHC is the detection of a particular protein or antigen on or within a cell with the use of a commercially available antibody. This antibody antigen complex is then magnified and tagged with a stain that is visible under a light microscope. The ability to use antibodies on formalin-fixed, paraffin-embedded tissue has improved the applicability of IHC [4]. IHC has found numerous applications in medicine, especially in cancer diagnosis. The aims of this study were to systematically evaluate immunohistochemical staining patterns of the expression of phosphatase and tensin homolog deleted on chromosome 10 (PTEN), tau-AP-3, thymidylate synthase (TS) in benign and malignant uterine smooth muscle neoplasms; to study whether the expression patterns of PTEN, tau-AP-3, and TS correlate with uterine smooth muscle neoplasms; and, to evaluate whether the expression patterns of PTEN, tau-AP-3, and TS are helpful in differentiating benign tumors from malignant uterine tumors and tumors with uncertain malignant potential.

Materials and Method

Formalin-fixed and paraffin-embedded surgical specimens of uterine leiomyoma (n = 10), leiomyosarcoma (n = 5), and tumors of uncertain malignant potential (n = 3) were subjected to the following procedures.

After cutting the wax-embedded tissues into 2 mm pieces, the wax was melted at 56°C in distilled water and the tissue samples were removed. The tissue sample was heated at 65~75°C for 20 min, triple soaked in xylene solution for 10 min, followed by rinsing in 100% alcohol, 95% alcohol, 75% alcohol, 60% alcohol, 30% alcohol distilled water and PBS buffer individually for 10 min. The tissue sample was boiled in citrate buffer (pH 6, > 95°C) for 20 min, cooled at room temperature and rinsed in PBS buffer for 5 min. A section was circled on the tissue sample and covered with H2O2 for 10 min. After washing twice in TBST buffer for 5 min, 10% horse serum was used to block the background of tissue sample. The primary antibodies PTEN-TS (Novocastra, Vision Biosystem, Norwell, MA) and Tau AP-3 (Neomarker, CA, USA) were applied, followed by TBST buffer washing for another 5 min, and HRP polymer conjugate (Zymed Laboratories, San Francisco, CA) was applied as a secondary antibody. Finally, DAB Chromogen (Zymed Laboratories) was added to stain the protein component of the circled sections. Immunostaining of protein expression and protein display were visualized under a light microscope after the tissue sample had been washed in hematoxylin and flowing water.
Results

In this study, two pathologists used the Allred immunohistochemistry scoring system to analyze (a) the proportion score (PS), (b) the intensity score (IS), and (c) the total score (TS) in leiomyoma specimens, leiomyosarcoma specimens, and STUMP specimens. The proportion score represents the estimated proportion of positively stained tumor cells (0 = none; 1 < 1/100; 2 = 1/100 to < 1/10; 3 = 1/10 to < 1/3; 4 = 1/3–2/3; 5 ≥ 2/3). The intensity score represents the average estimated intensity of positively stained cells (0 = none; 1 = weak; 2 = intermediate; 3 = strong). The total score was obtained by adding the PS and IS (range 0-8). One-way ANOVA and the paired t-test were used to evaluate significant differences.

All three IHC scores showed statistical significance among the three groups of tumor specimens (paired t-test).

Myoma vs leiomyosarcoma

In our analysis, all three of the immunostaining scores differed significantly between the myoma group and the leiomyosarcoma group. All three scores showed that the level of PTEN expression (Figure 1) was higher in the myoma group than in the leiomyosarcoma group and that the levels of TAU (Figure 2) and TS expression were lower in the myoma group than in the leiomyosarcoma group (Table 2).

Leiomyosarcoma vs STUMP

The PS and the IS for TS expression were both higher in the leiomyosarcoma group (Figure 3) than in the STUMP group (Table 2).

Myoma vs STUMP

All three immunostaining scores for TS were significantly higher in the STUMP group than in the myoma group, indicating that the expression of TS was markedly

Table 1. — One-Way ANOVA to measure differences in PS/IS/TS among the three biomarkers.

<table>
<thead>
<tr>
<th>Treatment Measure</th>
<th>PS</th>
<th>PTEN</th>
<th>IS</th>
<th>TS</th>
<th>TAU</th>
<th>IS</th>
<th>THYM</th>
<th>IS</th>
<th>TS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.43</td>
<td>3.74</td>
<td>7.06</td>
<td>6.12</td>
<td>16.01</td>
<td>10.40</td>
<td></td>
<td>43.64</td>
<td>18.55</td>
</tr>
<tr>
<td>F*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.017</td>
<td>0.048</td>
<td>0.007</td>
<td>0.011</td>
<td>0.000</td>
<td>0.001</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Note: Numbers of observation in myoma, leiomyosarcoma, and STUMP are 10, 5, and 3, respectively.
all three scores (proportion, intensity and total score) for group (malignant) than in the STUMP group. In addition, analogues [7]. In this study, the proportion score and the as fluorinated pyrimidine fluorouracil, or certain folate can be inhibited by thymidylate synthase inhibitors such as an anti-cancer chemotherapy target, thymidylate synthetase, for differentiating between leiomyosarcoma and STUMP.

Thymidylate synthetase is an enzyme that generates thymidine monophosphate (dTMP), which is subsequently phosphorylated to thymidine triphosphate for use in DNA synthesis and repair. Expression levels are often higher in malignant tumors than in normal cells. As an anti-cancer chemotherapy target, thymidylate synthetase inhibitors such as fluorinated pyrimidine fluorouracil, or certain folate analogues [7]. In this study, the proportion score and the intensity score for TS were higher in the leiomyosarcoma group (malignant) than in the STUMP group. In addition, all three scores (proportion, intensity and total score) for TS revealed that the expression of thymidylate synthetase was significantly higher in the STUMP group than the myoma group (benign).

Tau protein is a highly soluble microtubule-associated protein. In humans, these proteins are mostly found in neuronal cells. One of the main functions of tau is to modulate the stability of axonal microtubules [8]. The usage of this protein as a cancer biomarker in malignant tumors of non central nervous system origin has not been reported; however, we found that the expression of tau was highest in the leiomyosarcoma group.

Uterine leiomyoma is the most common benign tumor in women of reproductive age, but uncommon variants of leiomyoma, such as symplastic (atypical, bizarre, or pleomorphic) leiomyoma, mitotically active leiomyoma and cellular or highly cellular leiomyoma, may result in a diagnosis of leiomyosarcoma because of the presence of nuclear atypia, high mitotic index and high cellularity [9]. On the other hand, uterine sarcoma is rare, accounting for approximately 1% of female genital tract malignancies and 3-7% of uterine cancers [10]. The clinical diagnosis of leiomyosarcoma is based on the presence of abnormal vaginal bleeding, rapid growth of a palpable pelvic mass and pelvic pain. Histopathologic diagnosis of uterine leiomyosarcoma is usually straightforward because most clinically malignant smooth muscle tumors of the uterus show the microscopic constellation of hypercellularity, severe nuclear atypia, and mitotic rate that generally exceeds 15 mitotic figures per 10 high-power-fields (MF/10HPF) [10].

Another uterine tumor that frequently cannot be classified as benign or malignant is the uterine smooth muscle tumor of uncertain malignant potential. STUMP tumors represent a poorly defined subcategory of uterine smooth muscle tumors. One way to define STUMP is by exclusion, i.e., tumors that do not fit the definition for any of the other categories of uterine smooth muscle tumors are classified as STUMP [11]. Applying conventional morphological criteria to distinguish leiomyoma from STUMP and uterine leiomyosarcoma is problematic. Thus, additional parameters to distinguish between these tumors are needed.

**Discussion**

Uterine smooth muscle tumors are the most frequent neoplasms in the female genital tract [2]. The majority of the uterine smooth muscle tumors are readily classifiable as benign or malignant based on the gross and microscopic appearance [5]. However, there is substantial overlap in morphological features among leiomyomas, smooth muscle tumors of uncertain malignant potential (STUMP), and leiomyosarcomas, making it difficult to establish a definitive diagnosis. In this study, we used immunohistochemical staining to evaluate the potential of three cancer biomarkers, namely PTEN, tau AP-3 and thymidylate synthase, for differentiating between leiomyoma, STUMP and leiomyosarcomas.

The tumor suppressor gene PTEN (also known as MMAC or TEP1) is located on human chromosome 10q23. Mutation of PTEN is common in advanced stages of many human cancers and is one of the most commonly lost tumor suppressors in human cancer. In tumor development, mutations and deletions of PTEN inactivate its enzymatic activity leading to increased cell proliferation and reduced cell death [6]. In our study, PTEN showed higher immunostaining scores in leiomyoma than in leiomyosarcoma and STUMP.

Thymidylate synthetase is an enzyme that generates thymidine monophosphate (dTMP), which is subsequently phosphorylated to thymidine triphosphate for use in DNA synthesis and repair. Expression levels are often higher in malignant tumors than in normal cells. As an anti-cancer chemotherapy target, thymidylate synthetase can be inhibited by thymidylate synthase inhibitors such as fluorinated pyrimidine fluorouracil, or certain folate analogues [7]. In this study, the proportion score and the intensity score for TS were higher in the leiomyosarcoma group (malignant) than in the STUMP group. In addition, all three scores (proportion, intensity and total score) for

**Table 2. — Mean difference among groups.**

<table>
<thead>
<tr>
<th>Treatment Measure</th>
<th>PS</th>
<th>PTEN</th>
<th>IS</th>
<th>TS</th>
<th>TAU</th>
<th>IS</th>
<th>TS</th>
<th>THYM</th>
<th>IS</th>
<th>TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS (1)</td>
<td>1.10</td>
<td>0.95</td>
<td>1.20</td>
<td>0.92</td>
<td>3.00</td>
<td>0.60</td>
<td>2.00</td>
<td>0.70</td>
<td>1.10</td>
<td>0.95</td>
</tr>
<tr>
<td>IS (1)</td>
<td>1.30</td>
<td>0.68</td>
<td>2.00</td>
<td>0.45</td>
<td>3.67</td>
<td>0.57</td>
<td>1.00</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TS (1)</td>
<td>2.40</td>
<td>1.17</td>
<td>5.40</td>
<td>0.90</td>
<td>6.00</td>
<td>0.71</td>
<td>0.00</td>
<td>0.00</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Group: (1) Myoma, (2) Leiomyosarcoma, and (3) STUMP.

* significant at α = 0.05 level; ** significant at α = 0.01 level.

TS revealed that the expression of thymidylate synthetase was significantly higher in the STUMP group than the myoma group (benign).

Tau protein is a highly soluble microtubule-associated protein. In humans, these proteins are mostly found in neuronal cells. One of the main functions of tau is to modulate the stability of axonal microtubules [8]. The usage of this protein as a cancer biomarker in malignant tumors of non central nervous system origin has not been reported; however, we found that the expression of tau was highest in the leiomyosarcoma group.

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Another uterine tumor that frequently cannot be classified as benign or malignant is the uterine smooth muscle tumor of uncertain malignant potential. STUMP tumors represent a poorly defined subcategory of uterine smooth muscle tumors. One way to define STUMP is by exclusion, i.e., tumors that do not fit the definition for any of the other categories of uterine smooth muscle tumors are classified as STUMP [11]. Applying conventional morphological criteria to distinguish leiomyoma from STUMP and uterine leiomyosarcoma is problematic. Thus, additional parameters to distinguish between these tumors are needed.

**Conclusion**

Immunohistochemical staining for PTEN, tau-AP-3 and TS expression is helpful in differentiating benign tumors from malignant tumors and tumors with uncertain malignant potential.

**References**


PTEN, tau-AP-3, thymidylate synthase immunohistochemistry scoring expression in patients with uterine leiomyomas, uterine etc.

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Analysis of prognosis-related factors in patients with invasive cervical adenocarcinoma

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²Department of Gynecological Oncology, Jiamusi Municipal Cancer Hospital, Heilongjiang Province, Jiamusi (China)

Summary

Objective: To explore the prognostic related factors in patients with cervical adenocarcinoma. Methods: Clinical and pathological data were retrospectively analyzed in 144 patients with cervical adenocarcinoma between 1995 and 2004. Results Five-year survival rates were 80.1%, 59.7%, 63.3% and 0.0%, respectively, in patients with Stage I, II, III and IV cervical adenocarcinoma, and the overall 5-year survival rate was 59.0%. Univariate analysis indicated poor prognosis in non-exophytic tumor, tumor diameter > 4 cm, advanced clinical stage, mucinous adenocarcinoma and clear cell carcinoma, or poorly differentiated tumor. The prognosis was related to lymph node metastasis and deep myometrial invasion. Multivariate analysis indicated that besides clinical stage, myometrial invasion and lymph node metastasis, tumor shape was also an independent prognostic related factor. Conclusion: The prognosis is associated with tumor shape besides pre-confirmed clinical stage, myometrial invasion and lymph node metastasis. Ovarian preservation in young women remains to be further explored.

Key words: Cervical adenocarcinoma; Clinical stage; Lymph node metastasis; Myometrial invasion; Tumor shape.

Introduction

The incidence of cervical carcinoma is the highest in malignant tumors occurring in the female genital tract. Squamous cell carcinoma is the most common, accounting for 70%-75%. Cervical adenocarcinoma is rare, but its incidence is growing. Cervical adenocarcinoma accounts for 10%-34% of cervical carcinoma [1]. The choice of therapeutic strategy is important for treatment. In this study, clinical and pathological data of 144 patients with cervical adenocarcinoma were retrospectively analyzed to find prognosis-related factors, improving diagnosis and treatment of cervical adenocarcinoma.

Materials and Methods

All study methods were approved by the ethics committee of the Cancer Hospital affiliated with Tianjin Medical University. All subjects enrolled in this study gave written formal consent to participate.

General data

In our hospital, 144 patients who were first diagnosed with cervical adenocarcinoma were treated between January 1995 and December 2004. Clinical data were reviewed by gynecologists and pathological data were reviewed by pathologists.

Clinical and pathological data

The mean age of the 144 patients was 51.3 years (range 25-76). Nineteen patients (13.2%) were under 40 years old. Mean gravidity was 3.5 times (range 0-10) and mean delivery 2.7 times (range 0-8). Five patients (3.5%) were infertile. Clinical symptoms included irregular vaginal bleeding in 81 patients (56.2%), abnormality of vaginal secretions in 38 patients (26.4%), gas pain in the waist and abdomen in 14 patients (9.7%), urinary frequency in six patients (4.2%), lower extremity edema in two patients (1.4%), and no symptoms in three patients (2.1%). Tumor shapes included exophytic type (cauliflower-like, exophytic nodular, polyp-like and erosion-like cervical adenocarcinoma) in 70 patients (48.6%), endocervical type (bulky cervical adenocarcinoma) in 44 patients (30.6%), and ulcerative type in 30 patients (20.8%). Tumor diameters were assessed by clinical examination. If it was difficult to assess tumor diameters by clinical examination, thus B-ultrasonic imaging, CT or MRI was used. Different measurement methods were likely to obtain different diameters for the same tumor, and the greater diameter was selected in this study. Tumor diameter was 4 cm or less in 100 patients (69.4%), and more than 4 cm in 44 patients (30.6%). Based on the clinical stages made by FIGO in 2009, 47 patients (32.6%) were in Stage I, 77 patients (53.5%) in Stage II, 16 patients (11.1%) in Stage III and four patients (2.8%) in Stage IV. According to pathological type made by WHO in 2003, 108 patients (75.0%) had simple adenocarcinoma, 18 patients (12.5%) mucoid adenocarcinoma, eight patients (5.6%) endometrioid adenocarcinoma, seven patients (4.9%) clear cell carcinoma, two patients (1.4%) mesonephric tubular adenocarcinoma and one patient (0.7%) serous adenocarcinoma. Tumor cell differentiation was good in 38 patients (26.4%), moderate in 66 patients (45.8%), and poor in 40 patients (27.8%).

Therapeutic methods

Surgical treatment was performed in 105 patients who were mostly in Stage Ia-Ib. The patients with local advanced cervical adenocarcinoma (tumor size > 4 cm, invasion into the vagina or parametrial tissue) underwent surgery two weeks after neoadjuvant chemotherapy or local half-dose radiotherapy and (or) intracavitary afterloading radiotherapy. Radical hysterectomy, pelvic lymphadenectomy and unilateral or bilateral salpingo-oophorectomy were performed in 68 patients. Pelvic lymphadenectomy failed to be done in 37 patients due to senility,
severe complications and pelvic adhesions. For the patients who had high risk-factors including advanced-stage, tumor diameter > 4 cm, positive vaginal stump, lymph node metastasis, poor differentiation, deep myometrial invasion and cancer embolus, postoperative adjuvant radiotherapy and/or chemotherapy were given. Radiotherapy included extracorporeal irradiation of the vaginal stump or pelvic field. Chemotherapy mainly included cefotaxime, ifosfamide, cisplatin, carboplatin, adriamycin, 5-fluorouracil and taxol. For the inoperable and advanced patients, full-dose radiotherapy was given. In detail, extracorporeal irradiation of the large pelvic field was first performed, and then concomitant intracavitary radiotherapy and irradiation of four fields of the pelvic cavity were done.

**Follow-up**

All patients were followed up for more than five years (range 4-182 months). Median survival time and 5-year survival rate were used to evaluate the prognosis.

**Statistical analysis**

Statistical analysis was performed with SPSS 16.0 software. Survival rates were calculated with the Kaplan-Meier method. The log-rank test was used in comparison of survival rates. Cox proportional hazards model was used in multivariate analysis of prognosis. Statistical significance was established at $p < 0.05$.

**Results**

**Prognosis**

The overall 5-year survival rate was 59.0% and median survival time 52 months. In 36 patients (25.0%) recurrence or metastasis occurred. Local recurrence and pelvic metastasis was the most common (28 patients). Other metastasis sites included the liver (3 patients), lungs (2 patients), bone (one patient), inguinal lymph nodes (one patient) and supraclavicular lymph nodes (one patient).

**Univariate analysis of prognosis**

The relationships of prognosis with clinical and pathological factors are shown in Table 1. The prognosis was poor in the patients with non-exophytic tumors, tumor diameter > 4 cm, advanced clinical stage, mucinous adenocarcinoma or clear cell carcinoma, or poorly differentiated tumors ($p < 0.05$).

<table>
<thead>
<tr>
<th>Items</th>
<th>n (survival case)</th>
<th>5-years survival rate (%)</th>
<th>Median survival time (months)</th>
<th>$\chi^2$ value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 40 year</td>
<td>19 (8)</td>
<td>42.1</td>
<td>62</td>
<td>2.592</td>
<td>0.135</td>
</tr>
<tr>
<td>&gt; 40 Year</td>
<td>125 (77)</td>
<td>61.7</td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2 Times</td>
<td>92 (50)</td>
<td>54.3</td>
<td>72</td>
<td>2.307</td>
<td>0.259</td>
</tr>
<tr>
<td>&gt; 2 Times</td>
<td>52 (35)</td>
<td>67.3</td>
<td>68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor shape</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exophytic</td>
<td>70 (52)</td>
<td>74.3</td>
<td>119</td>
<td>20.558</td>
<td>0.000</td>
</tr>
<tr>
<td>Endocervical</td>
<td>44 (24)</td>
<td>54.5</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerative</td>
<td>30 (9)</td>
<td>30.0</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor diameter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 4 cm</td>
<td>100 (66)</td>
<td>66.0</td>
<td>84</td>
<td>6.578</td>
<td>0.016</td>
</tr>
<tr>
<td>&gt; 4 cm</td>
<td>44 (19)</td>
<td>43.2</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>47 (38)</td>
<td>80.1</td>
<td>133</td>
<td>145.895</td>
<td>0.000</td>
</tr>
<tr>
<td>II</td>
<td>77 (46)</td>
<td>59.7</td>
<td>65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>16 (1)</td>
<td>6.3</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>4 (0)</td>
<td>0/4*</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple AC</td>
<td>108 (71)</td>
<td>65.7</td>
<td>78</td>
<td>10.642</td>
<td>p &lt; 0.05**</td>
</tr>
<tr>
<td>Mucoid AC</td>
<td>18 (6)</td>
<td>33.3</td>
<td>34</td>
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<tr>
<td>Endometrioid AC</td>
<td>8 (4)</td>
<td>4/8*</td>
<td>34</td>
<td></td>
<td></td>
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<tr>
<td>Clear cell carcinoma</td>
<td>7 (2)</td>
<td>2/7*</td>
<td>28</td>
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</tr>
<tr>
<td>Mesonephric rubular AC</td>
<td>2 (1)</td>
<td>1/2*</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous AC</td>
<td>1 (1)</td>
<td>1/1*</td>
<td>64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Differentiation</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well</td>
<td>38 (28)</td>
<td>73.7</td>
<td>148</td>
<td>22.922</td>
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<tr>
<td>Moderately</td>
<td>66 (46)</td>
<td>69.7</td>
<td>80</td>
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<tr>
<td>Poorly</td>
<td>40 (11)</td>
<td>27.5</td>
<td>20</td>
<td></td>
<td></td>
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<tr>
<td>Myometrial invasion</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1/2</td>
<td>41 (33)</td>
<td>80.5</td>
<td>138</td>
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<tr>
<td>≥ 1/2</td>
<td>64 (30)</td>
<td>46.9</td>
<td>35</td>
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<td>Lymph node</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Metastasis</td>
<td>19 (5)</td>
<td>26.3</td>
<td>133</td>
<td>15.978</td>
<td>0.000</td>
</tr>
<tr>
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<td>49 (35)</td>
<td>71.4</td>
<td>26</td>
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<tr>
<td>Operation methods</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Radical</td>
<td>68 (40)</td>
<td>58.8</td>
<td>89</td>
<td>0.111</td>
<td>0.836</td>
</tr>
<tr>
<td>Hysterecctomy</td>
<td>37 (23)</td>
<td>62.2</td>
<td>71</td>
<td></td>
<td></td>
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<tr>
<td>Salpingo-oophorectomy</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>12 (9)</td>
<td>75.0</td>
<td>65</td>
<td>0.251</td>
<td>0.759</td>
</tr>
<tr>
<td>Bilateral</td>
<td>93 (54)</td>
<td>59.1</td>
<td>80</td>
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* indicates that the number of patients is less than 10 and percentage is not calculated. ** indicates that the number of cells is less than 5, and there is no accurate p value. AC indicates adenocarcinoma.
lymph nodes (47.4%) and deep inguinal lymph nodes (10.5%). The 5-year survival rate was lower in lymph node metastasis than in no lymph node metastasis ($p < 0.01$). Compared with the patients who underwent pelvic lymphadenectomy, the 37 patients who failed to undergo lymphadenectomy had no significant difference in 5-year survival rate. There also was no significant difference in 5-year survival rate between unilateral and bilateral salpingo-oophorectomy.

Comparison of prognosis between different therapeutic methods in Stage II cervical adenocarcinoma

Seventy seven patients were in Stage II. The patients with Stage IIA cervical adenocarcinoma were divided into operation group, radiotherapy group and operation + radiotherapy group. The patients with Stage IIB cervical adenocarcinoma were divided into a radiotherapy group and operation + radiotherapy group. Five-year survival rates were compared (Table 2).

Multivariate analysis of prognosis

Multivariate analysis indicated that besides clinical stage, myometrial invasion and lymph node metastasis, tumor shape was also associated with prognosis ($p < 0.05$), and was an independent prognosis-related factor (Figure 1-4).
Discussion

Diagnosis of cervical adenocarcinoma

The incidence of cervical adenocarcinoma has been increasing in recent years [1]. Cervical adenocarcinoma accounted for 3.7% of cervical cancer between 1980 and 1994, but it reached 15.9% between 1995 and 2009 in our hospital.

Early diagnosis of cervical adenocarcinoma is important for improving the prognosis of patients with cervical adenocarcinoma. Although the detection rate of cervical adenocarcinoma has increased, the rates of misdiagnoses and missed diagnoses are higher because of endocervical growth of most cervical adenocarcinoma. It has been suggested that if TCT indicates atypical glandular cells (AGC), colposcopic multiple punch biopsy and endocervical canal curettage, even cold knife conization should be performed to avoid misdiagnoses and missed diagnoses [2].

Cervical adenocarcinoma has not got definite tumor markers. It has been found that CA125 is related to the diagnosis and prognosis of cervical adenocarcinoma [3] and some molecular markers such as p53, survivin and PTEN are associated with cervical adenocarcinoma [4].

Prognosis-related factors of cervical adenocarcinoma

It has been reported that 5-year survival rates were 60%-90%, 37%-90%, 8%-38% and 0%-14%, respectively, in patients with Stage I, II, III and IV cervical adenocarcinoma, and the overall 5-year survival rate was 25%-68% [2, 3, 5-10]. In this study, 5-year survival rates were 80.1%, 59.7%, 6.3% and 0.0%, respectively, in patients with Stage I, II, III and IV cervical adenocarcinoma, and the overall 5-year survival rate was 59.0%. The 5-year survival rate in Stage III was lower in this study, which may be because: 1) of the 16 patients with Stage III cervical adenocarcinoma, 12 were diagnosed before 2000 – at that time chemotherapy failed to be widely used in clinical practice; 2) adenosquamous carcinoma was classed as cervical adenocarcinoma in many studies; 3) the period of follow-up was shorter in previous studies, leading to higher survival rate.

It has been described that prognosis-related factors of cervical adenocarcinoma include clinical stage, tumor size, tumor cell differentiation, myometrial invasion and lymph node metastasis [2, 3, 5]. In this study, besides clinical stage, myometrial invasion and lymph node metastasis, tumor shape also was an independent prognosis-related factor of cervical adenocarcinoma. In this study, tumor shapes included exophytic type (cauliflower-like), exophytic nodular, polyplike and erosion-like cervical adenocarcinoma), endocervical type (barrel-shaped cervical adenocarcinoma) and ulcerative type (local necrosis). Multivariate analysis indicated that endocervical and ulcerative tumors have poorer prognosis and are independent prognosis-related factors. This may be that compared with exophytic tumors, endocervical and ulcerative tumors are easy to invade into surrounding tissue and lead to metastasis. Tumor diameter, pathological type and tumor cell differentiation were associated with prognosis in univariate analysis, but were not related to prognosis in multivariate analysis. Age, delivery frequency, operation methods and bilateral salpingo-oophorectomy were not related to prognosis.

This study did not include adenosquamous carcinoma. Univariate analysis indicated poorer prognosis of mucinous adenocarcinoma and clear cell carcinoma. The prognosis was poorer in tumors with a diameter > 4 cm than in tumors ≤ 4 cm, and in poorly differentiated tumors than in well and moderately differentiated tumors. However, multivariate analysis indicated no statistical significance in the above factors.

Treatment of cervical adenocarcinoma

The patients with early (IA, IIA) cervical adenocarcinoma were mainly submitted to radical hysterectomy and pelvic lymphadenectomy, and the patients with high-risk factors also received postoperative adjuvant therapy. A study from Union Medical University indicates that in early cervical adenocarcinoma, survival rate was higher in single surgical treatment than in radiotherapy alone, and combined therapy had no advantage; but for the patients with high-risk factors or advanced clinical stage, combined therapy is given [3]. Another study suggests that in the patients with Stage IA2-IIA cervical adenocarcinoma who have high-risk factors such as lymph node metastasis, positive vaginal stump and paracervical involvement, adjuvant chemoradiation can improve prognosis; but in the patients with Stage IA2-IIA cervical adenocarcinoma who have no high-risk factors, postoperative adjuvant therapy has no advantage [6]. One study indicates that in the patients with bulky cervical adenocarcinoma, the therapeutic effect of postoperative chemoradiation is better than radiotherapy alone [7]. In this study, the 39 patients with Stage IIA cervical adenocarcinoma were divided into a single surgical treatment group, radiotherapy alone group and combined therapy group, and the prognosis of the combined therapy group was poorer, but there was no statistical significance. It may be that in the combined therapy group, all patients have high-risk factors including advanced clinical stage, tumor diameter > 4 cm, local residual tumor, lymph node metastasis, poor differentiation, deep myometrial invasion and cancer embolus, so combined therapy is likely to counteract the adverse effect of high-risk factors on prognosis.

The patients with Stage IIB cervical adenocarcinoma or over are generally given radical radiotherapy and adjuvant chemotherapy. Since cervical adenocarcinoma has lower sensibility to radiotherapy, there has still been debate about whether hysterectomy is performed after radiotherapy and chemotherapy. In this study, all the 38 patients with Stage IIB cervical adenocarcinoma first received radiotherapy. Of the 38 patients, 20 only received radiotherapy alone, seven received hysterectomy due to uncontrolled or recurrent tumor after radiotherapy, and 11 received hysterectomy (in 7 patients) or radical...
hysterectomy (in 4 patients) two weeks later because the 11 patients insisted on surgical treatment and the cervical tumor after half-dose radiotherapy might be excised. In Sun Yat-sen University, the patients with Stage II cervical adenocarcinoma were treated with different therapeutic methods, the therapeutic effect of single surgical treatment was the best, the therapeutic effects of radiotherapy alone and radiotherapy + chemotherapy were the worst ($p = 0.0014$), and there was no statistical significance in survival rate between surgical treatment group and surgical treatment + radiotherapy group [8]. In this study, the patients with Stage IIB cervical adenocarcinoma were divided into a radiotherapy alone group and surgical treatment + radiotherapy group, 5-year survival rate was slightly higher in the surgical treatment + radiotherapy group than in a radiotherapy alone group, but there was no statistical significance. The main therapeutic method is radiotherapy for Stage IIB cervical adenocarcinoma, but the rates of uncontrolled lesion and recurrence after radiotherapy are higher because adenocarcinoma has lower sensitivity to radiotherapy, so adjuvant hysterectomy may have a certain value, which requires more clinical studies be confirmed.

Radiotherapy is the first choice for the treatment of over Stage III cervical adenocarcinoma. However, chemotherapeutic drugs can decrease tumor size, relieve symptoms and reduce recurrence and metastasis. At present, concomitant radiotherapy and chemoradiotherapy is the first choice for the treatment of advanced cervical adenocarcinoma.

In this study, 105 patients received surgical treatment. Of the 105 patients, 68 underwent radical hysterectomy and 37 failed to undergo pelvic lymphadenectomy. However, there was no significant difference in 5-year survival rate between the two groups. Bilateral salpingo-oophorectomy was performed in 93 patients, and the ovaries were preserved in 12 patients, but there was no significant difference in 5-year survival rate between the two groups. Kasamatsu et al. [9] has reported that compared with squamous cell carcinoma, the rate of ovary metastasis has no significant difference in Stage IB and IIA cervical adenocarcinoma, but the rate of ovary metastasis is significantly higher in Stage IIB adenocarcinoma (23.8%) than in squamous cell carcinoma (2.6%) ($p < 0.05$). In this study, ovary metastasis occurred in four patients with Stage II cervical adenocarcinoma (2.78%). Of the 12 patients whose ovaries were preserved in this study, ovary metastasis occurred in a patient with Stage IIA cervical adenocarcinoma. At present, there has been debate about whether ovaries should be preserved in early cervical adenocarcinoma. Most scholars believe that there is not enough evidence to confirm the high rate of ovary metastasis in early cervical adenocarcinoma, so ovaries should be preserved in young women with early cervical adenocarcinoma. In this study, only 12 patients had ovarian preservation, which failed to strongly support ovarian preservation in young women with early cervical adenocarcinoma. We believe that ovarian preservation in young women with early cervical adenocarcinoma remains to be further explored.

Acknowledgement

This study was supported by the Science Foundation of Tianjin Medical University (2008KY26).

References


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Surgical management of invasive carcinoma of the vulva.  
A retrospective analysis and review

S. Konidaris, P. Bakas, O. Gregoriou, Th. Kalampokas, A. Kondi-Pafiti
2nd Department of Obstetrics and Gynecology, University of Athens, Aretaieion Hospital, Athens (Greece)

Summary

Purpose: A retrospective study aiming to assess the survival rate, recurrence rate and complications of patients with invasive squamous cell carcinoma of the vulva. Methods: 91 patients with invasive carcinoma of the vulva were included in the study. The following clinical factors were assessed: clinical stage, diameter of lesion, and degree of tumor differentiation. The Kaplan-Meier estimate for statistical analysis of survival was used. Results: Surgery was primary treatment for 76 patients. The 5-year survival for FIGO Stage I was 93.3%, Stage II 85%, Stage III 51% and for Stage IV it was zero as estimated by the Kaplan-Meier test. Of the 52 women who underwent inguinal lymphadenectomy, 11 or 21.1% had positive nodes and four patients underwent pelvic node resection. Patients with tumor size ≤ 2 cm had 16.7% positive inguinal nodes, while patients with tumor size > 2.1 cm had 29.4% of positive nodes. Conclusions: The right choice of surgical treatment after appropriate staging of the disease offers very good survival rates, while a more accurate assessment of the status of inguinal lymph nodes could reduce the extent of surgical treatment.

Key words: Vulvar cancer; Prognosis; Surgery; Recurrences.

Introduction

Cancer of the vulva is uncommon with an incidence of 3%-5% of all female genital malignancies but in recent years it has increased to 8% because of the continuing rise in the average age of the female population causing an increase in the number eligible to develop the disease [1]. The majority of all vulvar carcinomas are squamous in origin and often develop from vulvar dystrophies. The association of condyloma acuminatum and vulvar carcinoma is well known but no cause and effect relationship has been documented [2].

The disease can appear anywhere on the vulva but primarily on the labia, and uses the lymphatic mode for initial metastases. Invasive or in-situ squamous cell carcinoma of the cervix or vagina is seen before, during, or after treatment for carcinoma of the vulva in 5-25% of patients, and this suggests that the squamous epithelium of the whole lower genital tract is at risk and sensitive to whatever factors combine to produce squamous neoplasia [3, 4].

Vulvar cancer should be among the most curable of cancers if it could be detected early. Radical vulvectomy and bilateral inguinal node resection remain the primary treatment of the disease. However, the current earlier detection of more localized carcinomatous lesions and the approximate 90% 5-year survival rates in the absence of regional nodal involvement have led more gynecologists to consider more individualized therapy for smaller lesions [4-8].

FIGO and TNM stage, the clinical status of the inguinal nodes, the depth of invasion and vascular invasion are the most important prognostic factors for the survival [5, 9].

In this retrospective study we analyzed and present the survival rate, recurrence rate and complications of patients with invasive squamous cell carcinoma of the vulva who were treated in our department.

Material and Methods

During the period from January 1, 1990 to December 31, 2005, 91 patients with invasive carcinoma of the vulva were admitted for evaluation and treatment at the 2nd Department of Obstetrics and Gynecology, Aretaieion Hospital. Information on the following clinical factors was obtained by review of the clinical files and pathology reports:

1) The clinical (FIGO) stage and TMN system according to the International Federation of Obstetrics and Gynecology
2) Diameter of the lesion
3) Cell type
4) Tumor grade (well differentiated, moderately differentiated and poorly differentiated).

All data were processed for computer analysis. Fifteen patients were lost to follow-up. The follow-up intervals ranged from one to ten years or until death. The Kaplan-Meier estimate or actuarial survival curves for statistical analysis of survival was used [10].

We selected 76 cases of histologically proven squamous cell carcinomas. Thirty-one patients were Stage I, 18 Stage II, 19 Stage III and three had Stage IV, and five patients had recurrence.

Sixty-seven patients were treated by surgery as primary treatment and nine patients underwent excision biopsy only.

Results

The mean age of the 76 patients in the present study was 73.5 years. Surgery was the primary treatment for 67 patients (Table 1). Eleven patients underwent simple vulvectomy, four radical vulvectomy, ten radical vulvectomy and unilateral inguinal lymphadenectomy, 38 radical vul-
vectomy and bilateral inguinal lymphadenectomy and four radical vulvectomy and inguinal and pelvic lymphadenectomy.

Radical vulvectomy with bilateral inguinal lymphadenectomy was the major mode of treatment.

Of the 52 women who underwent inguinal lymphadenectomy, 11 (21.1%) had positive nodes and four patients underwent pelvic node resection.

Table 3 shows the relation of tumor size and node status. Patients with tumor size $\leq 2$ cm had 16.7% positive inguinal nodes, while patients with tumor size $> 2$ cm had 29.4% positive nodes.

The 5-year survival for FIGO Stage I was 93.3%, Stage II 85%, Stage III 51% and for Stage IV zero (Table 2) as estimated by the Kaplan-Meier test. Figure 1 shows the 5-year survival curves for FIGO stages.

Survival rate significantly decreased if inguinal nodes were involved (Figure 2) and in cases with tumor size greater that 2 cm in diameter (Figure 3).

Table 4 shows the sites of recurrence in relation to the mode of treatment and stage. Fifteen patients developed recurrence and the vulva was the most common site. The average time of recurrence was 30 months.

In Table 5 the immediate and late complications are shown. Incision break-down was the most common immediate complication (26.7%). Other complications were thrombophlebitis (5.9%), urinary tract infection (4.4%), and pneumonia (4.4%). From late complications chronic edema was the most common (32.8%) and following lymphangitis-cellulitis (10.4%) and stress incontinence (8.9%).

Discussion

Vulvar carcinoma should be among the most curable cancers if it could be detected in early stage, and therefore early diagnosis is strongly emphasized.

Radical vulvectomy with bilateral inguinal lymphadenectomy has been associated with the best survival rates and it has been the standard therapy for women with invasive vulvar carcinoma for many years. There is recently an ongoing attempt to do less than the standard operation for smaller lesions, especially in younger women with Stage I and II, in order to prevent complications and it appears to be associated with equally good survival results [5-7, 11-16].

In our study, 67 patients underwent surgery as primary treatment. Radical vulvectomy with bilateral inguinal lymphadenectomy was performed in 38 patients, 16 patients underwent simple or radical vulvectomy, ten patients underwent radical vulvectomy and unilateral node resection and four patients underwent radical vulvectomy and inguinal and pelvic lymphadenectomy.

Nine patients underwent only excision biopsy because of distant metastasis, poor health condition or they refused treatment; 15 patients were lost-in follow-up.

Five-year survival rate for that mode of treatment was 93.3% for Stage I, 85% for Stage II, 57% for Stage III and zero for Stage IV (only 3 patients had Stage IV, a small number for statistical evaluation). Our results for 5-year survival rate are in agreement with those from other authors [7, 11, 17, 18-23].

Lymph node status was related to stage, tumor size, tumor differentiation, depth of invasion, lymphatic and vascular invasion [18-22, 24, 25]. There was a highly significant association between the pathologic status of the inguinal nodes and survival [4, 9, 18-23]. In the present study the 5-year survival rate was 49% for positive inguinal nodes and 92.3% for negative nodes, and four patients underwent pelvic lymphadenectomy.
According to other investigators, about 20% of patients with positive inguinal nodes will also have pelvic lymph node metastases and the pelvic nodes are almost never involved unless the inguinal nodes are positive [24, 26-31]. Therefore, pelvic lymphadenectomy in recent years has been performed only if the inguinal nodes are positive or if the primary tumor is very large [32-35]. More recently, some authors have suggested pelvic irradiation rather than lymphadenectomy for patients with positive inguinal nodes [5].

In the present study 15 patients developed recurrence and the vulva was the most common site (8 patients). Moreover, many authors suggest that the development of recurrent vulvar carcinoma is significantly related to stage, tumor diameter ($p < 0.05$) and nodal metastases ($p < 0.002$), findings consistent with our study [7, 9, 21-23].

**Conclusion**

In conclusion, the right choice of surgical treatment after appropriate staging of the disease offers very good survival rates, while a more accurate assessment of the status of inguinal lymph nodes could reduce the extent of surgical treatment and subsequent complications by avoiding unnecessary inguinal node dissection.

**References**


Right colon laparoscopic resection with three-trocar access and associated gynecological procedures in patients with colorectal cancer and ovarian metastases

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Summary

Background: Right laparoscopic colectomy was introduced to colorectal surgery later than the left colon procedure. Three-trocar laparoscopy has already been used successfully in the treatment of gynecological cancers. In the present study, we aimed to analyze the feasibility of performing an associated gynecological procedure following abdominal laparoscopic exploration and to evaluate the suitability of laparoscopic right colectomy for treating elderly patients. Methods: We conducted a review of prospectively collected data on 100 consecutive patients who were treated with right laparoscopic colectomy using three trocars from January 2005 to April 2010. We recorded the patients’ age (< 70 or > 70 years), ASA status, body mass index (BMI), pain on postoperative days 1 and 2 (POD 1, 2), nodes retrieved, laparotomic conversion, mean operative time, time to intestinal recovery, and length of postoperative stay. Results: All subjects were treated for cancer. Conversion to the laparotomic procedure was performed in 13/100, with no difference in terms of age. Operative time was longer for laparotomic conversion (p < 0.05), with a longer postoperative stay. Elderly patients had higher ASA scores (p < 0.005); age did not influence the conversion rate or BMI status. Pain on POD 1 and 2 differed between the laparotomic and laparoscopic groups (p < 0.0001). Associated procedures were performed in five subjects (3 oophorectomy and 2 cholecystectomy). Conclusions: Laparoscopy using the three-trocar technique is a safe procedure for treating colon cancer, including in elderly patients, and enables associated gynecological laparoscopic procedures to be performed.

Key words: Colon cancer; Ovarian cancer; Laparoscopic colectomy; BMI; Elderly; Laparoscopy; Ultracision.

Introduction

The first laparoscopic colonic resection was described in 1991 [1]. Since then, there has been slow but ongoing development of these techniques in colorectal surgery, initially for benign conditions such as diverticular disease, and subsequently for oncologic diseases [1, 2]. The advantages of minimally invasive surgery including reduced postoperative pain, faster patient mobilisation, and decreased incidence of both hernias and wound infections, encouraged the use of laparoscopy in major colorectal procedures for malignant disease [3]. However, the learning curve for laparoscopic surgery is steep, and the procedure takes significantly longer in the early stages of training. The first colorectal procedures performed laparoscopically involved the left colon and rectum, with right/transverse colonic diseases only later being treated with this technique.

Laparoscopy with the three-trocar technique has emerged as a feasible alternative to laparotomy in managing gynecologic malignancies; this approach has repeatedly demonstrated advantages over laparotomy including shorter hospitalizations, lower blood loss, improved visualization, a reduction in need for postoperative analgesics, less morbidity, and more rapid recovery [4].

In the present study, we aimed to analyze the feasibility of performing an associated gynecological procedure following abdominal laparoscopic exploration and to evaluate the suitability of laparoscopic colectomy for treating elderly patients.

Materials and Methods

From January 2005 to April 2010, 100 consecutive patients underwent right laparoscopic colectomy using the three-trocar technique. Eight patients were excluded for oncological major problems.

Mechanical bowel preparation was performed, beginning with a fiber-free diet five days before surgery and ending with four liters of polyethylene glycol (PEG solution) the day before surgery. At this time, the patient received two liters of IV parenteral nutrition (Clinimix N3G20E, Baxter). In the operative room (OR), the patient was placed supine in the reverse Trendelenburg position, with his or her legs slightly bent and abducted, the right arm abducted at an angle of 90° to the body, and the left arm alongside the body. The bed was also slightly rotated to the left (15-20°).

A urinary catheter was placed prior to commencement of the procedure. The first incision was in the parambilical region with a 12 mm trocar, through which a pneumoperitoneum was induced.

After exploration of the abdominal cavity with a 30° laparoscope, two other trocars were introduced: a 10 mm in the left hypochondrium along the left midclavicular line, and another
10 mm in the suprapubic area along the midline. The surgeon and the first assistant were on the left side of the patient.

The last small bowel loop and the cecum were identified at the duodenal window in order to isolate, ligate, and transect the intestinal vessels at their origin from the superior mesenteric axis. The dissection proceeded along the right paracolic gutter from caudal to cephalad, mobilizing the right colonic flexure and the transverse colon up to the middle colic vessels, which were preserved. This maneuver has been significantly simplified since the introduction of the Ultracision Harmonic Scalpel (Ethicon Endosurgery, Cincinnati, OH), which enables more accurate hemostasis and decreased steam production. Several reports have described the use of other devices, such as LigaSure (Valleylab, Boulder, CO) [5].

The small bowel was then resected with an Endo GIA 45 mm stapler (Ethicon Endosurgery), which was subsequently used for the intestinal anastomosis. The specimen was then extracted through a small (5-6 cm) incision in the epigastrium. The abdominal wall incision was covered with a wound protector to prevent peritoneal-parietal contamination. Side-to-side ileocolic anastomosis was performed with a linear stapler extracorporeally. After the bowel was reintroduced into the abdominal cavity, complete abdominal exploration was performed. A drain was left in situ through one of the trocar incisions. If a nasogastric tube had been placed, it was removed at the end of the procedure.

On postoperative day (POD 1), patients were mobilized and encouraged to start a liquid diet. The progression to a normal diet took place as tolerated, usually when intestinal activity had been restored. Abdominal drainage was usually removed on POD 6 in the absence of complications.

For all patients, we considered the cancer stage, rate of laparotomic conversion according to body mass index (BMI), physical status (using the ASA classification system), and age. In terms of the procedure, we looked at the mean operative time, time to restoration of intestinal activity, mean number of lymph nodes retrieved, associated surgical procedure, and the postoperative stay of each patient.

The exclusion criteria were as follows: ASA IV, T4 tumor or tumor infiltrating adjacent organs, and obstructing tumor.

Patients were divided into two groups according to age: < 70 or > 70 years of age. They were also separated into two categories: laparoscopic vs open, depending on whether the entire procedure was completed laparoscopically, or required conversion to a laparotomy. Associated surgical procedures that were conducted laparoscopically were registered in our database. Postoperative pain was investigated at POD 1 and 2 in all patients, using a visual analogue scale (VAS) from 0-10. We compared the results between the laparoscopic and laparotomic conversion groups.

The t-test and chi-square test were used for data analysis, with p < 0.05 considered to indicate statistical significance.

Results

Of the 100 consecutive patients in our study who underwent laparoscopic right colectomy for cancer, 13 under- went laparotomic conversion. The indications for laparotomy are summarized in Table 1. There was no significant difference in the average age of patients requiring a laparotomy compared with those who underwent the procedure completely laparoscopically (77 ± 5.8 years vs 69.1 ± 9.8 years, respectively), (Table 2). While the mean operative time was longer for patients who were converted to a laparotomy (181 ± 44.2 min vs 136 ± 28.4 min, p < 0.05), there was no statistical difference in operative time between the two age groups (151.9 ± 34.6 min vs 137.2 ± 33.6 min).

Although the type of procedure did not influence the restoration of intestinal function (laparoscopic = 3.26 ± 1.12 days, open = 3.6 ± 0.54 days), the postoperative hospital stay was shorter in the laparoscopic-only group (7.18 ± 1.13 days vs 8.4 ± 1.14, p < 0.05). Conversely, patients in the younger age group (Table 4) had a quicker restoration of bowel function (3.4 ± 0.69 days vs 2.4 ± 0.63 days, p = 0.001), yet the mean postoperative stay did not differ between the two age groups (7.36 ± 1.13 days vs 7.34 ± 1.36 days).

Elderly patients had a significantly higher ASA score (2.76 ± 0.43 vs 2.27 ± 0.40 in patients < 70 years, p < 0.005), but the ASA score did not influence the conversion rate (laparoscopic = 2.42 ± 0.6, open = 2.8 ± 0.4).

The average BMI of the patients did not differ between the two groups (26.01 ± 2.93 vs 25.8 ± 2.58), suggesting that BMI does not influence the rate of laparotomic conversion. The postoperative mean pain scores on POD 1 between the laparoscopic and laparotomic groups were 3.09 ± 2.07 vs 5.66 ± 0.88, respectively (p < 0.0001); the scores on POD 2 were 1.81 ± 2.08 vs 4.5 ± 0.79, respectively (p < 0.0001).

Table 1. — Indications for conversion to laparotomy.

<table>
<thead>
<tr>
<th>Indications</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive adhesions</td>
<td>8</td>
</tr>
<tr>
<td>Intraoperative hemorrhage</td>
<td>3</td>
</tr>
<tr>
<td>Neoplastic infiltration</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 2. — Patient characteristics by procedure performed.

<table>
<thead>
<tr>
<th>Age &lt; 70 years</th>
<th>Age &gt; 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients operated laparoscopically</td>
<td>Patients converted to laparotomy</td>
</tr>
<tr>
<td>ASA score</td>
<td>2.27 ± 0.40</td>
</tr>
<tr>
<td>BMI</td>
<td>26.01 ± 2.93</td>
</tr>
<tr>
<td>Mean operative time (minutes)</td>
<td>136 ± 28.4</td>
</tr>
<tr>
<td>Nodes retrieved</td>
<td>23.7 ± 9.19</td>
</tr>
<tr>
<td>Time to intestinal transit recovery (days)</td>
<td>3.36 ± 1.12</td>
</tr>
<tr>
<td>Postoperative stay (days)</td>
<td>7.18 ± 1.13</td>
</tr>
</tbody>
</table>

Table 3. — Patient characteristics by age group.

<table>
<thead>
<tr>
<th>Age &lt; 70 years</th>
<th>Age &gt; 70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA score</td>
<td>2.27 ± 0.40</td>
</tr>
<tr>
<td>BMI</td>
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</tr>
<tr>
<td>Mean post-operative stay (days)</td>
<td>7.36 ± 1.13</td>
</tr>
</tbody>
</table>
As shown in Tables 2 and 3, there was no statistically significant difference in the average number of lymph nodes retrieved among patients based on the type of procedure (laparoscopic = 23.7 ± 9.19, open = 21 ± 12.3) or patient age (> 70 years = 24.01 ± 9.9, < 70 years = 22.3 ± 7.01).

In addition to the right colectomy, five patients received an associated surgical procedure: cholecystectomy in two patients and oophorectomy in three patients for incidental ovarian metastases from colon cancer. The additional cases of pelvic disease were observed during laparoscopic abdominal exploration. The three-trocar technique was used in all of the present cases. We did not encounter any new postoperative surgical complications not already published in 71 subjects who received laparoscopic right colectomy [6].

Discussion

Several authors have highlighted the advantages of colorectal laparoscopic surgery compared with traditional, open-access surgery [7-10].

Randomized, double-blinded clinical trials with long observational periods are still insufficient in terms of providing significant evidence in support of these techniques in the long term; this is the main factor limiting the large-scale application of laparoscopic surgery to colorectal malignancies. Numerous articles have reported comparable oncological radicality between the two approaches. In some cases, the magnification of laparoscopy offers a wider and clearer vision of the surgical field. This enhanced view leads to more extensive and anatomic dissections, simplifying the ligation of vessels and enabling the retrieval of mesenteric specimens containing the greatest amount of lymph node stations [11]. The possibility of performing an additional associated procedure does not change the safety and advantages of the laparoscopic procedure, and does not affect the possibility of using all three trocars to examine the abdominal cavity. The use of laparoscopic forceps and ultracision enables a large number of abdominal laparoscopic surgical procedures to be performed, e.g., the two cases of synchronous ovarian metastases from colon cancer. Ovarian metastases have a hematogenous pathway, and the anatomical location of the primary tumors within the colon did not appear to influence the site of ovarian metastases. The reported incidence of ovarian metastasis is estimated to be 3%-14%, with poor prognosis [12].

The previous limitations of this procedure to younger and otherwise healthy individuals have been overcome. In the present series, elderly patients with higher ASA scores were the most common candidates for laparoscopic resection. Furthermore, ASA scores and BMI did not influence the outcome, and were homogeneous between the groups. Western populations tend to have higher BMIs compared with other populations, with BMI > 30 considered a risk factor for conversion to laparotomy. In the present series, the average BMI was less than 30 in both groups. Because there was no significant difference in BMI in the laparoscopic and laparotomic groups the difference in conversion rates must be attributed to other factors (Table 1).

Previous studies regarding right laparoscopic colectomy report that a reduction in the mean operative time is observed for experienced laparoscopic surgeons [13-18]. Colorectal laparoscopic surgery is considered to be an advanced procedure, requiring not only significant technical skill but also a high level of understanding and cooperation among all the members of the surgical team. The assistant is required to maintain a fixed view without perspective or angulation distortion, whereas the surgeon must isolate the colon while preserving the organ’s adherence to the abdominal wall until the end of the procedure.

Our previous report regarding right laparoscopic colectomy showed a reduced mean operative time in patients who did not require conversion to laparotomy [16]. The fact that there was no difference in the recovery of intestinal function between the laparoscopic group and the laparotomic conversion group may be attributed to the brevity of bowel exposure, even for patients undergoing laparotomy. The significant difference in pain score at PODs 1 and 2 between the laparoscopic and laparotomic groups is related to major abdominal trauma [18].

The clear and important benefits of the laparoscopic approach compared with laparotomic procedure include shorter hospital stay, decreased impact on the abdominal wall (i.e., a lower rate of infection and incisional hernia), and faster recovery to normal life for the patient [19].

Oncologic radicality is confirmed by the number of nodes retrieved; this value was similar across the laparoscopic and the laparotomic groups.

When we stratified the patients by age, there were no differences in mean operative time, BMI, postoperative stay, or the number of nodes retrieved; however, a slower recovery of intestinal function was observed in the older age group.

These data suggest that once the operator overcomes the learning curve, laparoscopic right colectomy offers important benefits to the patient, including earlier mobilization, earlier feeding, and minimal postoperative pain, all of which lead to a shorter hospital stay and a faster return to normal life. To assess the long-term oncologic results of laparoscopic right colectomy, further trials with longer follow-up times are needed; however, the present study indicates that for elderly patients, right laparoscopic colectomy is as safe as the open approach. A recent report demonstrated that the laparoscopic approach is safe also for octogenarian patients, with less blood loss during the procedure, earlier recovery of bowel function, and a shorter hospital stay when compared with an open colectomy group [20].

It is important to remember that laparoscopic colorectal techniques have a steep learning curve, and that a large number of procedures must be performed before achieving the results evidenced in high-volume centres. The time required to overcome this curve depends on the aptitude of the surgeon, as well as previous experience. Moreover, all members of the surgical team, not just the
surgeon, require training in laparoscopic techniques to gain the competency needed for this procedure to run smoothly and to minimize technical complications that can increase the operative time and cause postoperative complications [21-24].

References


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Immunohistochemical analysis of p16 expression in uterine smooth muscle tumors

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²Department of Obstetrics and Gynecology, Faculty of Medicine, Mustafa Kemal University, Antakya, Hatay (Turkey)

Summary

The expression of p16 as a tumor suppressor protein was evaluated in a retrospective analysis of paraffin-embedded tissue specimens of leiomyosarcoma (LMS), leiomyoma (LM) and normal myometrium. In this study, we investigated by immunohistochemistry p16 expression in 15 LMSs, 15 LMs and ten normal myometrium. Strong expression of p16 was found in 12 of the 15 LMSs and in three cases weak expression; three LMs had focal and weak p16 staining but none of the normal myometrium. A statistically significant difference regarding the frequency of p16 protein expression was observed between LMS and LM (p: 0.0001). We concluded that the results of this study confirm the overexpression of p16 in LMS. Therefore, the present study suggests that p16 might be a useful immunohistochemical marker which could help in distinguishing uterine LMS from LM and its benign variants.

Key words: p16 expression; Uterus; Leiomyoma; Leiomyosarcoma.

Introduction

Uterine smooth muscle tumors (USMTs) are histologically categorized as leiomyoma (LM) or leiomyosarcoma (LMS) based on a combination of mitoses, cytotopic atypia, and coagulative tumor cell necrosis. Uterine leiomyomas are the most common benign smooth muscle tumors in women of reproductive age and occur in nearly 40% of women older than 35 years [1, 2]. Uterine leiomyomas are rare tumors, usually exhibiting diffuse moderate- to-severe atypia, a mitotic count of ≥ 10 MFs/10HPFs, and tumor cell necrosis. However, uncommon variants of leiomyoma, such as symplastic (atypical, bizarre or pleomorphic) LM, mitotically active LM, and cellular LM, may result in consideration of a LMS because of the presence of nuclear atypia, high mitotic index and high cellularity, respectively. These features are commonly present in LMS [3]. The smooth muscle tumor of uncertain malignant potential (STUMP) is a smooth muscle tumor that cannot be classified as benign or malignant based on established histopathologic criteria [4].

Immunohistochemistry has been used to evaluate uterine smooth muscle neoplasms for both pathologic classification and clinical correlations [3, 5-7]. The p16 protein has been identified as a tumor suppressor protein, which binds specifically to cyclin-dependent kinase CDK-4, inhibiting the catalytic activity of the CDK4-cyclin D complex, and thereby acting as a negative cell cycle regulator [8]. p16 is probably important in cell senescence, and recent studies have identified a role for p16 in cell spreading and angiogenesis [9, 10].

In the present study, we have investigated by immunohistochemical analysis, the tissue distribution of p16 protein in patients with uterine LMs, LM variants, LMSs and normal myometrium.

Materials and Methods

Specimens of tissues were obtained from 31 patients with smooth muscle tumors who had undergone hysterectomies and ten healthy myometrium samples that had hysterectomies for nonneoplastic reasons from January 2004 to December 2009 at the Department of the Pathology, Mustafa Kemal University Hospital, Antakya, Turkey. All routine hematoxylin and eosin (H&E)-stained slides were reviewed. Microscopic characteristics of all the smooth muscle tumors were analyzed and recorded, such as cellularity, mitotic activity, nuclear atypia, and necrosis. Pathologic diagnosis of the tumors was performed using criteria in the literature [1, 11]. According to this criteria, of the 31 cases of smooth muscle tumors of the uterus, 15 were diagnosed as LMs, 15 as LMSs (Figure 1), one as STUMP, and this case was excluded from the study.

Immunohistochemical study

One or two blocks from each tumor and normal myometrium were stained for immunohistochemical analysis using the avidin-biotin and immunoperoxidase methods. Formalin-fixed paraffin-embedded tissues were cut into 4 μm sections and dried on capillary-cap glass slides. The sections were deparaffinized with standard xylene and hydrated through graded alcohol into water. An antigen retrieval procedure was performed using citrate buffer and heating for 10 min in a pressure cooker. Slides were placed for 15 min into a 3% hydrogen peroxide blocking medium and then allowed to react with the primary antibody, anti-p16 antibody (DAKO North America; dilution 1:20). Immunoperoxidase detection was employed using AEC substrate. Counter staining was performed with hematoxylin.

Evaluation of immunohistochemical staining

All immunostained sections were analyzed by two different pathologists who had no knowledge of the patient’s clinical and pathological status. The interpretation of immunohistochemical staining was expressed as follows: both nuclear or/and cytoplasmic staining was regarded as a positive reaction. p16 expression was scored as negative, focal (fewer than 33% of cells) moderate (33% to 66% of cells), or diffuse (greater than 66% of cells). This cutoff is similar to the study by Bodner-Adler et al. [5].
The chi-square test was used to compare frequency distribution of p16 protein expression between the analyzed groups (LM and LMS); *p* values of less than 0.05 were considered statistically significant. The SPSS system (Chicago, IL, USA) was used for the calculations.

**Results**

Clinical findings in patients with LM and LMS

The median age of patients with LM was 45 years (range: 32-48). Hysterectomy was the standard surgical procedure in all cases of LM. All 15 patients with LM were alive and in good health during a median follow-up time of 43 months (range: 15-60 months).

The median age of patients with LMS was 50 years (range: 38-74). Four patients had Stage I, six patients Stage II, three patients Stage III, and two patients Stage IV. All patients with LMS had a hysterectomy and bilateral salpingo-oopherectomy as surgical therapy.

Expression of p16 protein in leiomyoma and LMS

The distribution and immunostaining intensity for p16 expression in uterine smooth muscle neoplasms are summarized in Table 1. p16 protein was expressed in 3/15 (20%) LM, and in 15/15 (100%) LMS. The intensity of p16 staining varied from weak to strong.

Table 1. — Immunohistochemical results with p16.

<table>
<thead>
<tr>
<th></th>
<th>Immuno</th>
<th>stained intensity for p16</th>
<th>0</th>
<th>(0%)</th>
<th>++</th>
<th>(33%)</th>
<th>+++</th>
<th>(66%)</th>
<th>++++</th>
<th>(66%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myometrium</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMS</td>
<td>15</td>
<td>0</td>
<td>3</td>
<td>7</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LM</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nos</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellular</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Epitheloid</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bizarre</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myxoid</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

LM: leiomyomas; LMS: leiomyosarcomas.

Discussion

p16 is a cyclin-dependent kinase inhibitor which is expressed in a limited range of normal tissue and tumors. p16 is integral to the retinoblastoma (Rb) gene-mediated control of the G1-S phase transition of the cell cycle [12]. Aberrant expression of p16 protein has been studied in a variety of human neoplasms, including uterine cervical and gastric cancer. Although it is clear that elevated p16 expression in cervical squamous cell carcinoma with its precursors is the surrogate marker for HPV infection, overexpression of p16 in other neoplasms is largely unknown but is not HPV-related [13, 14].

Uterine LM is distinguished from LMS using a combination of morphological criteria, including cellularity, the presence or absence of coagulative tumor cell necrosis, mitotic index and the degree of nuclear pleomorphism. Typically, LMS is characterized by high cellularity, marked nuclear pleomorphism, the presence of coagulative tumor cell necrosis and high mitotic activity. However, in a particular LMS, one or more of these features may be absent. Conversely any one of these features may be present in a LM that is entirely benign and, due to this, these may be classified as LM variants [15, 16].

Accurately diagnosing malignant from benign uterine smooth muscle neoplasms is important clinically for patient management. However, due to the overlapping features between malignant and benign smooth muscle tumors, it can be challenging depending on morphological criteria alone. This is particularly true between bizarre...
and cellular LM. Therefore, efforts in searching for biomarkers that can differentiate benign and malignant smooth muscle tumors have important clinical implications [17].

In a study of LM and LMS, the data of Bodner-Adler et al. [5], showed that there was p16 expression in 12% and 57% of cases, respectively. There was a statistically significant difference in both p16 staining and frequency and intensity between LM and LMS. In a more recent study by O’Neill et al. [3], p16 immunoreactivity of LMS was significantly higher than LM and benign LM variants.

We have analyzed the immunohistochemical staining of p16 in normal myometrium, LM and LMS. We found strong expression of p16 in 100% of LMS, but weak expression of p16 in 3/15 (20%) of LM and LM variants, and there was no expression of p16 in normal myometrium.

Conclusion
We have shown statistically higher levels of p16 in LMS compared to LM and normal myometrium. It has been suggested that p16 is a particularly useful marker in the differential diagnosis between LMS and difficult LM variants. The reason for the higher expression is, however, unclear. Although our results were statistically significant, our study was limited by its small sample size. The use of p16 in diagnostic settings should be explored further by a large-scale study.

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The prognostic and predictive value of ERCC-1, p53, bcl-2 and bax in epithelial ovarian cancer

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¹First Department of Pathology and ²Department of Clinical Therapeutics of Alexandra Hospital, Medical School, University of Athens; ³Department of Pathology, Medical School, University of Crete; ⁴Gynecological Oncology Unit, Iaso Women’s Hospital; ⁵Department of Pathology, Iaso Women’s Hospital, Athens (Greece)

Summary

Aim: To evaluate the expression of ERCC-1 in patients with epithelial ovarian cancer (EOC) and to correlate it with the expression of p53, bcl-2 and bax. Materials and Methods: Tumor samples from 60 patients with EOC were immunohistochemically investigated for the expression of ERCC1, p53, bcl-2 and bax. Results: ERCC-1 expression was significantly decreased in serous and endometrioid compared to clear cell carcinomas. P53 expression was significantly increased in serous compared to clear cell carcinomas. Bax expression was significantly increased in serous carcinomas as compared to MMTs. High disease stage was correlated with low ERCC-1 and high bcl-2 expression. ERCC-1 expression was associated with increased disease-free interval. Conclusion: ERCC-1 status seems to be correlated with disease-free interval, stage and tumor histologic subtype in patients with EOC. Nevertheless, our results indicate that single-gene expressions may be unreliable and thus caution is needed when used as potential prognostic or predictive markers.

Key words: Ovarian cancer, ERCC-1, p53, bcl-2, bax.

Introduction

Epithelial ovarian cancer (EOC) is the most common cause of death among women who develop gynecologic cancer [1]. The current management of EOC includes cytoreductive surgery followed by combination chemotherapy for all patients with FIGO Stage ≥ IB [2]. Yet, the majority of women with advanced EOC will develop recurrences and will die of their disease as chemotherapy drug resistance leads to uncontrolled cancer growth [3]. Therefore, the determination of parameters that could identify those patients who would or not benefit from platinum-based chemotherapy could be of clinical significance. Important candidates that could be characterized as biological predictors for response of EOC to chemotherapy include the excision repair cross-complementation group 1 (ERCC1) enzyme and the apoptosis-related proteins p53, bcl-2 and bax.

In recent years, studies on mechanisms of chemotherapy resistance have focused on the identification of molecular markers involved in critical pathways through which the antineoplastic action of the drug is exerted [4]. Unfortunately, some cancer cells are able to circumvent drug action through increased DNA-repair capacity. ERCC1 is a rate limiting DNA repair protein in the nucleotide excision repair (NER) pathway that is specifically in charge of removing DNA platinum compounds [5].

Drug resistance to chemotherapy may also be the result of resistance to and escape from apoptosis, a process modulated by various oncogenes and tumor-suppressor genes, such as the previously mentioned p53, bcl-2 and bax. Deregulation of all three genes represents a crucial step in EOC carcinogenesis [6]. The aim of the present study was to analyze by immunohistochemistry ERCC1 expression in patients with EOC and to correlate the results with the immunohistochemical expression of p53, bcl-2 and bax, as well as with other clinicopathological data (histology, grade, FIGO stage, response to chemotherapy).

Materials and Methods

Patient selection

Sixty patients with EOC who were operated on from 1999 through 2007 at “Iaso” Women’s Hospital were included in this analysis. Data extracted from the records included information regarding demographic details, initial stage, grade, and histological type of the carcinoma. Uniform optimal surgical staging and treatment according to FIGO guidelines were performed in all cases.

Immunohistochemistry

Sections 4-µm thick were cut from one representative paraffin block of each case. Antibodies used were ERCC1-1 (clone 8F1, 1:200 dilution, Neomarkers, Fremont, CA, USA), p53 (Dako, Denmark, 1:30), bcl2 (Dako, Denmark 1:50) and bax monoclonal (clone B-9, 1:80, Santa Cruz, Biotechnology Inc, Santa Cruz, CA, USA). Immunoreactivity was evaluated by combining the staining intensity and the percentage of positively stained cells. Staining intensity for all four antibodies was scored as follows: 0 = none, 1 = weak, 2 = moderate and 3 = strong. The positively stained cells were expressed as the percentage on the whole tissue section and scored as follows:
0 = none, 1 = 0-25%, 2 = 26-50%, and 3 = 51-100%. The sum of those two scores was defined as follows: 0 = negative, 2 or 3 = weak, 4 = moderate and 5 or 6 = strong. The staining pattern was nuclear for p53, cytoplasmic for bcl2, membranous and cytoplasmic for bax and nuclear for ERCC1. Cases were grouped as either negative \(\leq 3\) or positive > 3.

Statistical considerations

Correlation analysis was performed by applying the Spearman test or by evaluating the gamma co-efficient. Differences in immunohistochemical (IHC) scores between histological groups were assessed by the Mann-Whitney test. In the current study, the effect of p53, bcl-2, ERCC-1 and bax expression on disease-free survival (DFS) was analyzed using the Kaplan-Meier method. Differences between groups were evaluated by applying the log-rank test. All analyses were performed using the SPSS v18.0 (SPSS Inc, USA).

Results

The main clinicopathological characteristics of the sample under study and the distribution of the immunohistochemical scores are presented in Table 1. Positive immunohistochemical expression for p53, bcl-2, bax and ERCC-1 is shown in Figure 1.

There was a statistically significant correlation between the immunohistochemical expression of ERCC-1 and bcl-2 and stage of disease. High stage disease was related to decreased ERCC-1 expression and to increased bcl-2 expression. There was no correlation between the expression of p53 and bax and stage of disease or between any of the molecules under investigation and grade of the tumor (Table 2). No significant correlation was found among the molecules of study.

The immunohistochemical expression of ERCC1 was significantly reduced in serous and endometrioid carcinomas when compared to clear cell carcinomas (\(p = 0.007\) and \(p = 0.031\), respectively). There was a significantly increased p53 expression in serous carcinomas as compared to MMTs (\(p = 0.041\)). Further pairwise comparison of the several histological types regarding IHC scoring, revealed no statistically significant differences.
No statistically significant difference in DFS was found between groups considered negative or positive for p53, for bcl-2 and for bax. On the contrary, irrespective of histological type, ovarian carcinomas considered positive for ERCC-1 had a significantly higher DFS than those considered negative for ERCC-1 (82.89 ± 8.09 vs 42.13 ± 7.27 months respectively, \( p = 0.021 \)) (Figure 2).

**Discussion**

Epithelial derived ovarian tumors, when malignant, constitute one of the most lethal forms of cancer. These tumors are themselves a heterogeneous group of neoplasms. Of most importance are the specific genetic alterations encountered in each separate morphological subgroup of EOC. As proposed by Shih and Kurman [7], the model of ovarian carcinogenesis encompasses type I tumors, characterized by mutations of BRAF and KRAS for low-grade serous tumors, KRAS mutations for mucinous tumors and β-catenin and PTEN mutations for endometrioid tumors while the only distinct molecular event for the more aggressive type II tumors, high-grade serous carcinomas and undifferentiated carcinomas, is the accumulation of p53 mutations. Nevertheless, one should also consider the crucial role of the responsiveness of each tumor to cisplatin-based chemotherapy. Nucleotide excision repair (NER), has a central role in DNA repair and is associated with resistance to cisplatin-based chemotherapy. Likewise, apoptosis, when inefficient, may be an important cause of chemoresistance.

In the present study, the immunohistochemical expression of ERCC-1 has been evaluated in patients with epithelial ovarian cancer treated with platinum-based chemotherapy. Since the initial work of Olaussen et al. [8] on the predictive/prognostic role of ERCC1 on the clinical course of patients with small cell lung cancer treated with platinum-based therapy, many authors have tried to investigate its role on other tumors [9].

In the present study, patients with ERCC-1 positive carcinomas, irrespective of histological type, had a significantly higher disease-free interval in comparison to those with ERCC-1 negative tumors, the latter being statistically correlated with high-stage disease. Moreover, ERCC-1 positivity was found to be significantly reduced in serous and endometrioid carcinomas in comparison to clear cell carcinomas. It has been emphasized by some investigators that ERCC1 does not only act by removing the platinum adducts from DNA but it is also involved - as a repair mechanism - in the prevention of mutagenesis and cancer development [10]. This complex role may lead to an inconsistent effect of ERCC-1 expression on survival, providing a satisfactory explanation for the contradictory results of our study.

Recently, the existence of ERCC1 exon VIII alternative splicing in ovarian cancer cells has been demonstrated [11]. It was found that its overexpression did not change the protein level of ERCC1 in cancer cells but decreased the excision repair function of ERCC1 and enhanced the sensitivity of cancer cells to cisplatin in a dose-dependent manner. Taking under consideration the above observation, evaluating the protein expression of ERCC-1 might prove to be of limited value. Our results also question the validity of immunohistochemistry in the evalua-
The prognostic and predictive value of ERCC-1, p53, bcl-2 and bax in epithelial ovarian cancer

The expression of the cell growth regulators p53 and bcl-2 was found to be more inversely related than expected. The crucial point is the relation between a gene’s mutation and its protein immunohistochemical expression. In ovarian carcinogenesis, many of the common miss-sense mutations that occur in TP53 are associated with post-translational stabilization and relative overexpression of p53, allowing for its immunohistochemical detection [12]. Most authors speculate over a positive relation between p53 positive tumors, the immunohistochemical expression of bcl-2 and bax, their prognostic significance and their predictive value in patients treated with platinum-based therapy [13, 14]. Our results from this relatively limited series are more in agreement with those reported by Beale et al. [15]. Most probably, single-gene expressions are unreliable to be used as potential predictive markers. It appears that the most crucial feature of any ovarian tumor is the existence of genetic alterations that determine its development and its progression. It has been shown that tumor biomarkers have significantly different expression patterns in each tumor subtype and that more than half of those biomarkers lose their predictive value when survival analyses are made subtype specific [16]. Therefore,

Figure 2. — Kaplan-Meier curves of the disease free survival among EOC cases with positive or negative expression of the molecules of the current study.
despite the fact that - as shown in the present study - platinum-based chemotherapy had different effects in women with ERCC1 (+) and ERCC1 (-) EOC, significantly longer series probably with histological-type matched cell regulator genes should be evaluated to draw more distinct conclusions.

References


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Trends in the incidence of uterine cancer in Niigata, Japan: A population-based study from 1982 to 2007

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Summary

This study investigated trends in the incidence of uterine cancer in Japan. Data from the Gynecological Cancer Registry of Niigata comprising all new cases of uterine cancer registered for the entire female population aged 15 years and over a 25-year period were examined. The age-standardized ratio of carcinoma in situ has substantially increased among females < 40 years of age (from 3.8 (in the period of 1982-1989) to 40.9 (2000-2007). There was a significant trend in increasing incidence of invasive cervical cancer for those < 40 years of age (from 4.7 to 13.1), whereas a significant trend of decreasing incidence for the 50+ year age group. The ratios of corpus cancer were increased approximately two-folds both among the population aged < 50 years and those aged 50+ years and thus becoming equivalent to invasive cervical cancer. This prefecture-wide population-based study shows the practical trend in uterine cancer in Japanese females. The current health service must emphasize education among young adults concerning cervical cancer prevention while concentrating on screening. Avoiding risk factors, such as obesity, and increasing protective factors may lower risk for corpus cancer both in younger and older females.

Key words: Uterine cancer; Carcinoma in situ; Cervical cancer; Corpus cancer; Incidence; Population-based study.

Introduction

Uterine cancer is the fourth most common cancer in Japanese females with an estimated 24,240 cases in 2003 including 8,674 invasive cervical cancer, 6,955 carcinoma in situ, and 7,430 corpus cancer [1]. There is evidence that the incidence of cervical cancer has decreased in wealthy countries as a combined result of risk reduction from health education, changes in lifestyle, and the beneficial effects of screening programs. These factors have led to females being diagnosed at both an earlier stage of disease and also at a younger age. Moreover the incidence of corpus cancer is likely to increase in such countries, mainly due to the increasing obesity epidemic.

The national cancer incidence in Japan has been estimated by the Research Group for Population-based Cancer Registration in Japan since 1975, based on the data from 5-12 population-based cancer registries [2]. However, there are some biases for estimating the overall incidence in Japan since they use data from only a limited number of registries or limited area of the district (not district-wide). The primary objective of this study was to use data from the prefecture-wide gynecologic cancer registry in Niigata to describe the females diagnosed with cervical and corpus cancer within the prefecture. This analysis evaluated 25 years (1982-2007) of uterine cancer incidence data obtained from the Gynecologic Cancer Registry of Niigata in order to investigate the trend in the incidence of uterine cancer in Japanese females.

Materials and Methods

These analyses were based on cancer cases reported to the Gynecologic Cancer Registry of Niigata between 1982 and 2007. This registry was established in 1982 and is a population-based registry which covers the entire female population in Niigata prefecture of around 1.2 million inhabitants. All information on newly diagnosed gynecologic malignant tumors as well as pre-malignant tumors in females aged ten years and over has been collected. Information sources include all hospitals including gynecologic oncology departments as well as private clinics that diagnose and/or treat cancer patients in Niigata prefecture. This study investigated the trends in uterine cancer (WHO: International Statistical Classification of Disease and Related Health Problems, Tenth Revision, code C53 and 54) incidence in Niigata prefecture, according to the following sub categories: invasive cervical cancer (C53), corpus cancer (C54), and carcinoma in situ (D06) between 1982 and 2007.

The trend in uterine cancer incidence in Niigata prefecture from 1982 to 2007 was investigated. Age-standardized incidence rates (ASRs) were calculated with 95% confidence limits, for each disease with the world population as the standard. Patients were divided into three groups based on age: < 40 years, 40-49 years, and 50+ years for carcinoma in situ and cervical cancer, and < 50 years and 50+ years for corpus cancer. The change in ASRs in three chronological periods, 1982-1989, 1990-1999, and 2000-2007, were examined. Differences in ASRs between the first period (1982-1989) and the last period (2000-2007) were evaluated using rate ratios (RR) and the corresponding 95% confidence interval (CI).

Results

The trends in the age-standardized incidence rates are illustrated in Figure 1. A total of 9,605 females with uterine cancer including carcinoma in situ of the cervix, invasive cervical cancer, and corpus cancer cases were diagnosed between 1982 and 2007. The ASRs of carci-
The incidence rates of corpus cancer among females aged < 40 years and 40-49 years significantly increased during the period from 2000-2007 in comparison to the period from 1982-1989. The ASRs for carcinoma in situ have increased substantially among those aged < 40 years (approximately 11-fold, from 3.8 to 40.9), whereas the ASRs increased moderately among those aged 40-49 and age 50+ years, approximately three-fold and two-fold, respectively. There was a significant trend in increasing incidence of invasive cervical cancer in the < 40 years population, whereas a significant trend in decreasing incidence was observed for the 50+ year age group. The incidence rate was almost stable among those aged 40-49 years.

Trends in the incidence according to the histological type of cervical cancer are illustrated in Figure 3. The ratio of adenocarcinoma incidence (including adenocarcinoma and adenosquamous carcinoma) to all invasive cervical cancers steadily increased from 6% (in 1982) to 25% (in 2007). The trends in the ASRs of cervical cancer according to the histological type by age and period of diagnosis are shown in Table 2. The incidence of squamous cell carcinoma was significantly increased in the < 40 age group whereas it was significantly decreased in the 50+ age group. Significant increases (approximately two-fold) of ASRs for adenocarcinoma were observed in all age groups.

Discussion
This study investigated evolution of trends in the incidence of uterine cancer in Japanese females during the last 25 years using data from the prefecture-wide gynecologic cancer registry in Niigata. There was a significant and striking increase in the incidence of carcinoma in situ and a significant increase in the incidence of invasive cervical cancer in the < 40 age group. Whereas the incidence of invasive cervical cancer appeared to be more or less stable or to show a marginal significant increase in the 40-49 age group and a significant decrease in the 50+ age group. The incidence rate of corpus cancer has been dramatically increased by approximately eight-fold from 2.9 (in 1982) to 23.9 (in 2007) per 100,000 females. The incidence rates of uterine cancer (C53 and C54) increased from 12.7 to 16.9 reflecting the increased incidence rate in corpus cancer with an approximately three-fold increase from 2.6 to 7.9. Conversely, the invasive cervical cancer incidence rate slightly decreased from 10.1 to 9.0. The ratio of corpus cancer to invasive cervical cancer incidence increased steadily from 0.3 to 0.9 (Figure 2).

The trends in the ASRs of carcinoma in situ and invasive cervical cancer by age group and the period of diagnosis are shown in Table 1. The incidence rates of both carcinoma in situ and invasive cervical cancer among females aged < 40 years and 40-49 years significantly increased during the period from 2000-2007 in comparison to the period from 1982-1989. The ASRs for carcinoma in situ have increased substantially among those aged < 40 years (approximately 11-fold, from 3.8 to 40.9), whereas the ASRs increased moderately among those aged 40-49 and age 50+ years, approximately three-fold and two-fold, respectively. There was a significant trend in increasing incidence of invasive cervical cancer in the < 40 years population, whereas a significant trend in decreasing incidence was observed for the 50+ year age group. The incidence rate was almost stable among those aged 40-49 years.

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Trends in the incidence of uterine cancer in Niigata, Japan: A population-based study from 1982 to 2007

Table 1. — Trends in the ASRs of carcinoma in situ and invasive cervical cancer by age group and the period of diagnosis.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Age group</th>
<th>15-39</th>
<th>40-49</th>
<th>50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma in situ</td>
<td>1982-1989</td>
<td>3.8 (2.8-4.9)</td>
<td>11.5 (9.2-13.9)</td>
<td>4.7 (3.7-5.7)</td>
</tr>
<tr>
<td></td>
<td>1990-1999</td>
<td>18.6 (14.8-22.4)</td>
<td>25.2 (22.7-27.8)</td>
<td>7.9 (7.1-8.8)</td>
</tr>
<tr>
<td></td>
<td>2000-2007</td>
<td>40.9 (34.4-47.5)</td>
<td>36.8 (29.9-43.8)</td>
<td>9.1 (6.5-9.7)</td>
</tr>
<tr>
<td>Invasive Cervical Cancer</td>
<td>Rate ratio* (95% CI)</td>
<td>11.2 (9.6-12.8)</td>
<td>3.3 (2.8-3.7)</td>
<td>2.1 (1.6-2.6)</td>
</tr>
<tr>
<td>1982-1989</td>
<td>4.7 (4.0-5.4)</td>
<td>17.5 (14.8-20.1)</td>
<td>24.2 (20.1-28.2)</td>
<td></td>
</tr>
<tr>
<td>1990-1999</td>
<td>9.3 (7.9-10.7)</td>
<td>18.9 (17.1-20.7)</td>
<td>15.3 (13.5-17.0)</td>
<td></td>
</tr>
<tr>
<td>2000-2007</td>
<td>13.1 (10.7-15.4)</td>
<td>21.3 (18.6-24.0)</td>
<td>14.8 (13.2-16.3)</td>
<td></td>
</tr>
</tbody>
</table>

Gray boxes show statistically significant different compared with 1982-1989. Values are incidence rate (95% confidence interval).

Table 2. — Trends in the ASRs of cervical cancer according to the histological type by age and period of diagnosis.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Age group</th>
<th>15-39</th>
<th>40-49</th>
<th>50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCC</td>
<td>1982-1989</td>
<td>3.8 (3.5-4.2)</td>
<td>15.2 (13.8-16.5)</td>
<td>22.9 (21.1-24.7)</td>
</tr>
<tr>
<td></td>
<td>1990-1999</td>
<td>7.1 (6.4-7.8)</td>
<td>16.0 (14.7-17.4)</td>
<td>12.8 (11.8-13.8)</td>
</tr>
<tr>
<td></td>
<td>2000-2007</td>
<td>10.0 (9.6-10.5)</td>
<td>14.5 (13.3-15.7)</td>
<td>10.9 (10.5-12.4)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Rate ratio* (95% CI)</td>
<td>2.7 (2.3-3.3)</td>
<td>0.9 (0.6-1.2)</td>
<td>0.5 (0.3-0.8)</td>
</tr>
<tr>
<td>1982-1989</td>
<td>0.8 (0.6-1.1)</td>
<td>2.2 (1.6-2.8)</td>
<td>2.1 (1.7-2.5)</td>
<td></td>
</tr>
<tr>
<td>1990-1999</td>
<td>1.1 (0.7-1.5)</td>
<td>4.7 (3.2-6.3)</td>
<td>3.0 (2.3-3.7)</td>
<td></td>
</tr>
<tr>
<td>2000-2007</td>
<td>1.8 (1.3-2.5)</td>
<td>5.7 (2.6-8.8)</td>
<td>3.2 (2.3-4.1)</td>
<td></td>
</tr>
<tr>
<td>Aner mo carcinoma*</td>
<td>Rate ratio* (95% CI)</td>
<td>2.2 (1.3-3.2)</td>
<td>2.4 (1.3-3.8)</td>
<td>1.6 (1.1-2.2)</td>
</tr>
</tbody>
</table>

Gray boxes show statistically significant different compared with 1982-1989. Values are incidence rate (95% confidence interval).

Table 3. — Trends in the ASRs of corpus cancer by age group and period of diagnosis.

<table>
<thead>
<tr>
<th>Time period</th>
<th>Age group</th>
<th>15-49</th>
<th>50+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1982-1989</td>
<td>2.4 (1.9-2.8)</td>
<td>11.5 (9.6-13.4)</td>
<td></td>
</tr>
<tr>
<td>1990-1999</td>
<td>3.2 (2.6-3.7)</td>
<td>16.1 (14.3-17.8)</td>
<td></td>
</tr>
<tr>
<td>2000-2007</td>
<td>5.3 (4.7-6.5)</td>
<td>23.1 (20.3-25.9)</td>
<td></td>
</tr>
<tr>
<td>Rate ratio* (95% CI)</td>
<td>2.3 (1.9-2.6)</td>
<td>2.1 (1.7-2.4)</td>
<td></td>
</tr>
</tbody>
</table>

Gray boxes show statistically significant different compared with 1982-1989. Values are incidence rate (95% confidence interval).

The significant increasing trend of carcinoma in situ in the young adult age group was a remarkable finding in this study. This increasing trend may partly reflect changes in cervical cancer screening practices. The Japanese government revised the legislation in 2002 and lowered the starting age of the screening from 30 to 20 years of age. However, nationwide screening coverage for cervical cancer is still low in Japan with only 14% of one-year coverage [7]. Older females tend to demonstrate continued participation, but remarkably fewer younger females participate in such screening programs, and this finding highlights the need to optimize the coverage of the invited population.

Recently, many studies have shown a constant or increased incidence of adenocarcinoma with a decrease in the incidence of squamous carcinoma [8-10]. The relative frequency of adenocarcinoma increased from 12.4% of all cervical cancers during the period 1973-1976, to 24.9% during the period 2001-2004 in the US [11]. This study showed almost the same trend in the incidence of cervical adenocarcinoma with the increased incidence rates in all age groups. High-risk HPV infection is a significant cause of adenocarcinoma similar to squamous cell carcinoma, and therefore the increasing trend in adenocarcinoma may also be attributed to changes in sexual lifestyle and the resultant higher prevalence of HPV infection in Japanese females. Females with adenocarcinoma had a poorer prognosis than those with squamous cell carcinoma, especially in advanced stage cancer. Therefore, cancer screening is more important for adenocarcinoma to improve the prognosis.

The incidence of corpus cancer varies widely among countries, tending to be higher in Western countries and lower in the countries of Africa and Asia including Japan. Corpus cancer is both the most common type of uterine cancer and the most common cancer of the female reproductive system in the US [12]. In general, corpus cancer tends to be a disease of affluent societies and countries with Westernized lifestyles. Recent epidemiological studies show that the incidence rate of corpus cancer is steadily increasing in Japan and the current study is also consistent with those findings [13]. The magnitude of the increasing incidence rate was higher in females over 50 years than those under 50 years. This increased incidence has been due to certain factors; the greater longevity of the population, better nutrition, improved health care and living conditions have led most females to live long enough to develop corpus cancer. Although the exact cause of corpus cancer is still unclear, several major risk factors may be associated with its occurrence. Some of these factors include age, parity, age at first birth, age at menarche and menopause, use of oral contraceptives, and hormone replacement therapy. Additionally, lifestyle factors such as smoking and obesity may also contribute to the increased risk of corpus cancer.
factors for the development of corpus cancer include nulliparity, early menarche, late menopause, obesity, diabetes mellitus, hypertension, family history, tamoxifen therapy, and unopposed estrogen therapy. Of these risk factors, obesity may play the largest role with a recent study indicating that almost 40% of corpus cancer cases are secondary to obesity [14]. A steadily increasing trend in Japan suggests that corpus cancer will become the most common gynecological cancer in Japan in the near future.

The incidence rate of uterine cancer varies within Japan; however, the trend in the incidence rate in this prefecture-wide study is similar with the estimated trend of uterine cancer in Japanese females by the Japanese National Cancer Center. Since nationwide tumor registration has not yet been established in Japan, this prefecture-wide study gives the practical trend in uterine cancer in Japanese females.

The detection of carcinoma in situ or early stage invasive cervical cancer in young adults will be more important for female health in the future. Public information on the importance of regular cervical Pap smear screening must be continuously offered to all females, especially young adults, as an integral part of a nation’s health service. Finally, avoiding risk factors, such as obesity, and increasing protective factors may lower the risk for corpus cancer both in younger and older females.

Acknowledgements

We thank the members of the Gynecologic Cancer Registry of Niigata for data collection.

References


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Prognostic significance of increased urinary neopterin concentrations in patients with breast carcinoma

H. Kalábová, L. Krčmová, M. Kašparová, J. Plšek, J. Laco, R. Hyšpler, H. Klozová, D. Solichová, B. Melichar

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Summary
Increased serum or urinary concentrations of neopterin have been described in patients with tumors of different primary locations, but repeated neopterin in patients with breast carcinoma are relatively innumeros. We have evaluated urinary neopterin in 456 patients with breast carcinoma. Urinary neopterin was determined using high-performance liquid chromatography. Neopterin in patients was increased only in a minority of patients with breast carcinoma. Increased urinary neopterin was associated with inferior or overall survival. Prognostic significance of increased urinary neopterin was evident in patients with tumors expressing hormone receptors or and human epidermal growth factor receptor (HER)-2, but not in patients with triple negative tumors. Among other parameters determined, C-reactive protein, hemoglobin, peripheral blood neutrophil count and platelet count were significant prognostic factors. On multivariate analysis, age, expression of hormone receptors, neutrophils, stage and hemoglobin concentration were independent prognostic indicators. In conclusion, serum neopterin is increased only in a minority of patients with breast carcinoma. Increased urinary neopterin was predictive of poor survival in univariate, but not multivariate analysis. Age, expression of hormone receptors, neutrophils, stage and hemoglobin concentration were independent prognostic indicators.

Key words: Breast cancer; Estrogen receptor; HER-2; Neopterin; Progesterone receptor.

Introduction
Breast carcinoma is the most common malignant disease of women in the Western world [1]. The progress accomplished in the treatment of breast cancer over the last decades is now reflected in improved survival. There is now strong evidence that, in addition to early diagnosis, much of the improvement of the prognosis of women with breast cancer results from the use of systemic therapy, such as hormonal treatment and chemotherapy [2].

It is now evident that breast carcinoma is not a single nosologic entity, but a spectrum of malignant disorders affecting the same organ. Different breast tumors may be distinguished based on phenotypic characteristics including the expression of hormone receptors and human epidermal growth factor receptor (HER)-2. The phenotypic characteristics of tumor cells predict response to hormonal manipulations, cytotoxic agents or targeted therapy and have prognostic significance. In fact, most of the research on factors determining the prognosis of breast cancer in the past decades has focused on prognostic parameters that reflect the properties of the tumor cell. On the other hand, there is an increasing body of evidence indicating that parameters associated with host response to neoplasia are prognostic factors of similar importance. In the clinical laboratory, the host response to neoplasia may be assessed by measuring laboratory parameters of systemic immune and inflammatory response.

Revised manuscript accepted for publication February 22, 2011

The presence of inflammatory response is associated with poor survival in patients with breast carcinoma [3]. The presence of systemic inflammatory or immune response may be assessed by measuring serum or plasma cytokine concentrations. A significant problem associated with this approach is represented by sometimes marked fluctuations of systemic cytokine concentrations even within a short time frame. Neopterin is a pteridine produced from guanosine triphosphate (GTP) by activated macrophages in a reaction catalyzed by the enzyme GTP cyclohydrolase I. The activity of GTP cyclohydrolase I, induced by interferon-γ (IFN-γ), is produced by T-lymphocytes and natural killer cells, and serum concentrations of this cytokine are reflective of systemic immune response. However, the production of IFN-γ is enhanced by pro-inflammatory cytokines, such as interleukin-1 or interleukin-6. The pro-inflammatory cytokines are known to enhance or, to a lesser degree, induce neopterin production. Thus, systemic concentrations of neopterin reflect both systemic immune and inflammatory response [4]. Neopterin may be measured in serum or in urine, and both serum and urinary neopterin concentrations have been validated as indicators of systemic immune and inflammatory response in disorders ranging from cancer to viral infections, transplant rejection, or atherosclerosis.

The literature on neopterin as a marker of systemic immune activation in patients with cancer is relatively limited. In the present study, we retrospectively evaluated serum neopterin in patients with breast cancer.
Material and Methods

Four-hundred and fifty-six patients with histologically verified breast carcinoma who had urinary neopterin determined as part of different research projects, approved by the institutional ethical committee, between 1997 and 2008, were included in the present retrospective analysis. In all patients, morning urine samples were obtained during patient visits. The patients were subsequently followed at regular intervals. Multivariate analysis was performed using the log-rank test. Survival of different groups of patients was compared by the Kaplan-Meier method, and survival of patients was analyzed by the Mann-Whitney U test. Correlations were analyzed using Spearman’s rank correlation coefficient. Survival was measured from the time of sample collection to death or last follow-up. Urinary neopterin was determined within six months of diagnosis in 361 patients (79% of the whole cohort). In the present cohort, neopterin in patients was increased above the threshold of 205 µmol/mol creatinine, that was defined as the upper limits of normal in an earlier study [9], in 113 patients (25%). Urinary neopterin was significantly higher in 55 patients with metastatic or recurrent breast carcinoma compared to the other patients (mean ± standard deviation 224 ± 203 vs 176 ± 177 µmol/mol creatinine, p < 0.05). Urinary neopterin was increased in 20 out of 55 (36%) patients with metastatic or recurrent disease and 93 out of the 401 (23%) other patients. No significant differences were observed according to the stage in patients with non-metastatic disease (Stage I 170 ± 66 µmol/mol creatinine, n = 51; Stage II 161 ± 79 mol/mol creatinine, n = 203; and Stage III 198 ± 274 mol/mol creatinine, n = 147). Among 401 patients without metastatic or recurrent tumor, urinary neopterin was significantly increased in patients who had received previous therapy compared to therapy-naive patients (211 ± 274 vs 159 ± 97 µmol/mol creatinine, p < 0.001).

Ninety-eight patients died during the period of observation. The threshold of urinary neopterin concentration of 205 µmol/mol creatinine was used to dichotomize the neopterin values into normal and high for survival analysis. Median survival was not reached in patients with either high or normal neopterin, however, patients with urinary neopterin concentrations of 205 µmol/mol creatinine or higher had significantly inferior overall survival. Among patients with normal neopterin, estimated 5-year survival was 80% and 10-year survival was 74%, while the estimated 5- and 10-year survival of patients with high neopterin was 69% and 50%, respectively (p = 0.005). A significant difference in survival was observed in patients who had neopterin determined within six months of diagnosis (estimated 5- and 10-year survival 82% and 76% vs 72% and 52%, respectively; p = 0.02), but not in patients who had neopterin measurement later after diagnosis. Maximum follow-up in 95 patients who had neopterin measured more than six months after diagnosis was only six years, and estimated 5-year survival of patients with normal or high neopterin was 70% and 60%, respectively (p = 0.27).

Tumor expression of hormone receptors and HER-2 was determined in 434 patients (95% of the whole cohort). Data on tumor phenotype were not available in some patients diagnosed before 2000 when HER-2 expression was not assessed routinely. In addition, in a few patients with the expression of HER-2 2+ on immunohistochemistry, fluorescence in situ hybridization could not be performed because of technical reasons. A
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significant difference in survival based on urinary neopterin was observed among patients with tumors expressing hormone receptors and not expressing HER-2 (estimated 5- and 10-year survival 86% and 82% vs 75% and 41%, respectively; \( p = 0.009; n = 289 \); Figure 1) and in patients with tumors with high expression of HER-2 ( \( p = 0.01; n = 83 \); Figure 2). No events were observed among patients with HER-2 positive tumors after five years, and both 5- and 10-year survival among patients with normal or high neopterin was 80% and 57%, respectively. No difference in survival was observed in 62 patients with triple negative tumors (Figure 3).

Peripheral blood cell count was performed at the time of neopterin determination in 447 patients (98% of the whole cohort), with manual differential white blood cell count being performed in 395 patients (87%). A negative correlation was observed between urinary neopterin and platelet count ( \( r_c = -0.11, p = 0.02 \)), but no other correlation was evident between neopterin and parameters of peripheral blood cell count. Serum albumin was measured in 439 patients (96%), and a negative correlation with urinary neopterin of borderline significance was observed ( \( r_c = -0.09, p = 0.05 \)). CRP was determined in 386 patients (85%), and a positive correlation was observed between neopterin and CRP ( \( r_c = 0.24, p < 0.00001 \)).

Among other parameters determined, CRP, hemoglobin, peripheral blood neutrophil count and platelet count were significant prognostic factors (Table 1). On multivariate analysis, age, expression of hormone receptors, neutrophils, stage and hemoglobin concentration were prognostic indicators in patients without distant metastases (Table 2).

Discussion

The present data demonstrating increased serum neopterin concentrations only in a minority of patients with breast cancer are in agreement with earlier reports [9, 10]. An increase in serum or urinary neopterin concentrations in cancer patients has been amply documented, and in patients with tumors of different primary locations, increased serum or urinary neopterin concentrations were associated with poor prognosis [11, 12]. Correlations were observed between lower numbers or impaired function of lymphocytes or dendritic cells and neopterin concentrations [13-16]. Thus, increased neopterin concentrations are thought to reflect immune dysregulation [11]. Despite the fact that breast carcinoma is the most common malignant disorder in women, the literature on neopterin as a marker of systemic immune activation in patients with breast cancer is relatively limited. Increased levels of urinary neopterin were reported in less than 20% of patients at diagnosis [9, 10]. In an earlier study, elevated neopterin levels have been associated with higher grade or metastatic disease, and increased urinary neopterin concentration was a significant prognostic factor in both univariate and multivariate analysis [10]. In the multivariate analysis, presence of distant metastases, lymph node involvement and neopterin were significant predictors of survival [10]. Compared to the present study, the cohort reported by Murr et al. had longer fol-
The present retrospective cohort included patients examined around the time of diagnosis as well as patients who had neopterin determination during the course of follow-up. Patients with active or metastatic disease as well as patients with no evidence of disease were included. In most studies investigating the prognostic significance of inflammatory response, the collection of samples for the determination of neopterin or other indicators of systemic immune or inflammatory response was performed around the time of diagnosis [10]. On the other hand, in contrast to most other tumors, late recurrence is quite common in breast carcinoma and determination of the risk during follow-up is of practical significance. In a recent study, indicators of systemic inflammatory activity CRP and serum amyloid A were significant predictors of death in a population of breast cancer patients examined during follow-up approximately 31 months after the diagnosis [3]. Similarly to the report by Pierce et al. [3], CRP was a significant prognostic indicator in the present cohort of patients.

In multivariate analysis, in addition to age, stage and hormone receptor status neutrophil count and hemoglobin concentrations were indicative of prognosis. On the other hand, urinary neopterin and serum CRP were not prognostic factors, in contrast with earlier reports [3, 10]. There may be several reasons for negative findings regarding the prognostic significance of indicators of inflammatory response in multivariate analysis. The median follow-up was substantially shorter compared to the study by Murr et al. [10]. Breast cancer recurs relatively late, and, because of effective therapy, recurrences usually lead to death only after an additional delay. On the other hand, in the present analysis peripheral blood immune or inflammatory response was performed around the time of diagnosis as well as patients with no evidence of disease were included. In most studies investigating the prognostic significance of inflammatory response, the collection of samples for the determination of neopterin or other indicators of systemic immune or inflammatory response was performed around the time of diagnosis [10].

In conclusion, urinary neopterin is increased only in a small proportion of patients with breast carcinoma, but increased neopterin concentrations herald poor prognosis. Increased urinary neopterin was predictive of poor survival in univariate, but not multivariate analysis.

Acknowledgement

Supported by the grants of the Internal Grant Agency of the Ministry of Health of the Czech Republic NR9096-4 and NS10286-3 and Research Project MZO 00179906.

References


Table 1. — Results of univariate analysis of survival.

<table>
<thead>
<tr>
<th>Parameter (unit)</th>
<th>Values</th>
<th>n</th>
<th>5-year survival (%)</th>
<th>10-year survival (%)</th>
<th>p</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neopterin (µmol/mol creatinine) &lt; 205</td>
<td>343</td>
<td>80</td>
<td>74</td>
<td>0.005</td>
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</tr>
<tr>
<td>Age (years) &lt; 75</td>
<td>425</td>
<td>79</td>
<td>73</td>
<td>0.0003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/l) &lt; 5</td>
<td>281</td>
<td>84</td>
<td>80</td>
<td>0.00003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/l) &lt; 120</td>
<td>24</td>
<td>37</td>
<td>NE</td>
<td>0.0005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (10⁹/l) &lt; 120</td>
<td>422</td>
<td>79</td>
<td>72</td>
<td>0.05</td>
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<tr>
<td>Leukocytes (10⁹/l) &lt; 9.5</td>
<td>410</td>
<td>78</td>
<td>73</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes (10⁹/l) &lt; 5.68</td>
<td>360</td>
<td>80</td>
<td>75</td>
<td>0.01</td>
<td></td>
<td></td>
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<tr>
<td>Monocytes (10⁹/l) &lt; 0.68</td>
<td>356</td>
<td>79</td>
<td>74</td>
<td>0.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymorphonuclear leukocytes (10⁹/l) &lt; 6.8</td>
<td>346</td>
<td>79</td>
<td>72</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count (&lt; 6,800 per µl) &lt; 0.9</td>
<td>281</td>
<td>84</td>
<td>80</td>
<td>0.00003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormone receptor expression (no vs yes)</td>
<td>3.87</td>
<td>1.90-7.93</td>
<td>0.0002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage (I or II vs III)</td>
<td>0.44</td>
<td>0.23-0.87</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neopterin (µmol/mol creatinine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Table 2. — Results of multivariate analysis in patients without distant metastases.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt; 75 year vs above)</td>
<td>0.14</td>
<td>0.05-0.36</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hormone receptor expression (no vs yes)</td>
<td>1.08</td>
<td>0.69-1.69</td>
<td>0.73</td>
</tr>
<tr>
<td>Neutrophil count (&lt; 6,800 per µl vs above)</td>
<td>0.33</td>
<td>0.14-0.83</td>
<td>0.02</td>
</tr>
<tr>
<td>Stage (I or II vs III)</td>
<td>0.44</td>
<td>0.23-0.87</td>
<td>0.02</td>
</tr>
<tr>
<td>Hemoglobin (g/l) &lt; 120</td>
<td>4.07</td>
<td>1.20-13.79</td>
<td>0.02</td>
</tr>
</tbody>
</table>

low-up and was more homogenous with regard to the time between diagnosis and sample collection. Increased serum neopterin concentration along with increased concentrations of interleukin-1 receptor antagonist and soluble tumor necrosis factor receptor II have been observed in breast cancer survivors with chronic fatigue compared to those without chronic fatigue [17, 18]. Fatigued breast cancer survivors also had significantly lower serum cortisol and significantly higher numbers of CD3⁺ T-lymphocytes, CD4⁺ CD8⁻ T-lymphocytes and CD3⁺ CD56⁺ lymphocytes. Interestingly, in the present study increased neopterin was associated with poor prognosis in patients with tumor expressing hormone receptors and HER-2, but not in patients with triple negative tumors. Triple-negative breast carcinoma is characterized by an aggressive course, and systemic inflammatory reaction may not be as important in determining the prognosis in this group of patients.
Prognostic significance of increased urinary neopterin concentrations in patients with breast carcinoma


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Loop electrosurgical excision procedure in Greek patients with vaginal intraepithelial neoplasia and history of cervical cancer

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Summary

**Objective:** The aim of our study was to evaluate the therapeutic effectiveness of loop electrosurgical excision procedure (LEEP) in Greek patients with vaginal intraepithelial neoplasia (VAIN) and history of cervical cancer. **Materials and Methods:** Between January 2002 and January 2009, eight women with histologically confirmed VAIN and history of cervical cancer were included in our study. For the LEEP procedure we used a high frequency Electrosurgery Unit with at least 80 W output. **Results:** Complete response rate, at 12 months of follow-up, was 75%. Recurrence rate, at 12 months of follow-up, was 25%. Complete response rate, at 24 months of follow up, was 62.5%. Recurrence rate, at 24 months of follow up, was 37.5%. **Conclusion:** LEEP may constitute a valuable excisional method for the treatment of VAIN in cases with a history of cervical cancer. It provides an interpretable specimen of the whole lesion within a few minutes. It needs a short period of training and has low cost.

Key words: Electrosurgery; LEEP; Vaginal intraepithelial neoplasia; VAIN; Cervical cancer.

Introduction

Vaginal intraepithelial neoplasia (VAIN) is uncommon, representing 1% of lower genital tract intraepithelial neoplasias [1, 2]. The median age at diagnosis of VAIN is 41 years (range 16-87 years) [3-5]. However VAIN is now being diagnosed in younger women and this rise seems to be associated with the increased incidence of human papilloma virus (HPV) infections of the lower genital tract [6].

Generally, most patients are asymptomatic. If present, symptoms may include postcoital spotting, vaginal bleeding, unusual vaginal discharge and odor [3, 4, 7]. The majority of lesions are located in the upper one-third of the vagina and are often multifocal [3-5].

The natural history of VAIN is little known but is thought to be similar to that of cervical intraepithelial neoplasia (CIN) [3, 5]. VAIN is classified in a similar manner to CIN and HPV is the primary initiator of these lesions [6, 7]. In women with VAIN: 78% may regress, 13% may persist and 9% may progress to invasive vaginal cancer [3].

The management of women with VAIN remains controversial. Treatment protocols use topical medical therapy (5% 5-fluorouracil, imiquimod), immunotherapy (interferon), surgical procedures (local excision, partial vaginectomy), total vaginectomy, loop electrosurgical excision procedure (LEEP), laser surgery, cavitation ultrasonic surgical aspiration, chemosurgery (preoperative 5-fluorouracil followed by laser surgery or LEEP) or radiation therapy [4, 5, 8-17].

For LEEP a high frequency electrosurgery unit with at least 80 watts output was used. For electrodexcision a 10 x 4 mm or a 5 x 2 mm loop electrode was used and we selected blend cut mode with 50 watts power output. For electrotfulguration a 5 mm ball electrode was used and we selected blend coag mode with 60 watts power output.

All patients were advised to avoid intercourse during the first four to six weeks following the procedure and return for follow-up at six weeks. Post-treatment follow-up protocol included physical examination, vaginal smear and colposcopic assessment at three, six, nine and 12 months for the first year and yearly there after.

The aim of our study was to evaluate the therapeutic effectiveness of LEEP in Greek patients with VAIN and history of cervical cancer.

Material and Methods

Between January 2002 and January 2009, eight women with histologically confirmed VAIN and a history of cervical cancer were referred to the 2nd Department of Gynecology of St. Savvas Anticancer-Oncologic Hospital of Athens. Among them, three had been treated for cervical cancer Stage 1A1 with hysterectomy and five had been treated for cervical cancer Stage 1b with radical hysterectomy, lymphadenectomy and radiotherapy.
Complete response was defined as no cytologic and colposcopic evidence of any VAIN lesion. Recurrence was defined as cytologic and colposcopic evidence of a new VAIN lesion in complete responders.

When patients had more than one grade of VAIN, they were assigned the highest grade. Patients with one focus of VAIN were identified to have unifocal and those with two or more areas were identified to have multifocal disease.

The study was approved by the Ethical Committee of the Hospital. Informed consent was obtained from each woman. Statistical analyses were performed using the SPSS-13 for Windows.

**Results**

The median age at diagnosis of VAIN was 49 years (range 41-56 years). The median follow-up was 46.2 months (range 29-62 months). The demographics of women are shown in Table 1.

The median operating time was 15 min (range 10-20 min) depending on multifocal and extent of the lesion. The median healing time was five weeks (range 4-6 weeks) depending on the extent of the wound. All tissue specimens had free surgical margins. In our study population we had: three VAIN 2 and five VAIN 3.

Complete response rate at 12 months of follow-up was 75%. Recurrence rate at 12 months of follow-up was 25%. Complete response rate at 24 months of follow-up was 62.5%. Recurrence rate at 24 months of follow-up was 37.5%. None of the treated patients progressed to invasive vaginal cancer during a mean follow-up of 46.2 months. These data are shown in Tables 2 and 3.

**Discussion**

VAIN has histopathology similar to CIN [18]. VAIN development, following HPV infection, may require a greater period of time and may occur less frequently because of the different type of epithelium from which VAIN arises [4, 19]. HPV types with a preference for infection of vaginal tissue may be less oncogenic [20]. The vagina lacks an active transformation zone with immature epithelial cells susceptible to HPV infection [18, 21]. However, HPV entry may result from vaginal mucosal abrasions (from coitus or tampon use) and reparative metaplastic squamous cell activity [18].

VAIN may occur as an isolated lesion or as a lesion associated with CIN (65%) or vulvar intraepithelial neoplasia (VIN) (10%) [5]. These lesions may arise at the same time (synchronous lesions) or up to several years after the initial CIN lesion (metachronous lesions) [5, 22]. Most VAIN lesions occur on the vaginal vault after hysterectomy for CIN or invasive cervical cancer [3, 5, 23, 24]. The time interval from an initial diagnosis of CIN 3 to a current diagnosis of VAIN 3 varies from 2-17 years [7, 16, 24-27]. This shows the protracted, delayed onset of VAIN, requiring long-term cytological follow-up after hysterectomy [7, 10, 26, 27]. In our study three patients had VAIN lesions on the vaginal vault after hysterectomy for cervical cancer Stage 1A1 and five patients had VAIN lesions on the vaginal vault after radical hysterectomy for cervical cancer Stage 1B.

The majority of VAIN (82%) occur in the upper one-third of the vagina [5, 7, 28]. The middle and lower thirds of the vagina are involved by less than 10% of lesions [5, 28]. The majority of VAIN (61%) are also multifocal [3, 5, 25]. The upper one-third of the vagina and especially the angles of the vaginal vault must be carefully examined after hysterectomy [4, 28]. In our study, all women had VAIN lesions in the upper one-third of the vagina. Among them, three women had unifocal VAIN lesions and five women had multifocal VAIN lesions.

The most important risk factors for developing VAIN are previous abnormal Papanicolaou smear, HPV infection, genital warts, CIN or cervical cancer, immunosupression, radiation therapy, history of diethylstilbestrol exposure, low education, low family income, smoking and early hysterectomy [5, 29]. In our study three patients had VAIN lesions on the vaginal vault after hysterectomy for cervical cancer Stage 1A1 and five patients had VAIN lesions on the vaginal vault after radical hysterectomy, lymphadenectomy and radiotherapy for cervical cancer Stage 1B. None of the women had any history of immunosupression or diethylstilbestrol exposure.

Vaginal intraepithelial neoplasia is a rare disorder that, in most instances, will regress after initial treatment. VAIN lesions not associated with CIN or VIN tended to show a higher rate of spontaneous regression (91%) than...
VAIN lesions associated with CIN or VIN (67%) [3]. However, patients with VAIN require careful monitoring because of the risk of recurrence and even progression to invasion [3, 4]. Risk factors for recurrence of VAIN are multifocality, association with anogenital neoplastic syndrome, histologic grade, immunosuppression and treatment modality [3, 4, 5, 30]. In our study three women treated for VAIN 3 recurred after initial treatment. None of the women in our study progressed to invasive vaginal cancer during a mean follow-up of 46.2 months.

The choice of treatment modality for patients with VAIN was influenced by the number of lesions, location of lesions, length of vagina, sexual activity, previous radiation therapy, previous VAIN treatment, patient preference and operator experience [5, 11]. Multifocal lesions are more difficult to treat because some lesions can be missed during treatment [4, 5, 12].

LEEP for VAIN lesions has been proposed with excellent results in selected groups of patients [5, 12, 13, 14]. There are potential advantages of LEEP for treating VAIN lesions. These include: low cost of equipment, avoidance of operating room, avoidance of general anaesthesia, limited tissue damage, provision of a specimen, reduced bleeding and discomfort [12, 13, 14]. LEEP may be more accurate than laser CO2 in uncovering foci of reduced bleeding and discomfort [12, 13, 14]. LEEP may also provide a specimen, limited tissue damage, provision of a specimen, and rectovaginal fistulae [12, 13, 14, 31, 32]. In our study all tissue specimens had free surgical margins. The operating time ranged from 10-20 min depending on multifocal and extent of the lesion. We believe that every gynaecologist is capable of performing LEEP on VAIN after 10-15 supervised applications with a high index of confidence [12].

There are potential complications of LEEP for treating VAIN lesions. These include: bleeding, infection, vaginal perforation, bladder injury, rectal injury, vesicovaginal and rectovaginal fistulae [12, 13, 14, 31, 32]. In our study population there were no complications. Only a few cases had spot bleeding during the operation. The newly formed vaginal epithelium, after a mean period of five weeks, presents excellent topography. None of the women complained about post-treatment sexual dysfunction.

It is clear that current treatments for VAIN are suboptimal and continue to represent a clinical challenge. The best approach is individualized management based on clinical presentation, extent of disease and patient preference [12]. LEEP may constitute a valuable excisional method for the treatment of VAIN in cases with a history of cervical cancer. It provides an interpretable specimen of the whole lesion within a few minutes [12, 33]. The procedure needs a short period of training and has low cost [12, 33].

References


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Cervical conization - treatment for cervical intraepithelial neoplasia and carcinoma in situ

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Summary

Purpose: Cone biopsy is the best treatment for high-grade premalignant cervical changes. Cervical intraepithelial changes do not show any clinical picture until the process develops into carcinoma. Method: This retrospective study included 395 women who underwent conization at Gynecology and Obstetrics Clinic “Narodni front” during 2009. The chi-square test was used for comparing results. Results: Pathohistological findings from biopsy and conization were identical in 40.50% of patients, in 10.13%, the conization finding was more severe than the biopsy finding, while in 49.37% less severe than the biopsy finding. Resection margins status analysis showed that 12.66% of cones were positive. Comparison between cones with positive margins and operative techniques did not show any statistically significant difference; 64% of women with positive margins were over the age of 35. Conclusion: Operative conization techniques are equally represented. However in women over the age of 40 scalpel excision methods are recommended. In women over the age of 45 there is a statistically significant increase in the risk for positive resection margin with CIN3 and glandular lesions.

Key words: Biopsy; Conization; Cytology.

Introduction

Anatomic accessibility of the cervix enables us to detect all changes from the initial to the malignant stage. One of the indispensable issues in contemporary gynecologic oncology is early diagnosis of cervix cancer, the second-most frequent carcinoma in the female population [1]. The most significant risk factors for the initial occurrence of premalignant and malignant changes in the cervix are the human papilloma viruses (HPV), which are transmitted through sexual contact [2, 3]. Regular routine examinations and early detection of cervical intraepithelial changes are considered to be very important since those changes do not show any clinical image until the process progresses into invasive cancer [4, 5]. HPV identification, exfoliative cytology and colposcopy are irreplaceable non-invasive methods in the diagnosis of cervical changes [6, 7]. The above-mentioned non-invasive methods are complementary and in line with with biopsy; they represent a triad which is sufficient enough to establish diagnosis with certainty [4, 7, 8]. Cervical biopsy is performed in the case of suspicious colposcopic and cytological findings. For a well established diagnosis it is important that target biopsy in the so-called transformation zone is always performed under the control of a colposcope. This means that the cone specimen should contain atypically changed tissue (metaplasia zone), squamous and cylindrical epithelium as well as cervical stroma. CIN (cervical intraepithelial neoplasia) represents a pre-stage of invasive planocellular cancer [8]. In case of negative HPV findings, changes in CIN 1 (low grade CIN) are only monitored. However, if oncogenic HPV types are detected, then the change should be removed by one of the destructive techniques, most frequently by laser vaporization or electroscautery. CIN 2 (cervical intraepithelial neoplasia) and CIN 3 (high-grade squamous intraepithelial lesion) are treated by one of the excision techniques: scalpel conization - cold knife technique (SCCKT), scalpel conization with thermocauterization (SCT), CO₂ laser conization, loop diathermia by radiosurgical knife - LEEP (loop electrosurgical excision procedure) or LLETZ (large loop excision of the transformation zone). Conization is also performed in the case of recidivism of CIN 1 lesions as well as in the case of initial cancer provided that lymphatic and vascular zones in the cervical stroma are not affected in younger women in order to preserve their fertility [9]. The aim of the paper was to analyze the relation between the pathohistological findings obtained by cervical biopsy and the results of examination of cervical cone specimens in the same patients. Another aim was to evaluate different methods in the diagnosis and treatment of cervical intraepithelial neoplasia, i.e., determination of similarities between cytological findings, colposcopic image and histological result. A possible solution to the dilemma concerning the choice of operative technique in the treatment of high-grade premalignant cervical changes was the final aim of this work.

Material and Methods

The study included 395 patients who underwent conization at the Gynecology and Obstetrics Clinic “Narodni front” in 2009. Conization was performed by using one of the four excision techniques: cold knife, scalpel excision, CO₂ laser, and loop diathermia. Prior to conization, the Papanicolau cytological smear test, colposcopy and cervical target biopsy were performed in all patients. Procedures and devices that are regularly applied at the clinic were used for the above-stated diagnostic
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procedures. Adequate statistical methods were used for statistical data processing. The chi-square test ($p < 0.05$) was used for statistical analysis.

Results

Analysis included 395 patients at the age of 36 on average, with standard deviation age ± 9. The ratio of biopsy to conization pathohistological findings is shown in Table 1 and Figure 1. The findings were identical in 40.5%; in 10.13% conization findings were more severe than biopsy findings and in 49.37% they were less severe compared to biopsy findings (Table 1, Figure 1). By comparative analysis of cytological Papanicolau smears and pathohistological (biopsy) findings of tested patients, we confirmed that the cytological test showed high sensitivity (91.67% of women with suspicious and positive cytological findings had changes in various CIN grades or cancer) in pathohistological findings (Table 2). The ratio of operative technique to correspondence of biopsy with conization findings is shown in Figure 2. The most corresponding results were obtained by the cold knife method of conization. Calculation of the chi-square test resulted in a statistically significant difference ($p < 0.05$) in similarities of results obtained by the cold knife sawing technique to those obtained by laser and radiosurgical knife. The ratio of operative technique and cones with positive resection margins is shown in the Figure 3; 12.66% of the cones were positive. Comparisons between the number of cones with positive resection margins and operative techniques did not give any statistically important difference which is significant for further comparison. In several cases pathologists were not able to determine the status of the resection margin due to a higher grade thermal damage of the examined tissue. By analysis of the cone specimens with positive resection margins per age group, it was determined that 32 women (64%) with positive cone margins were over the age of 35. The percentage of conizations which were not actually indicated (minimum CIN 2) was 6.08%. The percentage of microinvasive cancers (Ca micro) detected by conization was 4.56% while the percentage of invasive cancer (Ca invas) was 2.03%.

Discussion

Cold knife conization gives more precise histological results than target biopsy (punch biopsy), but on the other hand, it also represents a more serious and more complicated method with less inconvenience for the patient. Until the appearance of more recent methods, conization was an operative procedure conducted only in hospital conditions, in an operating room under general anesthesia and with the use of surgical suturing material. The risk from anesthesia is small, but it still exists. Complications due to conization include hemorrhage, infection and uterine perforation. Late complications of conization
include cervical stenosis or incompetence which may result in infertility [10]. The advantages of biopsy are: no hospitalization required, fast diagnosis, less serious hemorrhage and fewer complications. They are a few types of biopsy: (single punch), multiple, from the selected site, and colposcope-guided target biopsy [11]. A dilemma concerning whether to perform trial biopsy first, and then, upon obtaining its results, to do the conization, is as old as these methods. There were three different opinions in the past. One suggested that in the case of suspicious cytological and colposcopic findings conization should be immediately performed [12]. The other extreme opinion advocated performing multiple repeated biopsies [11]. A compromised view speaks in favor of trial target biopsy as an initial test followed by conization in selected cases [13]. Our results support the moderate opinion. The percentage of our patients in which conizations were performed without any real indication (CIN2 at least) was 6.08%. This percentage is much lower than in reports formed without any real indication (CIN2 at least) was 16%, and with LEEP/LLETZ, it was 38% [17]. Comparisons between the number of cones with positive resection margins and operative techniques did not show any statistically significant difference which is relevant for any further comparisons. In several cases, the pathologists were not able to determine the status of the resection margin due to a higher grade of thermal damage of the examined tissue. Although the status of the resection margin is similar in all the applied operative techniques, the percentage of positive resection margins is still slightly lower in cone specimens obtained by scalpel in women over the age of 40. A great number of women over the age of 40 undergo menopause [19-22]. As a result, the squamocolumnar junction (SCJ) is retreated into the cervical canal together with the lesions which are mostly found in the transformation zone. To perform a complete excision of a cervical lesion, a deeper incision is required. It is not easy for a surgeon to control the depth of excision. However, it is easier to visualize and determine the depth in cases where a scalpel is used. The significant differences in the volume and depth of cone specimens obtained by scalpel compared to the ones obtained by laser and radiosurgical knife were reported. In our research, 64% women with positive resection margins were over the age of 35, which points to the fact that classic operative techniques should be chosen even in women under the age of 40. In spite of the fact that the percentage of cone specimens with negative resection margins is still slightly lower in cone specimens obtained by scalpel over the age of 45, which was proven to be at significantly higher risk for positive resection margins with CIN 3 [20-23]. LEEP/LLETZ is an important factor for occurrence of positive resection margins in women over age 45.

### Table 1. — Correlation of pathohistological findings of biopsy and conization.

<table>
<thead>
<tr>
<th>Conization biopsy</th>
<th>Cervicitis</th>
<th>CIN 1</th>
<th>CIN 2</th>
<th>CIN 3/AIS</th>
<th>CA micro</th>
<th>CA invas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervicitis</td>
<td>11</td>
<td>7</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>CIN 1</td>
<td>7</td>
<td>23</td>
<td>9</td>
<td>12</td>
<td>2</td>
<td>1</td>
<td>19</td>
</tr>
<tr>
<td>CIN 2</td>
<td>20</td>
<td>53</td>
<td>53</td>
<td>36</td>
<td>13</td>
<td>6</td>
<td>66</td>
</tr>
<tr>
<td>CIN 3/AIS</td>
<td>53</td>
<td>131</td>
<td>13</td>
<td>6</td>
<td>13</td>
<td>6</td>
<td>292</td>
</tr>
<tr>
<td>CA micro</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>CA invas</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>82</td>
<td>49</td>
<td>147</td>
<td>18</td>
<td>8</td>
<td>395</td>
</tr>
</tbody>
</table>

CA: cancer.

### Table 2. — Comparative analysis of cytological and pathohistological findings.

<table>
<thead>
<tr>
<th>PH</th>
<th>Cervicitis</th>
<th>CIN 1</th>
<th>CIN 2</th>
<th>CIN 3/AIS</th>
<th>Cancer micro</th>
<th>Cancer invas</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA II</td>
<td>11</td>
<td>7</td>
<td>7</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>43</td>
</tr>
<tr>
<td>PA III</td>
<td>0</td>
<td>12</td>
<td>55</td>
<td>219</td>
<td>0</td>
<td>0</td>
<td>286</td>
</tr>
<tr>
<td>PA IV</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>53</td>
<td>5</td>
<td>1</td>
<td>63</td>
</tr>
<tr>
<td>PA V</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

PH: parathyroid hyperplasia; PA: parathyroid adenoma; CA: cancer.
According to various authors, a positive resection margin is found in 34-56% patients with CIN [20-22]. The technique itself as well as adequate choice of methods and instruments represent key factors for satisfactory excision of CIN with a negative resection margin [24, 25].

Conclusion

Cytological screening on a regular basis should be performed in all women for the purpose of prevention and early detection of cervical cancer. In cases of suspicious and positive cytological findings and HPV identification, colposcope-guided target biopsy has to be done from the most suspicious spots with minimum thermal hemostasis to prevent unnecessary tissue damage and subsequent wrong diagnostic conclusions upon performed conization. When compared, operative conization techniques are equal (cold knife technique, scalpel conization with thermocoagulation, CO₂ laser and electrosection methods), though in women over the age of 40 and in those younger in whom the SCJ is not visible, scalpel excision methods are more recommended. Complete excision of a cervical lesion requires a deeper incision. Women over the age of 45 are at a statistically higher risk for positive resection margin with CIN 3 and glandular lesions. A well selected technique together with a proper choice of methods and instruments are key factors in satisfying excision of CIN with negative resection margins. In case of good postoperative pathohistological findings, the patient should be returned to the program of regular cytological screenings.

References


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Hormonal replacement therapy in ovarian cancer survivors: a survey among Greek gynecologists

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Summary

Purpose of investigation: In this survey we evaluated the prescription attitude of Greek gynecologists towards hormone replacement therapy (HRT) for ovarian cancer survivors. Methods: An anonymous questionnaire was sent to 900 members of the Hellenic Society of Obstetrics and Gynecology presenting a hypothetical case of an ovarian cancer survivor with indications for HRT follow-up by a series of relevant questions. Results: Two hundred and ninety-eight responses were analyzed with regards to age, gender and practice setting. HRT would be prescribed by 48% of Greek gynecologists; regarding type of regimen, 60% would prescribe tibolone, 19% estrogen alone and 21% estrogen plus progestagen. In contrast, 52% of Greek gynecologists would not prescribe HRT due to the fear of ovarian cancer relapse (83%), or the development of breast cancer (6%), or both cancers (9%); among them, 21% would alternatively prescribe CNS medications, 9% SERMs, phyto-estrogens or bisphosphonates, while the remaining 70% would not prescribe anything. Conclusions: One out of two Greek gynecologists would prescribe HRT in ovarian cancer survivors. An alternative therapy, mainly CNS medications, would be suggested by 21% of the opposers.

Key words: Ovarian cancer survivors; Hormone replacement therapy; Tibolone; Estrogen therapy; Estrogen-progestogen therapy; Prescription attitude.

Introduction

Ovarian cancer ranks as the second most common gynecological cancer worldwide. It has the highest mortality rate of all gynecological malignancies. It is estimated that the overall five-year survival is only 45% [1]. Ovarian cancer occurs most commonly in post-menopausal women (median age for epithelial ovarian cancer: 63 years; range: 40-65) [2]. However, there is a significant proportion of premenopausal women suffering from this disease [1, 3].

Although the majority of patients present with advanced disease (Stages III-IV), most patients attain complete clinical remission with a combination of aggressive surgery and chemotherapy [4]. This means that either women with ovarian cancer who are already in a postmenopausal status at the time of diagnosis or premenopausal women who become menopausal artificially after the initial treatment will survive for a relatively long time and thus, many of them will experience severe menopausal symptoms. This raises the question of the use of hormone replacement therapy (HRT) in symptomatic women after the first-line treatment for ovarian cancer, given that there is no convincing evidence that implicates estrogen to act as an initiating or promoting factor for the development of epithelial ovarian cancer, which is the most frequent type of ovarian cancer [2, 5].

The aim of the present study was to evaluate the current attitude of Greek gynecologists towards the possible prescription of replacement therapy for treatment of menopausal symptoms in ovarian cancer survivors.

Materials and Methods

A questionnaire was sent to obstetricians-gynecologists registered in the Hellenic Society of Obstetrics and Gynecology. The selection was random, from the alphabetic register of the Society, and every third active registry number was picked (1st, 4th, 7th, … etc). Of a total of 2,700 obstetricians-gynecologists in Greece at the time of the survey, the questionnaire was sent to 900 colleagues. It is noted that this work was a part of a more extended questionnaire concerning cases of cervical, endometrial, ovarian and breast cancer survivors.

The questionnaire was anonymous and included demographic data about age, gender, site of practice (academic setting, National Health System hospital or private office). The second part of the questionnaire included a hypothetical case of a patient with a history of ovarian cancer.

The following case was presented: a 52-year-old female Caucasian, para 2, was subjected at age 49 (premenopausal) to total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy because of ovarian cystadenocarcinoma FIGO Ia, grade 1. Clinical, laboratory and imaging follow-up until today (3 years) has been negative for any sign of recurrence.

The patient is complaining about menopausal symptoms (hot flushes, night sweats, anxiety, vaginal dryness, loss of libido etc), while the bone density digital radiography revealed beginning osteoporosis.

The gynecologists were asked whether (1) they would prescribe HRT (closed answer, yes/no), (2) if yes, which regimen they would prefer between estrogen alone, estrogen/progestogen combination or tibolone, (3) if no, why (open answer) and (4) if no, which alternative therapy they would suggest (open answer). The χ² test using SPSS for Windows version 11 (SPSS Inc, IL, USA) was used for statistical analysis.
Results

We obtained in total 303 responses (response rate 33%) with 298 valid answers.

Regarding the site of practice, 11% (34/298) worked in an academic setting, 24% (70/298) in a NHS hospital and 65% (194/298) in a private office. Eighty-one percent (243/298) were male and 19% (55/298) were female. Finally, 49% (146/298) of the responders were younger than 48 years and named “younger gynecologists” and 51% (152/298) were characterized as “older gynecologists”. The cut-off point was chosen because it was the median age of our responders.

In the first question “would you prescribe HRT in an ovarian cancer survivor?” in total 144 (48%) answered “yes” and 154 (52%) “no”. Regarding age and practice setting, there were statistically significant differences. Gynecologists working in an academic setting answered “yes” in greater percentage (74%) than their colleagues working in a NHS hospital (36%) as well as in a private setting (49%) \(p < 0.001\). As far as age, “younger gynecologists” were willing to prescribe HRT to a greater extent (53%) than their “older colleagues” (38%) \(p < 0.001\). Finally, there was no significant difference between male and female gynecologists.

Regarding the second question “if yes, which hormonal regimen would you prefer?” 86 doctors (60%) would prescribe tibolone, 31 (21%) estrogen plus progestogen and 27 (19%) estrogen alone. There were no significant differences regarding age, gender and practice setting.

In the third question “if no, why” among those not willing to prescribe HRT (154), 128 (83%) would not prescribe HRT because of the fear of recurrence of the same cancer, nine (6%) because of the fear of development of breast cancer, six (4%) of both cancers and 11 (7%) did not answer. There were no significant differences regarding age, gender or practice setting.

In the fourth question “if not, which alternative treatment would you suggest?”, the majority (105/154 - 70%) of gynecologists were not willing to prescribe any medication at all, 33 (21%) would prescribe CNS medications and the remaining 13 (9%) SERMs, phytoestrogens or bisphosphonates. There was no significant difference regarding age and gender. As far as practicing status, 33% of academic hospital colleagues were unwilling to prescribe any medication vs 89% of NHS hospital colleagues and 66% of private – working gynecologists \(p < 0.001\).

Discussion

On average, women in Western countries live about one-third of their lives in the menopausal state [6]. Consequently, the question of hormonal replacement therapy (HRT) is justified due to the well established positive effects on vasomotor symptoms and the prevention of osteoporosis. These symptoms are being noticed in patients who have been treated for ovarian cancer and experience a regression of their disease. There is a debate still ongoing about the connection of estrogens and carcinogenesis in the ovary, but there are no consistent data linking duration of HRT with development of epithelial ovarian cancer [7]. These issues are related with the possibility of HRT in ovarian cancer survivors. The expected benefit from the treatment should be calculated and individualized.

In the international literature, there is a sufficient number of reports, but after careful evaluation, as documented in a review by Hopkins et al., only three of the published papers provide important data. More recently, a Swedish study by Mascarenhas et al. [8] also contributed to the current discussion. All other studies are either non-randomized or are reviews.

As shown, the attitude of gynecologists in Greece towards the prescription of HRT in an ovarian cancer survivor is shared. Forty-eight percent of all gynecologists would support a hormonal treatment, while 52% are not willing to prescribe substitution therapy. It seems that physicians in academic settings (74%) and younger colleagues (59%) are less afraid to prescribe HRT in this subset of patients. A similar survey in the literature could not be found in order to have our results compared.

Regarding our second question about the kind of HRT which could be given to an ovarian cancer survivor with menopausal symptoms, there are no available data considering comparison of different HRT regimens given after the diagnosis of ovarian cancer. As a result, it is not possible to select a specific kind of treatment. Only one recent study about the use of tibolone was available at the time of our search. Lee et al., reviewed retrospectively 42 patients who received tibolone after surgical treatment for ovarian cancer and 33 non-users [9]. The authors concluded that there were no detrimental effects in the two groups with respect to progression-free survival (60% vs 61.5%, respectively; \(p = 0.92\)) or overall survival \((p = 0.30\), an indication for the possible safe use of tibolone in those patients. At least this study justifies the choice of the majority of gynecologists willing to prescribe some medication in our survey (overall 60%) to prescribe tibolone for menopausal symptoms.

In an attempt to explain the study results, one should raise the question why Greek gynecologists are reluctant to prescribe HRT in ovarian cancer survivors. The answer appears to be simple. There is a diffuse fear that - mainly - estrogen could eventually increase the possibility of recurrence. Our results regarding the open question No. 3, show that overall 83% of the gynecologists who would not prescribe HRT, express this fear. Although gynecologists in University hospitals are afraid to a lesser extent of a recurrence, the majority of them (56%) avoided giving a precise answer for the reason of not prescribing HRT.

However, the available literature does not justify this fear. The older retrospective study by Eeles et al. resulted in a risk of relapse in the HRT group of 0.90 (95% CI 0.52-1.54) [10], while in the study by Guidozzi and Daponte, 54% recurrences were observed in the estrogen group, compared to 62% in the second group, but this difference was not statistically significant [11].
Furthermore, in a study by Ursic-Vrscaj et al., relapse was confirmed in five (21%) patients in the HRT group and in 15 (31%) in the non-HRT group [12]. Again, this difference was not statistically significant.

Finally, in the recent report of Mascarenhas et al., based on the follow-up of 649 women diagnosed with epithelial ovarian cancer who participated previously in a nationwide control study, unfortunately ovarian cancer recurrence was not evaluated [8].

Few data are available on the use of alternative therapies. Only a small percentage (overall 1%-4%) of the gynecologists who participated in our survey would prescribe SERMs or bisphosphonates for the treatment of menopausal symptoms and beginning osteoporosis, obviously only for the osteoporotic part. Although the importance of increased occurrence of hot flushes in postmenopausal women seems to be overestimated [13], it is known that there is no relief of those symptoms with use of SERMs. On the other hand, raloxifene although not evaluated in ovarian cancer survivors, seems not to be associated with an increased risk for ovarian cancer in postmenopausal women without cancer, as was shown in an analysis with data from seven randomized, placebo-controlled trials of raloxifene (N = 9837) [14].

According to our survey, some gynecologists would prescribe phytoestrogens for the relief of hypoestrogenic symptoms. The at least partial effect of phytoestrogens on hot flushes when combined with life style changes has been established in several studies [15]. Additionally, an inhibitory effect of isoflavonoids on ovarian cancer cell lines has also been documented although clinical data are not available [16]. However, data about phytoestrogen use in ovarian cancer survivors are missing. Recently, a case report about prolonged stabilization of platinum-resistant ovarian cancer in a patient consuming unfermented soy beverage could be an indicator about the possible role of alternative therapies in such patients [17].

As mentioned in the results, the majority of gynecologists who would not prescribe HRT for the treatment of menopausal symptoms were unwilling to prescribe any medication at all. From the available data this fear is not justified, not only because there seems to be no association with the possibility of a recurrence, but also HRT does not seem to have a negative influence either on disease-free survival or overall survival. In the study of Eeles et al., there was no statistical difference in overall and disease-free survival between women receiving HRT and those who did not (despite the survival benefit after 11 years of follow-up in the HRT group, p = 0.07) [10]. The authors concluded that there is no evidence from their study that ovarian cancer survivors should be denied HRT.

Similarly, in the study of Guidozi and Daponte, the overall survival was 44 months in the estrogen group and 34 in the non-estrogen group and the median disease-free survival was 34 vs 27 months, respectively [11]. Again, these differences were not significant.

In the study of Ursic-Vrscaj et al., the estimated risk of death of invasive ovarian cancer in patients receiving HRT after the first operation was 0.90 (OR = 0.90; 95% CI 0.24-5.08) when corrected for known risk factors as age, stage of disease, differentiation, type of surgery and residual disease [12]. Another important parameter of the latter study was the follow-up of the severity of menopausal symptoms by using a modified Kupperman index. In all HRT-users the index diminished from ≥ 35 to ≤ 19. Although there are more reliable and valid scales for menopausal research available today, the assessment of the effects of menopause on quality of life is precious because it is the only study which evaluated this parameter [6].

Finally, the results of the recent study of Mascarenhas et al. are even more positive [8]. It was shown that ovarian cancer survivors who received HRT after the diagnosis were at a significantly lower risk of dying compared to never users (hazard ratio = 0.57; 95% CI 0.42-0.78) after adjustment for age, tumor stage and differentiation. Although the authors cannot rule out a subtle selection process, these results are very promising.

Finally, the limitations of our study should be taken into consideration; the questionnaire was sent only to a part of all Greek gynecologists and the response rate was not high. However, we believe that the randomization (every third registered member was picked) of the sample, eliminates the strength of the above limitations.

Conclusions

Taking into account all available data from the few related studies, it seems that HRT is a secure option in symptomatic ovarian cancer survivors, but the data are limited. According to our survey, this knowledge is being accepted by approximately half of the Greek gynecologists. The majority of those gynecologists would suggest a therapy with tibolone which is considered to be safe in patients already experiencing a malignant disease and especially ovarian cancer. However, half of the gynecologists would not prescribe HRT, mainly because of the fear of recurrence of the disease. An interesting finding is that these gynecologists are unwilling to prescribe any alternative therapy for the relief of the patients’ symptoms.

References

Hormonal replacement therapy in ovarian cancer survivors: a survey among Greek gynecologists


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Activity of pegylated liposomal doxorubicin for extragenital mullerian adenosarcoma with sarcomatous overgrowth: a case report and a review of the literature

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Summary

A 47-year-old woman was diagnosed with extragenital mullerian adenosarcoma with sarcomatous overgrowth. One month after her initial surgery, the patient developed pelvic recurrence, which was completely excised by surgery. However, one month later, the patient developed further recurrences in her pelvis and upper abdomen. A clinical complete response was achieved with three cycles of liposomal doxorubicin and is currently clinically free of disease. So far, including the present case, 23 cases of extragenital mullerian adenosarcoma have been reported in the English literature. Because of the rarity of the reported cases, there are no treatment guidelines based on a good level of evidence. In the current report, through a literature review, we provide information on the activity of pegylated liposomal doxorubicin for extragenital mullerian adenosarcoma with sarcomatous overgrowth.

Key words: Extragenital adenosarcoma; Sarcomatous overgrowth; Endometriosis; Liposomal doxorubicin.

Introduction

Mullerian adenosarcoma, a variant of mixed mesodermal tumor (MMT), is a rare neoplasm composed of benign epithelial and malignant stromal components [1]. Its usual site of origin is the endometrium; however, it can originate from various organs such as the uterine cervix, vagina, ovary, bladder, colon, pelvis, and peritoneum [2-8]. Extragenital sites of origin and sarcomatous overgrowth are reported to be prognostic factors associated with aggressive clinical behavior [4-8]. We herein describe a case of extragenital mullerian adenosarcoma with sarcomatous overgrowth which showed a clinical complete response to liposomal doxorubicin. Moreover, through a literature review, we provide information on the clinical management of extragenital mullerian adenosarcoma with sarcomatous overgrowth.

Case Report

A 47-year-old nulligravida Japanese woman, who had been regularly followed up for her subserosal uterine myoma in our department, presented with acute lower abdominal pain. She had been diagnosed six years before with infiltrating ductal breast carcinoma and was treated with surgery followed by five years of tamoxifen therapy. On evaluation, a transvaginal sonography (TVS) revealed a 14 × 8 cm pedunculated subserosal myoma. Although the size of the myoma had not changed, given the fact that the painful area was in the same area as the subserosal myoma, our preoperative diagnosis was degeneration or torsion of the pedunculated subserosal myoma.

Her laboratory findings were unremarkable except for a raised serum LDH level (993 IU/ml). Exploratory laparotomy revealed torsion of the pedunculated subserosal uterine myoma and a 3 cm tan-yellow hemorrhagic mass adherent to the left pelvic sidewall. Her ovaries, fallopian tubes, and upper abdomen were grossly normal. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, and a resection of the pelvic tumor were performed. No gross residual disease was detected after the completion of surgery. Her serum LDH levels were markedly decreased after surgery (Figure 1). The final pathological diagnosis for the pelvic tumor was adenosarcoma with sarcomatous overgrowth arising from a background of endometriosis in the pelvis (Figure 2). Her uterus demonstrated benign leiomyoma, but was negative for malignant tumor.

Four weeks after her initial surgery, TVS examination and pelvic magnetic resonance imaging (MRI) revealed an 8 cm recurrent tumor in her right pelvis. Interestingly, as shown in Figure 1, her serum LDH levels were markedly elevated during the development of the recurrence. Salvage surgery, which was performed two months after the initial surgery, revealed a recurrent tumor extending from the posterior cul-de-sac through the left pelvic sidewall. The tumors were completely excised, and the pathologic diagnosis was adenosarcoma with sarcomatous overgrowth.

One month after her second surgery, a computed tomography (CT) scan of the abdomen and pelvis demonstrated new lesions in her pelvis and upper abdomen between her descending aorta and left kidney. She was then treated with salvage chemotherapy: 40 mg/m² of liposomal doxorubicin was administered intravenously every four weeks. A clinical complete response was achieved with three cycles of liposomal doxorubicin. Her serum level of LDH significantly decreased and returned to the normal range after two cycles of chemotherapy (Figure 1). She has completed another two cycles of chemotherapy and is currently clinically free of disease.
Table 1. — Summary of reported cases of extragenital adenosarcoma.

<table>
<thead>
<tr>
<th>Article (reference)</th>
<th>Age</th>
<th>Location of primary tumor</th>
<th>Associated endometriosis</th>
<th>Sarcomatous overgrowth</th>
<th>Initial treatment</th>
<th>Adjuvant therapy</th>
<th>Recurrence</th>
<th>Salvage treatment</th>
<th>Follow-up results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douglas et al. [8]</td>
<td>18</td>
<td>Pouch of Douglas</td>
<td>NA</td>
<td>NA</td>
<td>Chemotherapy with MTX</td>
<td>No</td>
<td>Persistent</td>
<td>No</td>
<td>DOD 1 month after initial presentation.</td>
</tr>
<tr>
<td>Kao et al. [9]</td>
<td>42</td>
<td>Round ligament</td>
<td>NA</td>
<td>NA</td>
<td>Surgery (suboptimal)</td>
<td>Radiotherapy</td>
<td>Yes</td>
<td>No</td>
<td>DOD 10 mths after surgery.</td>
</tr>
<tr>
<td>Clement et al. [2]</td>
<td>45</td>
<td>Pelvic wall</td>
<td>Yes</td>
<td>NA</td>
<td>Surgery (suboptimal)</td>
<td>Radiotherapy</td>
<td>Yes</td>
<td>No</td>
<td>DOD 9 mths.</td>
</tr>
<tr>
<td>Russell et al. [10]</td>
<td>29</td>
<td>Broad ligament</td>
<td>No</td>
<td>NA</td>
<td>Surgery (optimal)</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>DOD 18 mths after the initial surgery.</td>
</tr>
<tr>
<td>Roman et al. [12]</td>
<td>55</td>
<td>Pelvic peritoneum</td>
<td>Yes</td>
<td>NA</td>
<td>Surgery (optimal)</td>
<td>Radiotherapy</td>
<td>Yes</td>
<td>Surgery followed by TAM or MPA, chemotherapy with Cis+Ifos+Dox.</td>
<td>DOD 120 mths after the initial surgery.</td>
</tr>
<tr>
<td>N’Senda et al. [13]</td>
<td>54</td>
<td>Liver</td>
<td>Yes</td>
<td>NA</td>
<td>Surgery (optimal)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NED 24 mths after surgery.</td>
</tr>
<tr>
<td>Yantiss et al. [14]</td>
<td>36</td>
<td>Colon</td>
<td>Yes</td>
<td>NA</td>
<td>Surgery (optimal)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NED 24 mths after surgery.</td>
</tr>
<tr>
<td>Visvalingam et al. [16]</td>
<td>50</td>
<td>Omentum (optimal)</td>
<td>NA</td>
<td>NA</td>
<td>Surgery (optimal)</td>
<td>No</td>
<td>Yes</td>
<td>Surgery followed by MPA</td>
<td>DOD 16 mths after the initial surgery.</td>
</tr>
<tr>
<td>Hines et al. [17]</td>
<td>43</td>
<td>Pouch of Douglas</td>
<td>Yes</td>
<td>NA</td>
<td>Surgery (suboptimal)</td>
<td>MPA</td>
<td>No</td>
<td>No</td>
<td>NED 10 mths after surgery.</td>
</tr>
<tr>
<td>Chang et al. [18]</td>
<td>37</td>
<td>Pouch of Douglas</td>
<td>Yes</td>
<td>NA</td>
<td>Surgery (suboptimal)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NED 36 mths after surgery.</td>
</tr>
<tr>
<td>Milam et al. [19]</td>
<td>47</td>
<td>Peritoneum</td>
<td>Yes</td>
<td>NA</td>
<td>Surgery (optimal)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>NED 12 mths after surgery.</td>
</tr>
<tr>
<td>Ostor et al. [20]</td>
<td>49</td>
<td>Pouch of Douglas</td>
<td>No</td>
<td>NA</td>
<td>Surgery (optimal)</td>
<td>Radiotherapy followed by MPA</td>
<td>Yes</td>
<td>Surgery followed by chemotherapy with Cis+Ifos</td>
<td>AWD 18 mths after the initial surgery.</td>
</tr>
<tr>
<td>De Jonge et al. [21]</td>
<td>16</td>
<td>Pelvic peritoneum</td>
<td>NA</td>
<td>Yes</td>
<td>Surgery (optimal)</td>
<td>Chemotherapy with 8 cycles of Dox+Ifos followed by 3 cycles of Cis+Ifos+Carbo</td>
<td>No</td>
<td>Surgery followed by chemotherapy with Cis+Ifos+Dox</td>
<td>NED 57 mths after the last chemotherapy.</td>
</tr>
<tr>
<td>Dincer et al. [22]</td>
<td>50</td>
<td>Pelvic peritoneum</td>
<td>Yes</td>
<td>Yes</td>
<td>Surgery (optimal)</td>
<td>Antiangiogenic agent</td>
<td>Persistent</td>
<td>No</td>
<td>AWD</td>
</tr>
<tr>
<td>Huang et al. [5]</td>
<td>41</td>
<td>Pelvic peritoneum</td>
<td>Yes</td>
<td>Yes</td>
<td>Surgery (optimal)</td>
<td>Chemotherapy with Ifos+Cis</td>
<td>Yes</td>
<td>Surgery followed by chemotherapy with PLD</td>
<td>NED 18 mths after the last chemotherapy.</td>
</tr>
<tr>
<td>Present case</td>
<td>43</td>
<td>Pelvic peritoneum</td>
<td>Yes</td>
<td>Yes</td>
<td>Surgery (optimal)</td>
<td>No</td>
<td>Yes</td>
<td>Surgery followed by chemotherapy with PLD</td>
<td>NED 3 mths after the last chemotherapy.</td>
</tr>
</tbody>
</table>

NA, not available; NED, no evidence of disease; AWD, alive without disease; DOD, died of disease; DOU, died of unknown reason; MTX, methotrexate; Dox, doxorubicin; Carbo, carboplatin; Ifos, ifosphamide; Cis, cisplatin; Etopo, etoposide; PLD, pegylated liposomal doxorubicin.
Discussion

In 1974, Clement and Scully first described Mullerian adenosarcoma as an uncommon mixed mesodermal tumor (MMT) composed of benign epithelial and malignant stromal components [1]. Its usual site of origin is the endometrium; however, it can originate from various organs such as the uterine cervix, vagina, ovary, bladder, colon, pelvis, and peritoneum [2-8].

Extragenital Mullerian adenosarcoma is histologically similar to its uterine counterpart, however, there are marked clinical differences between the extragenital cases and cases of uterine origin [3-8]. It has been reported that extrauterine Mullerian adenosarcomas occur in younger women and are more aggressive than uterine tumors. A previous report suggested that recurrence occurs in approximately 25% of cases with uterine adenosarcoma and that approximately 10% of patients die of the disease. In contrast, in patients with extragenital adenosarcoma, recurrence developed in over 65% of cases, and was associated with a mortality rate of approximately 40% [5, 6].

As shown in Table 1, including our case, 23 extragenital Mullerian adenosarcomas for which detailed treatment and survival data are available have been reported [2, 5-22]. The median age of these patients was 45.

The prognostic factors in patients with extragenital Mullerian adenosarcoma have not been fully investigated; however, concurrent endometriosis might be a prognostic factor in these patients. It has previously been reported that adenosarcoma is the second most common gynecological malignancy (after clear cell carcinoma of the ovary) in patients with endometriosis [23]. In a recent review of 18 cases of extragenital adenosarcoma, it was demonstrated that recurrence-free survival was 88% in patients with endometriosis-associated disease compared with 17% in non-endometriosis-associated extragenital sarcoma patients, which may indicate that concurrent endometriosis is a favorable prognostic factor in patients with extragenital adenosarcoma [5]. As shown in Table 1, of the 23 extragenital Mullerian adenosarcomas, 13 had concurrent endometriosis. Consistent with a previous report [5], the median and mean survival in patients who had concurrent endometriosis was 24 months and 30 months, respectively, which is longer than that observed in patients without concurrent endometriosis (12 months and 15.8 months, respectively).

Sarcomatous overgrowth in uterine adenosarcoma was first described in 1989 by Clement and was defined as an adenosarcoma that exhibits a high-grade sarcomatous component constituting at least 25% of the tumor [4]. In contrast to the good prognosis observed in patients with uterine adenosarcoma without sarcomatous overgrowth, this variant of adenosarcoma is associated with clinically aggressive behavior [2-8]. However, because of the rarity of the reported cases, its prognostic significance in patients with extragenital adenosarcoma remains unclear.

As shown in Table 1, 22 out of these 23 extra genital Mullerian adenosarcomas were initially treated with surgery. Of the 16 patients initially treated with optimal surgery, ten patients were recurrence free. In contrast, only one out of six patients who had undergone suboptimal surgery was alive without disease, indicating that optimal surgical resection may be the most important primary treatment for extrauterine Mullerian adenosarcoma. Radiotherapy, chemotherapy, or hormonal therapy has been used as an adjuvant therapy or as a component of salvage treatments; however, due to the rarity of reported cases, the clinical value of these treatments remains unclear.

Including our case, we found five extragenital Mullerian adenosarcomas with sarcomatous overgrowth [5, 6, 21, 22]. Treatment failures have been observed in 60% (3 out of 5) of these patients, which is similar to 50% (9 out of 18) observed in patients without sarcomatous overgrowth. Of the four patients whose tumors were optimally excised at initial surgery, two were alive without developing recurrence. Various adjuvant chemotherapies with or without radiotherapy have been added following initial surgery for four out of these five patients with sarcomatous overgrowth [5, 6, 21, 22]. For recurrent or persistent disease, salvage treatments including surgery, chemotherapy, or an anti-angiogenic agent have been tried. However, due to the rarity of reported cases, the clinical value of these treatments remains unclear.

In the present case, we employed liposomal doxorubicin for the treatment of recurrent tumors. The administration of 40 mg/m² liposomal doxorubicin every four weeks was well tolerated, and a clinical complete response was achieved with three cycles of chemotherapy. So far, including the present case, only three cases of Mullerian adenosarcoma treated with liposomal doxorubicin have been reported in the English literature [5, 24]. Two involved extragenital Mullerian adenosarcoma with sarcomatous overgrowth which showed a complete response to liposomal doxorubicin (Table 1), and the other involved uterine adenocarcinoma with sarcomatous overgrowth which showed a partial response to this agent [24]. Due to the small number of patients, it is difficult to draw a clinical conclusion; however, these cases may indicate that liposomal doxorubicin is a useful agent in
patients with Mullerian adenosarcomas, especially for extragenital Mullerian adenosarcoma with sarcomatous overgrowth.

Interestingly, in our case, the serum level of LDH correlated well with the clinical course (Figure 1), was markedly elevated during the progression of the recurrent tumors, and then normalized in response to treatment with liposomal doxorubicin. The value of serum LDH as a tumor marker has been demonstrated in patients with Ewing’s sarcoma [25]. The clinical value of LDH in patients with adenosarcoma has never been investigated; however, our clinical data from the present case may suggest that the serum LDH level can be used as a tumor marker in the clinical management of extragenital adenosarcoma with sarcomatous overgrowth.

Conclusion

We have presented a case of extragenital adenosarcoma with sarcomatous overgrowth, which showed a clinical complete response to liposomal doxorubicin. This agent may be a useful for the treatment of extragenital adenosarcoma. Given the rarity of extragenital adenosarcoma, we believe that it is of great importance to report even individual cases so that an optimal treatment can be established.

References


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An extremely rare presentation of relapse in endometrioid endometrial adenocarcinoma: isolated metastases to the tibia and humerus. Case report and review of the literature

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Summary

In endometrial carcinoma patients, metastases to bones are rare and isolated metastases to extremities are extremely rare. We describe the case of a 59-year-old patient who underwent surgery followed by adjuvant radiotherapy due to endometrioid endometrial adenocarcinoma (grade 2, FIGO Stage II). After intervals of nine and 18 months respectively, she was diagnosed with metastatic tumors located in the right tibia and in the left humerus. The metastases were confirmed by biopsy. Following irradiation of metastatic lesions, the relief of symptoms was observed, and the patient remains under observation. We conclude that patients presenting a history of endometrial carcinoma with chronic pain in the extremities should be carefully evaluated, because although extremely rare, the carcinoma can metastasize to bones. Treatment of bone metastasis from endometrioid endometrial carcinoma by irradiation may increase quality of life and prolong survival.

Key words: Endometrial carcinoma; Endometrioid; Relapse; Bone extremities.

Introduction

Endometrial carcinoma is the most common invasive neoplasm of the female genital tract and accounts for 7% of all invasive cancer in women. The majority of patients are diagnosed with no evidence of extrauterine spread (70-80% Stage I), which gives patients a better prognosis [1]. In more advanced disease the sites commonly affected outside the uterus are the pelvic and paraaortic lymph nodes and ovaries [2]. Distant metastases in advanced or recurrent endometrial cancer most commonly involve the lungs, liver, central nervous system and skin [2, 3]. Metastases to bones have been described only in 2-15% of patients with recurrent disease [2, 4]. In such cases, the primary tumor is usually poorly differentiated (G3), of a high stage, and indicative of recurrent disease [5]. Metastatic tumors are usually seen together with abdominopelvic recurrences and/or other organ metastases and generally are located in the axial skeleton. The most common site of osseous metastases are vertebrae, with pelvic bones, ribs and sternum being less common sites [1, 4-6]. Metastases to extremities are extremely rare and thought to result from the hematological spread of carcinoma cells [3, 5].

A review of the English literature indexed in Medline was done. By searching the items endometrial carcinoma and metastases to extremities 20 such cases were found [1-19]: 11 cases of single osseous relapses of endometrial carcinoma in the extremities (Table 1) and nine cases when metastatic tumour of the foot was the first manifestation of endometrial carcinoma (Table 2). Although local recurrences of endometrial carcinoma often occur early with evident symptoms, development of metastatic disease to the bones may cause difficulties in a prompt diagnosis.

Case Report

A 59-year-old patient presented with postmenopausal vaginal bleeding. Computed tomography (CT) scans showed an enlarged uterus and no other suspicious abdominopelvic lesions. An endometrial biopsy confirmed endometrioid endometrial adenocarcinoma. The patient was treated with total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection in January 2008. The histological diagnosis was a moderately differentiated (G2) endometrioid endometrial adenocarcinoma invading the outer half of the myometrium (> 1/2) with cervical stroma. However, the fallopian tubes and ovaries showed no signs of tumor invasion and the pelvic lymph nodes were negative. No evidence of abdominopelvic metastases was found at surgery. Her disease was classified as clinical Stage II according to FIGO 2009 staging and in the TNM classification it was pT2 N0 M0.

The patient was treated with external and intracavitary irradiation until April 2008. External pelvic irradiation was delivered to the pelvis by Co60 through four fields and a total dose of 44 Gy was given in 22 fractions. The intracavitary treatment was performed during the external irradiation using a high-dose-rate Co60 unit, with 18 Gy being delivered to the vaginal surface in three fractions.

The patient was disease-free and asymptomatic during the first six months after treatment. However in October 2008, pain and swelling of the right shin appeared. After a month, bone
scintigraphy demonstrated hot spots in the right tibia and in the left humerus (Figure 1). A biopsy of the right shin tumour was taken, and metastatic carcinoma was confirmed (Figure 2). The patient underwent irradiation by Co60 up to a total dose of 8 Gy, and received chemotherapy AP1 (doxorubicin and cisplatin). Treatment ended in April 2009 and relief of symptoms was observed.

In June 2009 pain in the left arm appeared. The X-ray picture showed metastasis to the head of the left humerus (Figure 3), which was later confirmed by biopsy. After irradiation by Co60 until a total dose of 20 Gy, relief of symptoms was observed. However, in February 2010, pain and swelling returned – this time in the left arm. In CT, massive neoplastic infiltration was visualized involving the head of the humerus and the soft tissues of the left arm with regional nodal involvement. The patient was disqualified from surgery and treated by palliative irradiation by Co60 until a total dose of 20 Gy in the tumour area. The treatment was well tolerated, relief of symptoms was observed and the patient remains under observation. During observation from surgery from January 2008 to July 2010, no another locations of metastases were detected.

### Table 1. — Isolated metastasis to the bone extremities as the presentation of relapse in endometrial carcinoma patients – review of the literature.

<table>
<thead>
<tr>
<th>Author/year (references)</th>
<th>Age (years)</th>
<th>Histology</th>
<th>Stage / Grade</th>
<th>Interval to relapse (months)</th>
<th>Bone involved</th>
<th>Other metastasis</th>
<th>Treatment</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
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<td>endometrioid</td>
<td>II / 2</td>
<td>9</td>
<td>–</td>
<td>No</td>
<td>radiotherapy</td>
<td>&gt; 29</td>
</tr>
</tbody>
</table>

Figure 1. — Whole body bone scintigraphy demonstrating hot spots in the right tibia and the left humerus.

Figure 2. — Carcinoma cells in the fine needle aspiration of the metastatic tumour of the foot – (H+E, 200x magnification).

In June 2009 pain in the left arm appeared. The X-ray picture showed metastasis to the head of the left humerus (Figure 3), which was later confirmed by biopsy. After irradiation by Co60 until a total dose of 20 Gy, relief of symptoms was observed. However, in February 2010, pain and swelling returned – this time in the left arm. In CT, massive neoplastic infiltration was visualized involving the head of the humerus and the soft tissues of the left arm with regional nodal involvement. The patient was disqualified from surgery and treated by palliative irradiation by Co60 until a total dose of 20 Gy in the tumour area. The treatment was well tolerated, relief of symptoms was observed and the patient remains under observation. During observation from surgery from January 2008 to July 2010, no another locations of metastases were detected.
An extremely rare presentation of relapse in endometrioid endometrial adenocarcinoma: isolated metastases to the tibia and etc.

Discussion

In patients with female genital tract carcinomas, despite the rarity of metastases to the extremities, clinicians must have a high index of suspicion for metastasis in patients with a history of carcinoma who present with swelling or bony tenderness [2, 4, 5, 7-14]. Since symptoms may mimic other benign conditions [2], it is important to consider bone metastasis as a possible diagnosis in patients with osseous pain which does not respond to conservative treatment [9, 10]. Appropriate imaging of suspected bone extremity metastases may include plain X-rays and radionuclide bone scans [1]. Technetium biphosphonate bone scans are extremely useful and can be positive up to 18 months before a lesion is detectable on a plain X-ray image [13]. Therefore, a biopsy should be performed in patients with suspected lesions, and who demonstrate evidence of bony destruction [2]. In the case of a confirmed isolated metastatic lesion in a bone extremity, treatment by irradiation, with or without surgery, hormones and chemotherapy, is reported as effective in most cases, and may be curative [2, 3, 6, 10, 12, 13, 15-19].

The case report presented in the previous section has three main peculiar features: 1) it demonstrates an endometrial carcinoma presenting with an osseous metastasis, which is a rare occurrence, 2) the metastatic tumours were located in the extremities, which is extremely rare, 3) the bone lesions were single bone metastases, which again, is unusual in such cases. Additionally, the case is not only the first known to us of an isolated relapse of endometrial carcinoma in the tibia but also the third case of isolated relapse of the carcinoma in the humerus (Table 1) [5,13].

Finally, patients with chronic pain in the extremities and who demonstrate evidence of bone destruction, especially presenting a history of endometrial carcinoma, should be carefully evaluated because although extremely rare, it is possible for the carcinoma to metastasize to bones. Treatment of bone metastasis from endometrioid endometrial carcinoma by irradiation may increase quality of life and prolong survival.

References


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Myofibroblastic inflammatory breast tumor and fibrosarcoma: a case report

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Introduction

An inflammatory pseudotumor is a benign lesion which can occur in any human tissue, being more frequent in young patients [1]. It is a lesion composed of spindle cells in fascicles, interspersed with cells of chronic inflammatory response, including histiocytes, lymphocytes and eosinophils [2]. Its occurrence in the breast is rare and was first reported by Pettinato et al. [3] in 1988. It presents a great variety of synonyms: plasma cell granuloma, plasma cell pseudotumor, fibroxanthomatous pseudotumor, pseudosarcomatous myofibrohistiocytic proliferation and inflammatory myofibroblastic tumor. It can be a solitary or multifocal tumor and it has a great risk of recurrence after excision, although benign. It can present regional infiltration, vascular invasions and sometimes malignant transformation (inflammatory fibrosarcoma) [2].

Inflammatory fibrosarcoma has been recognized as part of a spectrum of inflammatory myofibroblastic proliferations [4]. This report presents a rare case of inflammatory myofibroblastic breast tumor with characteristics of low-grade sarcoma.

Case Report

A 41-year-old patient was admitted with a stellate nodule of high density, poorly delimited, measuring 2.5 x 1.5 cm in the superior lateral quadrant of the left breast, classified as BIRADS-5. Ultrasound (US) showed a heterogeneous nodule with poorly defined borders and without posterior acoustic shadowing. A core biopsy was performed and the pathological examination showed proliferation of the spindle cells in dense fascicles interspersed by collagen among frequent plasmocytes, lymphocytes and eosinophils, associated with scarce typical mitosis. In the same site ten years before the patient had undergone a nodulectomy and the diagnosis was a benign filloid tumor. The patient returned with a nodule in the surgical scar at follow-up and the incisional biopsy showed a malignant filloid tumor with a sarcomatous component. A mastectomy was performed.

Discussion

An inflammatory myofibroblastic tumor is a rare disease, and there are few cases of breast involvement reported in the literature [3, 5-11]. Its diagnosis is important because it can be confounded with malignant diseases in clinical and histological examinations.

Inflammatory myofibroblastic tumor can occur in any tissue. It is more common in children and young adults, but it can occur in any sex or age. The majority occurs in the lungs and in the upper airway of young patients, in addition to other sites, such as the urinary tract, retroperitoneum, peritoneum, mesentery, pancreas, intraabdominal spaces, liver, thyroid, spleen and lymph nodes [8]. Clinically, it is a nodular circumscribed lesion which can range from 1-17 cm in diameter [3, 4, 12-14]; it is mobile with slight adhesion to the skin [9]. In mammography, it can present itself as a round nodule of very well defined limits [1, 6, 15], but in some cases it can show a nodule...
suspicious for malignancy [2], as occurred in our patient. At US a hypoechoic and homogeneous nodule is usually found [2, 6].

Initially, it was thought that this disease could be an inflammatory response to local cytokines. Then, it was named inflammatory pseudotumor [12]. However, other findings were contradictory to the purely inflammatory nature, such as local recurrence, appearance of metastasis [16], invasive regional growth, vascular invasion and the occasional malignant transformation [4, 17-19]. Few cases have been reported with vascular invasion and metastasis [16, 20]. It would probably be considered a tumor of the soft tissue with low potential for malignancy. These aggressive characteristics suggest that some inflammatory myofibroblastic tumors clonally show characteristics, with rearrangement in regions in 2p22-24 [9, 12, 17-19, 21].

Thus, they can have a more aggressive behavior, although unusual, with progression to sarcoma (“inflammatory fibrosarcoma”) [4, 9, 13]. The recurrence can occur in up to 25%, which is related to the area of the body and if the resection was complete [3, 4, 12-14].

This tumor can have a tendency to recur soon after the excision [8]. Khanafshar et al. [2] reported three cases of the disease; two with recurrence in the third month of follow-up.

At microscopy, it is composed of cells in fascicles producing a loose, edematous stroma mixed with inflammatory cells, predominantly lymphocytes and plasma cells. The presence of mitotic figures is common. Usually there is epithelial atypia or malignancy in the adjacent mammary tissue. Immunohistochemical study generally shows cellular reactivity for SMA, and focal or negative positivity for pancreatin [2, 7]. There can also be positivity for CD68, S-100 protein and actin in the spindle cells, and immunoreactivity of the macrophages for CD68, Mac 387 and S-100 protein. Lymphocytes can be from B or T cells, and polyclonal plasma cells [17]. Others, are positive for actin, vimentin and alpha-1 antitrypsin1 [5]. In our case the tumor was positive for vimentin, actin, S-100 and CD-68. The differential diagnosis includes malignant breast neoplasia, plasmocytomas, neoplastic, pseudolymphoma, mastitis of plasma cells, and benign or malignant mesenchymal neoplasms. In cases with extensive hyalinization, an amyloid tumor should be considered [3, 9].

Inflammatory pseudotumor (inflammatory myofibroblastic tumor) is a distinct lesion of the inflammatory pseudosarcoma, and it occurs more commonly in children and young adults; but it can occur in any age and sex, generally presenting a benign course. Inflammatory fibrosarcoma has been recognized as part of a variety of diseases referred to as inflammatory myofibroblastic proliferations. It is a potentially aggressive tumor which occurs predominantly in the mesentery of children and young adults. Méis-Kindblom et al. evaluated the ultra structural and immuno-phenotypical characteristics. From the 26 cases of inflammatory fibrosarcoma they studied Ki67 (MIB1), PCNA, bcl2, and p53, and showed that inflammatory fibrosarcoma has low proliferative activity, being possible to be considered as a low-grade sarcoma [4].

Myofibroblastic inflammatory tumor is a benign lesion but it has a great probability of recurrence after excision. The treatment is surgical and the clinician must be alert to possible recurrences; strict follow-up must be carried out.

Acknowledgments

Thanks to the National Council for Scientific and Technological Development (Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPq) and the Research Support Foundation of the State of Minas Gerais (Fundação de Amparo à Pesquisa do Estado de Minas Gerais, FAPEMIG).

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A case of squamous cell carcinoma arising from endometriosis of the ovary

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Summary

Ovarian endometriosis sometimes develops into ovarian cancer, especially clear cell adenocarcinoma and endometrioid adenocarcinoma. However, endometriosis rarely develops into squamous cell carcinoma. We present a case of squamous cell carcinoma arising from endometriosis. A 47-year-old Japanese woman was given a diagnosis of ovarian squamous cell carcinoma arising from endometriosis. She was treated with combination chemotherapy consisting of paclitaxel and carboplatin once every three weeks. Four months after the initial chemotherapy, multiple liver tumors appeared, and her treatment was changed to palliative therapy. Based on this case, in which ovarian squamous cell carcinoma arose from endometriosis, endometriosis should be followed-up strictly.

Key words: Squamous cell carcinoma; Ovarian cancer; Endometriosis.

Introduction

Malignant transformation of endometriosis is sometimes observed in ovarian cancer, especially to clear cell adenocarcinoma and endometrioid adenocarcinoma [1, 2]. Ovarian squamous cell carcinoma is usually associated with either a benign cystic teratoma or a Brenner tumor [3]. We present an extremely rare case of ovarian squamous cell carcinoma arising from endometriosis.

Case Report

A 40-year-old unmarried woman with no previous history of disease underwent a Papanicolaou test in 1999 and a cystic mass in her left adnexa was found. In 2003, at age 44, she underwent laparoscopic cystectomy of a left ovarian endometrial cyst with a postoperative pathological diagnosis of endometriosis. She had been administered GnRH analogue six times before this operation. We followed her up every six months, however, the left ovarian cyst recurred two years after the first operation. In 2006, at age 47, she underwent a re-operation. She had a fever of 39°C and complained of melena three months before the second operation. Magnetic resonance imaging (MRI) scans suggested that the left ovarian 100 × 90 mm mass was infected. Colonofiberoscopy revealed stenosis of the sigmoid colon with inflammation but no tumor. We believed this stenosis had been caused by endometriosis. Her infection was treated with antibiotics, and she recovered. Thereafter we administered GnRH analogue to her four times before the second operation.

During laparoscopic surgery, a left ovarian mass 100 × 60 mm with marked adhesion to the sigmoid colon was found, causing the frozen pelvis. The mass ruptured during the cystectomy and we found that the mass had an internal solid component. Intraoperative frozen-section revealed poorly differentiated transitional cell carcinoma. Therefore, we converted from laparoscopic surgery to a laparotomy, with total hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomies, omentectomy, and sigmoidectomy. There was no residual tumor.

The postoperative, pathological diagnosis revealed that most of the tumor was squamous cell carcinoma (Figure 1) with the remained being transitional cell carcinoma. The International Federation of Gynecology and Obstetrics classification (FIGO) was Stage II C. Blood samples obtained just before the second operation showed her SCC serum levels to be 15 ng/ml. She was then treated with adjuvant combination chemotherapy consisting of paclitaxel (175 mg/m² day 1) and carboplatin (AUC 5, on day 1) every three weeks for a total of six courses. Eight months after the operation, her SCC serum levels were elevated and her abdominal MRI scans showed a 64 × 60 mm pelvic mass that was located in contact with the bladder, which we considered to be a relapse. Second-line chemotherapy was given, irinotecan (60 mg/m², on days 1, 8, and 15) and cisplatin (60 mg/m², on day 1). After two courses, the pelvic mass was enlarged, so the patient was treated with radiation therapy – whole pelvic irradiation totaling 60 Gy. After irradiation, computed tomography (CT) scans demonstrated multiple liver masses, at which time, the patient was changed to palliative therapy.

Discussion

Endometriosis is a common disease, which sometimes develops into ovarian cancer. Recent reports have shown that 0.5-1% of endometriosis causes ovarian cancer. We applied the Sampson and Scott criteria regarding the diagnosis of ovarian cancer developing from endometriosis in this case [4]. These criteria are: (1) Endometriosis and carcinoma occur in the same ovary and the relationship between the benign tissue of endometriosis and the malignant tumor tissue is comparable to that observed in cases of carcinomas developing in the orthotopic endometrium of the uterine corpus. (2) The malignant neoplasm must grow from the endometriosis, not into it. (3) The presence of endometrial stroma, old hemorrhage, or hemosiderine deposits supports the diagnosis of endometriosis. (4) Microscopically, it is possible to demonstrate transition of non-neoplastic into neoplastic epithelium. Since these criteria were fulfilled in this case, we believed that this carcinoma had developed from endometriosis (Figure 1).
A case of squamous cell carcinoma arising from endometriosis of the ovary

Endometriosis is usually associated with clear cell adenocarcinoma or endometrioid adenocarcinoma, and ovarian squamous cell carcinoma usually develops from either a benign cystic teratoma or a Brenner tumor [1-3]. In this case, since most of the tumor consisted of squamous cell carcinoma consistent with endometriosis, we diagnosed ovarian squamous cell carcinoma arising from endometriosis.

A search of Pubmed revealed that 16 ovarian squamous cell carcinoma cases have been reported [3, 5-12] (Table 1). The median age of the patients was 49 (range 29 to 86), and the median size of the tumor diameter was 10.8 cm. All cases were resected and adjuvant chemotherapy was given in ten cases, radiation therapy in five cases, and both in four cases. The overall survival was only four months in these cases, implying no response to treatment and extremely poor prognosis.

We could not make a correct diagnosis of ovarian cancer in this case before the second operation. Kobayashi et al. [13], previously showed the risk factors of malignant change from endometriosis to be age greater than 45 years old, a postmenopausal state, and cystic diameter above 100 mm. Furthermore, the risk signs of malignant change on ultrasound examination have also been reported as tumor size increasing in a short period, an intracystic component, and the disappearance of the strong echogenic pattern with increasing diffuse hypoechoic areas. Tumor marker serum level elevation, especially CA-125, is also a risk factor of malignant change.

Preoperative adjuvant treatment, such as GnRH analogue, was performed in this case, but the ovarian tumor was increased. Ovarian carcinogenesis from endometriosis may be reactive to GnRH analogue. Kobayashi et al. [13] reported that an ovarian endometrial cyst was decreased at the beginning of GnRH analogue, but although administration was continuous, tumor size was
enlarged which increased the risk of developing ovarian cancer. Squamous cell carcinoma of the ovary associated with endometriosis has an extremely poor prognosis. The average overall survival was only four months in past cases because of minimal response to therapy. In the literature, a few cases demonstrated good response to the therapy that used cisplatin or carboplatin with paclitaxel after radical surgery. However, there is no evidence that these improve overall survival in patients. Ovarian endometriosis should be recognized as a pre-cancerous lesion for which more careful further investigation has to be performed.

Acknowledgements

The authors would like to thank the Language Consultant at the Department of International Medical Communications, Tokyo Medical University, Professor J.P. Barron, for his editorial assistance.

Table 1. — Clinical features of 16 previously reported cases and the present case.

<table>
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<td>RSO</td>
<td>DOD at 6 months</td>
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<td>TR</td>
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<td>TR, Rad, Chemo</td>
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<td>9</td>
<td>41</td>
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<td>IIb</td>
<td>ATH, BSO, Rad</td>
<td>DOD at 8 months Chemo</td>
</tr>
<tr>
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<td>59</td>
<td>12</td>
<td>IIc</td>
<td>BSO, Rad, Chemo</td>
<td>DOD at 6 months</td>
</tr>
<tr>
<td>11</td>
<td>70</td>
<td>8</td>
<td>IIc</td>
<td>ATH, BSO, Rad</td>
<td>DOD at 6 months Chemo</td>
</tr>
<tr>
<td>12</td>
<td>29</td>
<td>8</td>
<td>IV</td>
<td>ATH, BSO, Rad</td>
<td>DOD at 2 months</td>
</tr>
<tr>
<td>13</td>
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A rare ovarian Leydig cell tumor (hilar type) causing virilization in a postmenopausal woman

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Summary

All patients with virilization signs, increased levels of androgen hormones and rapidly progressive hirsutism should be evaluated for an androgen-producing tumor. The ovarian origin of virilization can be suspected by the presence of elevated levels of circulating androgens, with normal levels of cortisol metabolites and a negative dexamethasone suppression test. A case report of a 50-year-old postmenopausal patient with rapidly progressive hirsutism is presented. After an extensive preoperative investigation a right oophorectomy was performed and a Leydig-hilus cell tumor was diagnosed.

Key words: Hilus-cell tumor; Leydig-cell tumor; Sex cord-stromal tumors; Ovary; Virilization.

Introduction

Leydig cell neoplasms are rare sex cord-stromal ovarian tumors of postmenopausal women, that represent 0.1% of all ovarian tumors and 20% of steroidogenic cell tumors of the ovaries [1-3]. It is important to distinguish these tumors that are benign from the otherwise non-specified steroid cell tumors, which present similarities in morphology but occur in younger women and present malignant behavior in about 20-45% of the reported cases.

Case Report

A 50-year-old postmenopausal white woman, gravida 2, para 1, was admitted to our hospital for evaluation of hirsutism. From her past medical history, a sigmoidectomy was reported because of a well differentiated adenocarcinoma (Stage 1) with negative lymph nodes. The patient has been free from neoplastic disease for the last three years but has reported progressive hirsutism for the last two years as well as an advanced stage of acne and weight increase. No evidence of breast flattening or change in libido has been noted.

The initial physical examination revealed signs of virilization such as facial hair (beard) and male distribution of pubic hair. The gynecological examination disclosed a normal uterus; the clitoris was enlarged but no pelvic mass was palpable. Her weight was 93 kg, height 164 cm, and body mass index (BMI) 34.58.

Measurements of circulating hormones revealed increased levels of testosterone. Androstenedione, dehydroepiandrosterone (DHEAS) and cortisol metabolites were within normal range. Cushing's syndrome was ruled out by an overnight dexamethasone suppression test. An abdominal computed tomography (CT) scan and pelvic ultrasound (US) showed no tumor mass in the adrenals. Transvaginal ultrasound (TVS) of the ovaries showed a cystic enlargement of the right ovary that measured 5 cm in mean dimension. A right oophorectomy was performed and frozen section examination was negative for malignancy.

On macroscopic examination the right ovary measured 5 x 2.3 x 1.8 cm, and the cut section revealed cysts with a diameter of 0.5-2 cm. After formalin fixation of the specimen, semiserial sections were stained with hematoxylin-eosin. Microscopic examination of the ovary revealed a circumscribed neoplasm brown in color, measuring 2 cm, containing a cystic hemorrhagic area measuring 1 cm at the ovarian hilus (Figure 1). It was composed of large uniform polyhedral cells characterized by spherical vesicular nuclei containing one to two nucleoli, and granular cytoplasm (Figure 2). Adjacent ovarian tissue showed hilus cell clusters and stromal hyperplasia. Although no Reinke crystalloids were observed in the multiple sections examined, the overall pathological diagnosis was that of a Leydig (hilus) cell tumor of the right ovary. After two months the circulating hormones of the patient were within normal levels and the facial and body hair had disappeared.

Discussion

In a postmenopausal woman mild hirsutism is generally idiopathic and the hormonal screening is frequently normal. However, a patient with virilization, increased levels of androgen hormones and rapidly progressive hirsutism should be evaluated for an androgen-producing tumor. The adrenal glands and ovaries should be examined. The ovarian origin of virilization can be suspected by the presence of elevated levels of circulating androgens, with normal levels of cortisol metabolites and a negative dexamethasone suppression test.

The majority of hormone producing ovarian tumors are derived from specific stromal and sex cord cells of the ovary. Steroid cell tumors account for approximately 0.1% and are composed of large round or polyhedral cells that resemble lutein, Leydig and adrenocortical cells. In the past, the term lipoid or lipid cell tumors has been used but currently the term steroid cell tumors is generally accepted. The new term was proposed because 25% of the tumors do not contain intracellular fat. Steroid cell
menopause, ovaries atrophy to a mean volume of 4.0 ± 1.8 cm, and TVS is particularly useful to estimate the ovarian volume and detect possible cancerous conditions. Recently the suppression of androgen levels with GnRH analogues has been described as a diagnostic method [2, 3]. These methods are non invasive, sensitive and widely available. Only by histological examination can a definitive diagnosis be established.

Macroscopically hilus cell tumors are typically small (less than 5-6 cm), and usually well circumscribed or lobular with a reddish brown to yellow appearance on sectioning and rarely bilateral [5]. In our case the tumor was circumscribed and partly cystic on cut section. Hilus (Leydig) cell tumors originate from normal hilus cells in the ovarian hilus, called hilus cells. These tumors are almost unilateral but in the literature four cases of bilateral hilus cell tumors have been reported [2, 4, 5]. Hilus cell tumors typically occur in postmenopausal women at a mean age of 58 years, but occasionally they may be detected in pregnant women or children [2, 4]. These tumors are frequently the cause of increased circulating levels of androgenic hormones, but estrogenic effects as polyps, endometrial hyperplasia and adenocarcinomas have been reported as well [2, 3]. In 80% of patients, hilus cell tumors cause hirsutism or virilization as in our patient [6, 7]. The physical examination may reveal facial hair, masculine alopecia and male distribution of pubic hair, seborrheic skin and acne as well as atrophy of the breast and enlargement of the clitoris. Hypertension, diabetes, and Cushing’s syndrome have also been described [2]. In the literature hilus cell tumors have also been associated with polycystic ovarian syndrome and thrytoxicosis [2]. The ovarian origin of the hirsutism in the current study was suspected by the presence of elevated levels of circulating androgens, with normal levels of cortisol metabolites and a negative dexamethasone suppression test. The first radiological studies for diagnosis of ovarian and adrenal tumors are CT scan and TVS. Imaging studies in this case did not detect any obvious mass of the adrenal glands or ovaries. TVS revealed an enlargement of the right ovary (5 cm), as found in the 96% of hilus tumors reported by other authors [8]. During the first five years after menopause, ovaries atrophy to a mean volume of 4.0 ± 1.8 cm, and TVS is particularly useful to estimate the ovarian volume and detect possible cancerous conditions. Recently the suppression of androgen levels with GnRH analogues has been described as a diagnostic method [2, 3]. These methods are non invasive, sensitive and widely available. Only by histological examination can a definitive diagnosis be established.

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A rare ovarian Leydig cell tumor (hilar type) causing virilization in a postmenopausal woman

References


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Lobular carcinoma of the breast metastasizing to leiomyoma in a patient under letrozole treatment

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Summary
Metastasis of extragenital neoplasms to the uterus is extremely rare. Lobular breast cancers metastasize to the uterus more than ductal carcinomas, but they metastasize as tiny nodules that can be missed with the standard diagnostic workup. Uterine involvement by a metastatic tumor is usually a manifestation of end-stage disease; patients are reported to die within weeks to months. Therefore surgery is not recommended. Here we report a case of lobular breast cancer metastasizing to a leiomyoma in a patient using letrozole. Our patient was submitted to surgery because the leiomyoma had grown to the level of the xiphoid process. She is alive one year after the operation. In conclusion growth of leiomyomas under aromatase inhibitors should be considered as a sign of metastases and surgery can be planned in selected cases.

Key words: Breast cancer; Aromatase inhibitors; Metastases; Leiomyoma.

Introduction
Extragenital neoplasms mostly metastasize to the ovaries and vagina and the uterus is involved only in 10% of the cases [1, 2]. In 1878 Legg reported the first case of extragenital tumor metastasizing to the uterus; the patient had malignant melanoma with widespread metastases [3]. Breast cancer and gastrointestinal malignancies are the most common extragenital cancers that metastasize to the uterus [2, 4].

Tamoxifen has been the gold standard for the adjuvant treatment of breast cancer and has increased the survival of patients. It has partial agonist activity on the endometrium and increases the risk of both benign and malignant endometrial pathology [5]. It was reported that postmenopausal breast cancer patients receiving tamoxifen for more than five months have cystic and edematous changes in leiomyomas [6], and one report showed increased mitotic figures in a leiomyoma under tamoxifen treatment [7]. Letrozole is an aromatase inhibitor that is as effective as tamoxifen in the treatment of postmenopausal women suffering from estrogen receptor-positive advanced breast cancer [8, 9]. We can expect growth of a leiomyoma when the patient is receiving tamoxifen, but in a patient receiving aromatase inhibitor growth of a leiomyoma is suspicious. Here we report a case of lobular breast carcinoma metastasizing to a leiomyoma in a postmenopausal woman receiving letrozole for advanced breast cancer.

Case Report
A 48-year-old woman with a left mammary mass was diagnosed as having invasive lobular carcinoma. The tumor was estrogen receptor (ER)-positive but progesterone and HER-2 receptor were negative. The specimen was stained with GCDFP-15 (Gross Cystic Disease Fluid Protein-15). The patient was inoperable at the time of diagnosis because extensive investigations demonstrated multiple liver and bone metastases and thus she received chemotherapy. During her abdominal investigations a leiomyoma with a 10 cm diameter was detected. Letrozole and ibandronate were given. She presented with increasing abdominal girth and urinary incontinence 15 months after her chemotherapy. Abdominal computed tomography revealed a giant leiomyoma with heterogenous architecture and foci of massive calcifications, reaching the level of the xiphoid process. She was referred to the gynecology polyclinic and a total abdominal hysterectomy was planned. The leiomyoma was extracted with myomectomy (Figure 1); only after this could total abdominal hysterectomy and bilateral salpingo-oophorectomy be performed. Both the ovaries, tubes, abdominal washing fluid, myometrium and the huge leiomyoma specimen were infiltrated with the metastatic tumor of the breast. The endometrium was spared. She received chemotherapy and is alive one year after the operation.

Discussion
One of the main causes of mortality for women is breast cancer, with more than one million new cases and 410,000 deaths worldwide each year [10]. Seventy to eighty percent of all breast cancers are infiltrative ductal carcinoma, with infiltrative lobular carcinoma as the second most frequent type, accounting for approximately 8% of the cases [11]. Infiltrative lobular carcinoma has a very high risk of peritoneal and retroperitoneal metastases. Metastases from infiltrative lobular carcinoma are as tiny nodules that tend to coalesce. This pattern of involvement is rarely associated with clinical manifestations. On the other hand infiltrative ductal carcinomas metastasize as large masses or nodules [12]. Our patient had infiltrative lobular carcinoma with tiny peritoneal metastases that appeared similar to inflammatory membranes. There was no observable lesion mass. Infiltrative
Lobular carcinoma of the breast metastasizing to leiomyoma in a patient under letrozole treatment

Lobular carcinoma is also the most common histologic type metastasizing to the female genital tract [12, 13]. Breast cancer is known to metastasize by the lymphatics, contiguity and hematogenous spread. Most common sites for disseminated metastases of breast cancer include the lungs, bone and liver, but breast cancer metastasis to the uterus occurs rarely. Most uterine metastases are due to local retrograde lymphatic spread from preceding ovarian metastases, and when there is isolated uterine metastases, spread is most probably hematogenous [1, 14]. When metastatic spread to the uterus occurs, the myometrium is more often involved than the endometrium [14]. Metastasis to the myometrium is usually asymptomatic. When the endometrium is attacked the tumor tends to infiltrate the stroma sparing the endometrial glands [14] and leads to uterine bleeding. In our case the presenting symptom was the increasing abdominal girth and there was no bleeding because the endometrium was not attacked. Uterine bleeding is most of the time the first sign of uterine metastases from another primary malignant tumor [15], but asymptomatic cases have also been reported. In asymptomatic cases positron emission tomography can be used to detect metastases to leiomyoma that escape standard metastatic workup [16]. In this case the patient had multiple metastases to the bones and liver therefore further workup of metastases to the genital organs was not considered.

Plexiform leiomyomas of the uterus can be confused with infiltrative lobular carcinomas of the breast and they should be included in the differential diagnosis. Immunohistochemical staining with cytokeratin and smooth muscle actin can confirm the diagnosis [17]. In our patient the pathological result was confirmed as lobular carcinoma metastases to leiomyoma.

Until recently tamoxifen has been the standard regimen for endocrine treatment of breast cancer in premenopausal and postmenopausal women with positive ERs. The partial agonist activity of tamoxifen leads to the development of tamoxifen-induced endometrial pathology within five years in 10% of the patients [18, 19]. Tamoxifen has been associated with increasing size of uterine leiomyomas and the development of new leiomyomas [20], and disseminated peritoneal leiomyomatosis [21]. Cystic and edematous changes are expected in leiomyomas in patients receiving tamoxifen [6] and a case of mitotically active leiomyoma [7] has been reported. Tamoxifen is also reported to increase the risk of uterine sarcoma [22]. Therefore it is not surprising to detect a growing leiomyoma in a patient using tamoxifen. In that case after stopping tamoxifen a benign leiomyoma would be expected to decrease in size, but a uterine sarcoma or a metastasis would continue to grow. Because of these side-effects our patient received letrozole instead of tamoxifen. Letrozole is an aromatase inhibitor and it blocks estradiol production in the breast and adipose tissue. Aromatase inhibitors are as effective as tamoxifen in the treatment of postmenopausal women suffering from ER-positive breast cancer and they should be the treatment of choice in advanced breast cancer in postmenopausal women [8]. Aromatase inhibitors prolong disease-free survival, increase time to recurrence, decrease metastases and decrease contralateral breast cancer. Letrozole is superior to tamoxifen in efficacy and tolerability in ER-positive, advanced breast cancer in postmenopausal women and does not increase the risk of endometrium cancer as tamoxifen does [23]. Aromatase inhibitors have been reported to reduce the size of uterine leiomyoma in premenopausal women [24], and have been used successfully in the treatment of disseminated peritoneal leiomyomatosis [25, 26] and benign metastasizing leiomyoma [27]. A case of uterine rhabdomyosarcoma has been reported in a patient receiving anastrozole [28], but there is no sufficient data in the literature to comment on a possible association. Growth of leiomyomas or uterine enlargement in patients receiving letrozole should always be considered as a sign of uterine metastases. Letrozole treatment is associated with osteoporosis and fractures, therefore we combined it with a biphosphonate.
Uterine involvement by a metastatic tumor is usually a manifestation of obvious dissemination and in the literature prognosis of breast cancer with uterine metastases was reported to be extremely poor and surgery was not recommended [1, 2]. In the current case the leiomyoma was huge and we believe that the operation improved the quality of life of the patient, and it may have improved the survival vastly. In contrast to the previous reported cases who lived a few weeks to months, our patient has been alive for one year since the operation.

In conclusion especially in patients with advanced lobular breast cancer the possibility of uterine metastases should always be considered when there are symptoms as vaginal bleeding, hyperplastic endometrium and a diffusely growing uterus or leiomyoma. Aromatase inhibitors reduce the size of leiomyomas, therefore growth of a leiomyoma under aromatase inhibitors should be considered as a sign of metastases. Surgery can improve survival and quality of life even in the presence of metastases.

References

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Metastasis from endometrial carcinoma to bilateral breasts presenting as inflammatory breast lesions

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Summary

Background: Endometrial carcinoma rarely metastasizes to the bilateral breasts and presents as an inflammatory breast lesion. In this paper, we report a case of bilateral breast metastatic endometrial carcinoma and describe the clinical and pathological features. It is the second case of this kind of disease and the first case report with full clinical data. Case report: A 56-year-old Chinese woman (G3, P3) with endometrial carcinoma received cytoreductive surgery and chemotherapy. Approximately 22 months later, she presented with pain in the right axillary region and edema of the right breast. The pathology report confirmed multifocal invasive papillary adenocarcinoma of the right mammary gland, consistent with endometrial carcinoma metastasis. Although she received many lines of chemotherapy, the disease still progressed and metastasized to the contralateral breast. Gefitinib (Iressa) improved symptoms temporarily. Conclusions: Bilateral breasts metastasis of endometrial carcinoma is rare and difficult to treat. Molecular targeted therapy may be an effective treatment for breast metastasis.

Key words: Endometrial carcinoma; Metastasis; Breast cancer.

Introduction

Endometrial carcinoma is the fourth most common gynecologic cancer in the United States. The American Cancer Society estimated that 42,160 women were diagnosed with endometrial cancer and 7,780 died of their disease in 2009 [1]. Primary gynecologic malignancies rarely metastasize to the breast and account for about 0.17% of all cases of metastases to the breast [2]; furthermore, only 10% of those originate from endometrial carcinoma [3]. To the best of our knowledge, metastasis to the breast from an endometrial carcinoma has seldom been described in the literature. Metastases to the breast have distinct clinical, radiographic, and histological features and should be suspected in a patient with a breast mass and a known extramammary primary cancer.

Here, we report on a case of metastatic adenocarcinoma of endometrial cancer in the breast which presented as an inflammatory breast lesion.

Case Report

A 56-year-old Chinese woman (G3,P3) presented with vaginal bleeding accompanied by lower abdominal pain in June 2006. Menarche had occurred at the age of 13 years after normal breast and pubic hair development. The patient menstruated regularly until she reached menopause at the age of 50 years and had no history of oral contraceptive usage or exposure to exogenous hormones. There was no family history of malignancies.

Transabdominal ultrasonography revealed complex cystic structures in both ovaries measuring 5 cm x 4 cm, with an overall increase in uterine volume. Fractional curettage of the uterus showed poorly differentiated adenocarcinoma of the uterus. Therefore, she received cytoreductive surgery and nine cycles of postoperative systemic chemotherapy with cyclophosphamide and cisplatin. During the procedure, metastatic disease of the stomach, liver and greater omentum was found. The pathology report (Figure 1A) described uterine papillary serous carcinoma (UPSC) with moderate differentiation at Stage IVB (according to the Federation of Gynecology and Obstetrics (FIGO) staging system).

Approximately 22 months after chemotherapy, the patient presented with edema of the right breast and pain in the right axillary region. Physical examination did not reveal any obvious breast mass. A chest computed tomography (CT) scan detected many nodules in the lungs, multiple enlarged lymph nodes in the right axillary region, a swollen breast, and thickened skin and muscles of the chest wall. Biopsy of the lymph nodes in the right axillary region showed metastatic adenocarcinoma (moderately differentiated). She was presumed to be suffering from a second primary breast cancer. After one cycle of chemotherapy with docetaxel and pharmorubicin, she received a right breast and right axillary region lymph node resection. However, pathology (Figure 1B) showed multifocal invasive papillary adenocarcinoma of the right mammary gland consistent with endometrial carcinoma metastasis. The pathology specimen was negative for estrogen receptor, progesterone receptor, Her-2/neu, CA-153 and carcino-embryonic antigen.

After three cycles of chemotherapy with docetaxel and cisplatin, her right upper extremity swelled progressively, accompanied by limitation of movement, soreness, prostration and multiple blisters on the skin of the right axilla and right anterior part of chest. She then received two cycles of chemotherapy with pemetrexed and pharmorubicin. Unfortunately, the right upper extremity symptoms still progressed. Oral etoposide did not improve symptoms and neither did a later single cycle of palliative chemotherapy with gemcitabine and cisplatin (Figure 1C, D).

Revised manuscript accepted for publication February 10, 2011
After that, targeted therapy with gefitinib, an epithelial growth factor receptor (EGFR) inhibitor, was administered at 250 mg per os daily for 20 days. The edema and soreness of her right upper extremity were significantly relieved after five days of treatment, although the improvement lasted only five days. One month later, the patient developed a metastasis to the contralateral breast and the skin of the chest wall. The metastatic infiltration presented as diffuse thickening of the skin and increased density of the breast, resembling inflammatory disease or damage after radiotherapy (Figure 1E). Mammograms demonstrated that dense glandular tissue occupied almost the entire breast (Figure 1F). Because of extreme exhaustion, she could not tolerate further chemotherapy or radiotherapy and she was directed to receive supportive care. Finally, she was unable to overcome the aggressive metastatic course of the primary tumor and expired 3.5 years after her initial diagnosis. All these treatments obviously prolonged her survival.

**Discussion**

Women with metastatic endometrial cancer have an overall poor prognosis, with estimated survival of less than one year. The breast is an unusual site for metastasis. Between 0.5% and 2% of the breast tumors have been identified as originating from metastatic deposits elsewhere [4]. The most common origin of metastasis to the breast is contralateral primary breast carcinoma. Therefore, the Medline database was searched in order to find relevant published reports from...
Metastasis from endometrial carcinoma to bilateral breasts presenting as inflammatory breast lesions

Figure 1. — E) Diffuse thickening of the skin and increased density of the left breast, accompanied by decreased skin elasticity. There were multiple nodules in the skin of left axillary and left breast. F) Mammograms of the left breast demonstrated that dense glandular tissue occupied almost the entire breast tissue.

Figure 2. — Origin of metastasis to the breast in 135 patients.

January 1969 to December 2005 so as to analyze the origin of the metastatic disease to the breast [5-10]. These findings are summarized in Figure 2. The five most common extramammary malignancies which metastasized to the breasts were identified as lymphoma, bronchogenic carcinoma, malignant melanoma, leukemia, and soft tissue malignancies. These data are partially in agreement with those published by O’Donnell et al. [11].

Metastasis of UPSC to the breast is an extremely rare event with only one case reported in the English literature since initially described [5]. Here, we have reported the second case and it is the first case report with full clinical data.

Treatment options for advanced stage endometrial cancer include the use of surgery, chemotherapy, radiotherapy, targeted therapy, or a combination [12]. A retrospective multi-institutional study of cytoreductive surgery for Stage III/IV UPSC showed a trend toward survival.
benefit in women who were optimally cytoreduced compared with women who had bulky residual disease, a finding that needs to be confirmed by prospective studies [13]. The chemotherapy approach has focused largely on platinum-based combinations. Most studies investigating the treatment for advanced-stage disease indicate that chemotherapy is the preferred modality of treatment [14]. Whole abdominal radiotherapy vs doxorubicin and cisplatin in women with advanced endometrial carcinoma has been investigated in a Gynecologic Oncology Group (GOG) trial which concluded that chemotherapy was superior [15]. A multi-center retrospective analysis of patients with surgical Stages III and IV endometrial cancer indicated that chemotherapy followed by radiation and then further chemotherapy was associated with improved survival for both overall survival and progression-free survival in women with advanced stage disease [16].

A better understanding of the molecular genetic mechanisms of non-endometrioid endometrial cancer has led to the development of targeted therapies that inhibit angiogenesis and malignant cell growth and proliferation [17]. Several of these targeted agents are currently being investigated in endometrial carcinoma [18]. Chemotherapy is the preferred treatment modality in most cases of advanced-stage endometrial cancer. However, our patient was resistant to many effective chemotherapy drugs and the disease progressed. We therefore tried gefitinib, indicated for the treatment of certain types of metastatic cancer. In contrast to chemotherapy, gefitinib significantly improved symptoms. However, the curative effect was still unsatisfactory. Further studies are needed to illustrate the key signal transduction pathway in endometrial carcinoma, which may help identify effective biological targets suitable for tailored therapies.

Metastatic endometrial carcinoma to the bilateral breasts is extremely rare and might appear within two years after the diagnosis of primary tumor. This possibility should be considered when an unusual biomorphic pattern appears in a tumor. As with other distant metastases of endometrial carcinoma, mammary gland involvement is associated with difficult management strategies and poor prognosis. Molecular targeted therapy may represent a promising option for this kind of cases [19].

References

Adenoid cystic carcinoma of the Bartholin’s gland: case report and systematic review of the literature

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Summary

Adenoid cystic carcinoma (ACC) of the Bartholin’s gland is a rare malignancy of the female genital tract. Seventy-nine cases have been reported in the literature. A 40-year-old women presented to our clinic with twice locally recurrent ACC of Bartholin’s gland of the left vulva despite hemivulvectomy. Adjuvant radiotherapy was delivered after the third resection. There was no local recurrence after three years follow-up, although she developed lung metastases that remain under control with oral cyclophosphamide. Our case confirms the literature review, which indicates a slow growing tumor with frequent local recurrences (30%) and distant metastases (31%). Adjuvant radiotherapy and/or chemotherapy should be considered in the management of ACC of Bartholin’s gland.

Key words: Adenoid cystic carcinoma; Bartholin’s gland.

Introduction

Vulvar carcinoma is the fourth most frequently encountered malignancy of the female reproductive tract [1]. Among vulvar neoplasms, 0.1-5% are of Bartholin’s gland origin, with primary carcinoma of Bartholin’s gland constituting less than 1% of neoplasms of the female genital tract [1-3]. Adenocarcinomas and squamous cell carcinomas account for 90% of primary Bartholin’s gland neoplasms [4-20]. Adenoid cystic carcinoma (ACC), formerly designated cylindroma [5], is a very rare variant of Bartholin’s gland carcinoma, accounting for 10-15% of Bartholin’s gland malignancies [6, 7, 19]. The most common histologic type of ACC of Bartholin’s gland is cribriform or mixed (with minor foci of tubular or solid areas) pattern [20]. Infiltration of perineural space is characteristic of ACC. To date, only about 79 cases of Bartholin’s gland ACC have been reported [10, 16, 18, 21-52]. We present a case and a review of the literature.

Case Report

A 40-year-old woman, gravida 3, para 2, presented with a recurring burning sensation due to a lesion on the left vulvar area; the lesion was excised. Pathological examination revealed ACC with perineural invasion. After three years, the symptoms and a 3 x 5 cm mass recurred in the same region and excisional biopsy was repeated at another institution; the lesion was diagnosed as ACC with perineural and widespread perineural invasion. The surgical border was positive. After 16 months, the patient reported pain, and a local 1.5 cm mass was detected. Abdominopelvic magnetic resonance imaging (MRI) showed a hypoechoic lobular solid mass (19 x 15 mm) located posterior and inferior to the anal canal. The biopsy again revealed the ACC. After two months of observation, the mass grew to 6-7 cm, extending to the lower third of the vagina and laterally to the left pelvic bone. Left hemivulvectomy was performed. During the operation, the tumor was observed to be adherent to the left ischiopubic bone. Microscopically, the tumor was composed of uniform basoloid cells forming cribriform and solid patterns in a fibrous stroma (Figure 1). In the cribriform pattern, microcystic spaces filled with basophilic or eosinophilic material were detected (Figure 2). Perineural and lymphovascular invasion were present. The pattern confirmed the diagnosis of ACC.

Postoperative radiotherapy (RT) was delivered, with a dosage of 50.40 Gy (1.8 Gy x 28 fractions) applied to the perineal region. During the treatment, a grade 2 skin reaction (wet desquamation) and dysuria (grade 2) occurred. After one week, an external boost of 16 Gy (2 Gy x 8 fractions) was applied.

During post-RT follow-up, pelvic examination and abdominopelvic MRI showed no local recurrence. Thirty-six months after external beam RT, multiple pulmonary nodules were detected by thoracic computed tomography (CT). Nine cycles of chemotherapy (cisplatin, ifosfamide, and bleomycin) were administered. After the last round of chemotherapy, follow-up thoracic CT showed progressive disease in the thorax. Liposomal doxorubicin was given as second-line therapy, followed by maintenance with oral cyclophosphamide. At 76 months post-RT, the patient has stable disease.

Discussion

Literature review

We searched the literature for cases of ACC of Bartholin’s gland using Medline and the Web of Science. We also retrieved all of the references listed in each article. Table 1 summarizes the literature review. We
Table 1. — Summary of the literature.

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15 y
Obermair 01 [33] | 1 | 44 | LE+BILND | N  | 4 y | N  | Y  | Pul | 9 y | After 5.3 y |
| Postop died |     |     |     |     |     |     |     |     | 3 y AWD |
| DePasquale 96 [34] | 1 | 41 | LE | 1 y (LE) | Y  |     |     |     | 45 GyRT+rnd |
| After 25 y |     |     |     |     |     |     |     |     | 45 GyRT+rnd |

Exenteration after 5 y
NED 3 y
45 GyRT+rnd
After 6 y
NED 37 m
identified 49 articles reporting on 79 patients. The median age of the patients was 48 years (range, 25-80 years). The age distribution showed no particular pattern, suggesting that ACC of Bartholin's gland occurs with the same frequency in younger and older patients (Figure 3).

Two types of treatment predominated: simple excision in 54% of the 79 patients and radical vulvectomy with or without lymph node dissection in the remaining 46%.

Recurrence was reported for 30% of the patients. Twenty-six percent of patients who had simple excision had more
than one recurrence as compared to only 7% of the patients who had radical vulvectomy. The resection margin status was known in 57 patients and the recurrence rates were 35% in the positive margin group and 10% in the negative margin group (Figure 4). However, one-half of the patients with positive resection margins received adjuvant RT, which could explain the apparent paradox that patients with positive margins had fewer recurrences than did patients with negative margins.

Thirty-three ipsilateral or bilateral lymph node dissections were reported and four showed positive nodes [6, 8-10]. All patients with positive lymph nodes developed distant metastases. Twenty-one patients received adjuvant RT. Only two of these 21 patients experienced recurrence versus 21 of the 56 patients who did not receive RT (chi-square, $p = 0.010$). The RT-associated reduction in recurrence was observed among patients with negative margins (14% vs 40% without RT), among patients with positive margins (0% vs 20%, respectively), and among patients with unknown margin status (25% vs 44%, respectively).

Distant metastases were reported for 31% of the patients. Bone and lung were the most common sites of metastasis [6, 9, 11]. Metastases were twice as frequent among patients with positive margins (50%) than among patients with negative margins (24%; chi-square $p = 0.05$).

Patients with metastatic disease received various chemotherapies, including combinations of methotrexate, dactinomycin, and adriamycin [11, 12-17]. The outcomes for patients receiving chemotherapy were stable disease in two patients [11, 16], no response in two patients [14, 17], and a positive response in three patients [12, 13, 15].

Overall survival based on 70 cases was 64% at ten years, with a median of 15 years. Survival was longer among patients with negative margins (median survival = 31 years) than among patients with positive margins (median survival = 8 years; log-rank $p = 0.015$).

In summary, ACC of Bartholin’s gland is a rare malignancy. It can occur in relatively young patients, with one-half of the cases reported in women younger than 48 years of age. It is associated with long survival except in patients with positive surgical margins. Recurrences are common. RT is associated with a reduction in the rate of
reocurrence irrespective of margin involvement. Distant metastases also occur frequently; unfortunately, the optimal systemic therapy is unknown.

Conclusion

Based on our case and the review of the literature, we argue that patients with ACC of the Bartholin’s gland should be managed by a multi-disciplinary team that includes gynecological oncology, radiation oncology, and medical oncology. Postoperative RT should be considered. For patients with metastatic disease, systemic treatment with liposomal doxorubicin appears encouraging.

References


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Synchronous clear cell adenocarcinoma of the cervix and endometrioid carcinoma of the endometrium

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Summary

Synchronous primary malignant neoplasms of uterus are uncommon. Patients with synchronous cervical and endometrial cancers are even rarer. We describe a case of cervical clear cell carcinoma and endometrial adenocarcinoma occurring simultaneously in a 54-year-old woman presenting with intermittent vaginal bleeding. The concept of synchronous primary malignancies of the genital tract is also reviewed in this report.

Key words: Cervical carcinoma; Endometrial carcinoma; Synchronous tumor.

Introduction

Multiple synchronous malignant neoplasms in the female genital tract are rare. Most of them are diagnosed as metastatic disease. Most cases of more than one gynecologic neoplasm are reported as synchronous endometrial and ovarian cancer. Synchronous primary malignant tumors of the uterus are exceptional, though. In this paper, a case is reported of synchronous clear cell adenocarcinoma of the cervix and endometrioid carcinoma of the endometrium.

Case Report

A nulliparous 54-year-old postmenopausal female was admitted to hospital with intermittent vaginal bleeding of one year’s duration. She had very little bleeding at first, but the bleeding lasted longer and became heavier in time. The patient did not have a history of coitus or gynecological problems. Her left foot had been operated on for poliomyelitis when she was a child, after which she underwent osteomyelitis treatment three to four times. Otherwise, she had a relatively unremarkable medical and surgical history. Her family history revealed no evidence of cancer among her first-degree relatives.

A punch biopsy of the patient’s vaginal protruding mass revealed clear cell adenocarcinoma with extensive necrosis, and colposcopy confirmed a bleeding protruding mass. A pelvic computed tomography (CT) and magnetic resonance imaging (MRI) scan revealed widening of her endometrial cavity, and right corneal area; her endometrial cavity was occupied by an intermediate-signal-intensity mass that extended and protruded into the vagina and widened her cervix; she had no suspected lymph node or distant metastasis (Figure 1). The results of the subsequent cystoscopic and sigmoidoscopic examinations were normal. The results of all the blood tests, which included tumor markers (SCC, CEA, CA125, and CA19-9), were within normal values.

Because the cervical cancer was at the IB2 clinical stage, a radical hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and common iliac and paraaortic lymph node dissection, and partial omentectomy were performed four days after the patient’s admission. A small amount of ascites was found in the peritoneal cavity. The cytologic evaluation of the ascites revealed that they were non-malignant. Both ovaries were atrophied. Macroscopically, the size of the uterus was 11 x 6 x 4.2 cm, it weighed 160 g, and it had the usual serosal surface. When it was opened, a 4.5 x 1.0 cm large friable mass was found in the fundus, and 1.5 cm apart from it, in the endocervix, was a 5.5 x 4.0 cm large polypoid mass. The latter mass protruded into the vagina. There was no gross lymphadenopathy in the pelvic lymph nodes or the paraaortic lymph nodes. The other internal organs were grossly free.

Histologic examination showed that the endometrial mass was characterized by well formed glands that resembled those of normal endometrium. The tumor cells showed mild nuclear atypia and invaded more than half of the myometrium. The endometrial lesion was diagnosed histologically as grade 1 endometrioid adenocarcinoma (Figure 2). The endocervical mass showed a solid and tubule-papillary growth pattern with extensive necrosis. The tumor cells were characterized by abundant clear cytoplasm and hobnail cells with marked cytological atypia. The endocervical mass was histologically diagnosed as clear cell adenocarcinoma (Figure 3). A total of 45 pelvic lymph nodes and paraaortic lymph nodes were retrieved, but no lymph node metastasis was observed.

The patient was thoroughly evaluated, and the FIGO stages were found to be IB2 clear cell carcinoma of the cervix and Stage IB adenocarcinoma of the endometrium. Concurrent chemoradiation therapy (CCRT) with a cisplatin (60 mg) regimen was performed post-operatively at the outpatient department. During the 5th cycle, the whole process was smooth and the patient tolerated it well.

Discussion

Billroth first reported the development of different primary malignant tumors in the same patient in 1879 [1]. Warren and Gates [2] defined the criteria for the diagnosis of multiple primary tumors as follows: (1) each of the...
tumors must present a definite picture of malignancy; (2) each tumor must be clinicopathologically distinct; and (3) the probability of one tumor being a metastasis or recurrence must be excluded. The incidence of synchronous primary tumors of the female genital tract is only 1-6% of all genital neoplasms. The most frequently associated tumors are endometrial and ovarian carcinomas [3, 4]. Concurrent neoplasms of the cervix and endometrium are rarer. Ayhan et al. showed that 29 patients who were diagnosed as having had synchronous tumors constituted as 1.7% of all patients with genital malignancy (29/1,690) [4]. The most common cancer was that of the ovary concomitant with other gynecologic malignancies, and the endometrial and ovarian cancer group consisted of 15 patients. Furthermore, three patients had concurrent squamous carcinoma of the cervix and adenocarcinoma of the endometrium. To the best of our knowledge, only 13 cases of synchronous cervical and endometrial carcinoma have been published. Most of them were squamous cell carcinoma of the cervix and adenocarcinoma of the endometrium. This is the first report of synchronous primary clear cell carcinoma of the cervix and adenocarcinoma of the endometrium [5].

The etiology of a synchronous neoplasm is not clear. It has been postulated, however, that embryologically similar tissues of the genital tract, when simultaneously subjected to hormonal influences or to carcinogens, may develop a synchronous neoplasm [6]. An association between in-utero DES exposure and clear cell carcinoma of the cervix and the vagina was especially identified in the early 1970s, but in this case, the patient’s mother had no history of DES exposure. HPV is also well known to have oncogenic potential. HPV DNA is detected in >90% of cases of squamous cell carcinoma of the cervix. It could not be detected in the surgical specimen in this study, though. This is consistent with the demonstration of Pirog et al. of the lack of association of HPV with clear cell adenocarcinoma [7].

The prognosis of synchronous neoplasm is more favorable than that of metastatic lesions of individual tumors [3]. Because of the early symptoms of endometrial cancer such as vaginal bleeding, the second primary cancer that occurs in an individual with endometrial cancer may have a more favorable prognosis. Ayhan et al. reported similarly favorable outcomes in the endometrial and ovarian cancer group and in other synchronous tumor groups [4].
Synchronous clear cell adenocarcinoma of the cervix and endometrioid carcinoma of the endometrium

Lin et al. reported a favorable prognosis in adenocarcinoma of the endometrium and squamous cell carcinoma of the cervix [8]. The clinical characteristics associated with clear cell carcinoma of the cervix (CCCC) differ from those associated with squamous cell carcinoma of the cervix, including advanced age, lack of smoking history, and lower frequency of abnormal cervical cytology. A clear cell histology alone, however, does not appear to portend a poor prognosis. Many studies have reported a similar case of survival from early CCCC [9, 10]. Hanselaar et al. reported negative prognostic factors similar to those of patients with squamous cancers. In the case in this study, the size of the clear cell carcinoma of the cervix was > 4 cm. CCRT was performed as an adjuvant treatment which is the same as the treatment of squamous cell carcinoma of the cervix.

In summary, a rare case of synchronous clear cell carcinoma of the cervix and endometrial adenocarcinoma was presented in this study. The etiology and pathogenesis were not clear. Despite the use of the recently introduced advanced diagnostic technique, it is still difficult to detect synchronous neoplasms. Therefore, the possibility of a synchronous neoplasm should be kept in mind.

References


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Figure 3. — (A) Clear cell carcinoma (x10): Scanning power field showed clear cell carcinoma. (B) Solid sheet of tumor cells with plump clear cytoplasm. Black arrow; normal endocervical glands (x100). (C) The tumor cells were characterized with abundant clear cytoplasm and hobnail cells by marked cytological atypia (x400).
Proliferative Brenner tumor of the ovary.
Clinicopathological study of two cases and review of the literature

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Summary

Background: Ovarian Brenner tumors are rare epithelial tumors that account for 1%-2% of all ovarian neoplasms. They can be subdivided into benign, borderline or proliferative, and malignant neoplasms. In the vast majority of cases, these lesions are benign. Tumors of borderline malignancy are less frequent and only about 1% of Brenner tumors are malignant. We present two cases of Brenner tumors with borderline malignancy which were treated in our Department together with a review of the literature. Cases: A 50-year-old, gravida 1, para 1, patient was admitted for abnormal vaginal bleeding. Clinical examination, abdominal ultrasound (US), and computed tomography (CT) revealed a cystic multiloculated tumor of the right ovary with solid elements measuring 20 x 19 x 15 cm in diameter. In the other case a 70-year-old, gravida 2, para 2, patient presented with severe urinary difficulties. Palpation revealed a mobile abdominopelvic tumor 10 x 15 in diameter. US and CT exhibited a cystic tumor with multiple solid elements and calcifications of the left ovary. Both patients underwent exploratory laparotomy. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and total omentectomy were performed in both cases, while pelvic lymphadenectomy was decided only in the second case. Histologically, in both cases the diagnosis confirmed borderline Brenner tumor. Conclusion: Although Brenner tumors are rare and the majority of them are benign, the correct histological diagnosis at frozen section with identification of the small proportion of malignant tumors, allows the extent of the operation to be adapted if needed.

Key words: Ovarian Brenner tumor; Borderline ovarian tumor; Ovarian cancer.

Introduction

Ovarian Brenner tumors are rare epithelial tumors that account for 1%-2% of all ovarian neoplasms. They are usually unilateral, while a bilateral appearance of Brenner tumors is reported in about 7-15% of the cases [1]. Previously they were called transitional cell tumors because of their similarity to urothelial epithelium. Proliferating Brenner tumor of the ovary was first described in 1971 by Roth and Sternberg [2]. This entity was confirmed by Miles and Norris in 1972, who referred to a similarly defined group of cases as proliferative Brenner tumors [3].

The terms of borderline malignancy and proliferating in reference to Brenner tumors were equated in the World Health Organization (WHO) publication of 1973 Histologic Typing of Ovarian Tumors [4]. It is a separate category of Brenner tumor which is intermediate in its histologic appearance and biologic aggressiveness as compared with the benign and malignant types of Brenner tumors [2, 5]. We present two cases of borderline Brenner tumors treated with surgery in our department in order to study correlations with symptoms, tumor markers, imaging findings, treatment methods, histological differential diagnosis and prognosis.

Case Reports

The first patient, a 50-year-old gravida 1, para 1 Greek woman presented with a complaint of abnormal vaginal bleeding. She had a history of thrombocytopenia and obesity, while her past surgical history was unremarkable. Physical examination of the pelvis revealed a large, mobile tumor in the right lower abdomen. CT and US of the abdomen showed a large cholelith 2.5 cm in diameter, splenomegaly, multiple uterine fibromyomas, and an almost entirely cystic tumor with solid elements and papillary projections of the right ovary 20 x 19 x 15 cm in diameter. Preoperative CA-125 levels were within normal ranges (21.4 U/ml, nr < 35.0).

The second patient, a 70-year-old gravida 2, para 2, Greek woman presented with urinary retention. She had a history of hypertension and osteoporosis, while her past surgical history was unremarkable. Physical examination of the pelvis revealed a large, mobile tumor in the right lower abdomen. CT and US of the abdomen showed a large cystic tumor with multiple solid elements and calcifications of the left ovary, with synchronous dislocation of the bladder from this mass. The preoperative CA-125 levels were mildly elevated in this case (CEA 4.7 ng/ml, CA-125 40.7 U/ml, CA 19-9 108.6 U/ml).

Preoperative chest X-ray, mammography, and vaginal swab/cervical smear of both patients were negative for abnormal findings. The second patient also underwent preoperative colonoscopy and urethrocystoscopy without signs of invasion, but with signs of pressure on the bladder from the tumor.

Both patients underwent exploratory laparotomy. Total abdominal hysterectomy with bilateral salpingo-oophorectomy and total omentectomy was performed in both cases, while pelvic lymphadenectomy was decided in the second case. In both cases there was no presence of ascitic fluid and there were...
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no peritoneal implants, adhesions or metastases to other abdominal organs. In both cases the peritoneal washings were negative for malignant cells.

Both patients had a normal postoperative recovery without any complications. The diagnosis of borderline Brenner ovarian tumors in both cases was established from the histopathologic examination. The gross section revealed in both cases a large, multicystic component containing a polypoid mass and foci of white-yellowish solid areas. The cysts were lined by broad papillae with fibrovascular cores covered by transitional cells resembling low-grade papillary transitional cell carcinoma of the urinary tract. In the first case tumor cells showed mild atypia, nuclear grooves and sparse mitoses while in the second one severe atypia as well as squamous and mucinous metaplasia. No invasion was demonstrated in either case. The tumor immunoprofile was positive for CK7, pankeratin, EMA, EGFR, CEA, P63 and negative for CK20, S100, Vimentin, SMA, estrogen, progesterone, CA-125, and p53. In both cases histology showed that the uterus, the contralateral ovary, omentum and the pelvic lymph nodes that were removed in the second case, were negative for malignancy.

The patients were treated with surgery only. They remain disease-free, 21 and 23 months after diagnosis and surgical treatment, respectively. Follow-up with physical examination, US of the abdomen and serum marker CA-125 is performed every six months, without signs of persistent disease or recurrence.

Discussion

The histogenesis of Brenner tumors has provoked considerable debate. Origin from granulosa cells [6], Walthard cell nests [7], rete ovarii [8], teratomas of the ovary [9], or stromal cells [10] has been proposed. However, it is now generally accepted that Brenner tumors derive directly from the epithelium of the ovarian cortex or from celomic inclusion cysts, which are formed by invaginations of the ovarian celomic epithelium [11-13].

The majority of benign Brenner tumors of the ovary occur between ages 30 and 59 years [14]. The peak incidence of borderline and malignant Brenner tumors, between ages 45 and 60 years, is older than their benign counterparts [5]. Our patients were 50 and 70 years old, respectively.

Patients with proliferative Brenner tumors usually present with abdominal masses or abnormal vaginal bleeding because of irregular estrogen synthesis [11]. One of our patients presented with abnormal vaginal bleeding, while in the other case urine retention was the main symptom. In both cases physical examination and US, CT revealed large abdominal masses. Benign Brenner tumors usually measure less than 5 cm in diameter. On the other hand borderline and malignant Brenner tumors are larger, measuring 8 to 10 cm in diameter [5, 15]. In both cases, borderline Brenner tumors were too large, measuring 20 and 14 cm in maximum diameter, respectively.

The CT appearance of Brenner tumors varies according to tumor type. Benign tumors are homogeneous, solid or unilocular cystic, borderline tumors and are usually multilocular cystic with solid elements and malignant tumors are heterogenenous solid or multilocular cystic [16]. In both cases CT revealed cystic tumors with solid elements.

The gross appearance of borderline or malignant Brenner tumors differs from that of benign tumors. That is, borderline and malignant tumors are almost entirely cystic with solid papillary projections, described as mixed cystic and solid lesions, while benign are characterized by solid nodules with lobulated surfaces. Intracystic projections in benign tumors are rare, being much more common in borderline and malignant Brenner tumors.

Histologically, benign Brenner tumors have solid or microcystic epithelial cell nests surrounded by dense fibrous stroma. Borderline Brenner tumors resemble low-grade transitional carcinoma without stromal invasion, whereas malignant Brenner tumors resemble malignant invasive transitional carcinoma with stromal invasion. There is less intervening fibrous stroma in borderline and malignant Brenner tumors than in benign Brenner tumors [5].

Considering that Brenner tumors of different types

Figure 1. — Cystic areas of the tumor, filled with serous fluid and gelatinous material, coexisting with solid areas of white-yellow color.

Figure 2. — HE x40 Intracystic papillary configuration composed of transitional type epithelium similar to a low-grade non invasive papillary transitional cell neoplasm of the urinary tract.
have common features it is suggested that the proliferative and malignant variants derive from their benign counterpart by cellular proliferation and malignant transformation [17]. Thus, benign Brenner tumors may be potentially malignant and must be excised completely [11, 18]. In cases of malignant Brenner tumors, the surgical procedure has to be extended as in other epithelial ovarian malignancies [19]. Thus, precise histological diagnosis at frozen section allows the extent of the operation to be adapted only if needed, in order to avoid unnecessary risky surgery as well as under-treatment of a malignant neoplasm [11].

The most important feature for distinguishing intermediate forms of Brenner tumors from malignant ones at frozen section is the presence of stromal invasion in the latter. This feature has generally been considered difficult to identify because of the fundamental fibroepithelial nature of Brenner tumors, and the fact that their stroma is derived from ovarian stroma. Even more, in proliferative Brenner tumors the degree of nuclear hyperchromatism is mild to moderate, the mitotic rate may be high, and tumor necrosis is often present [18]. Thus, these latter features are not helpful in distinguishing proliferative from malignant Brenner ovarian tumors.

In our second case the presence of tumor cells with severe atypia and the difficulty to identify the presence or absence of stromal invasion at frozen section suggested that more extensive surgery, including pelvic lymph node sampling, was warranted. The absence of stromal invasion as well as immunohistochemistry established the diagnosis of atypical proliferative Brenner tumor at the final pathological examination.

The prognosis of a borderline Brenner tumor is excellent. It is considered to be a tumor of very low risk for recurrence or metastases even many years after excision. Proliferative Brenner tumors presumably have a non-aggressive biologic behavior, possibly because treatment involves the complete removal of the papillary tumor which typically grows intracystically together with the involved ovary. Similar tumors in the urinary bladder, on the other hand, may persist after treatment, since the urinary bladder mucosa may give rise to new papillary tumors after their removal [18]. In one series of ten cases of borderline Brenner ovarian tumors, there was no evidence of recurrence or metastases up to eight years after excision [5, 18].

No therapy in addition to surgery is needed [20]. There is now convincing evidence in the literature that chemotherapy is indicated only for cases of serous borderline tumors associated with invasive implants [21]. Our patients were treated with surgery only and they remain well, without evidence of disease 21 and 23 months after surgery, respectively.

Conclusion

Although Brenner tumors are rare and the majority of them are benign, the correct histological diagnosis at frozen section, with identification of the small proportion of malignant tumors, allows the extent of operation to be adapted if needed. The prognosis of a borderline Brenner tumor is excellent and no adjuvant therapy is needed.

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The application of a newly developed linear stapler preloaded with tissue reinforcement for distal pancreatectomy in the management of ovarian cancer

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Summary
Advanced ovarian cancer may extend into the spleen, and even the pancreatic tail, in which a splenectomy associated with distal pancreatectomy is crucial for optimal cytoreduction. A new linear stapler preloaded with tissue reinforcement is currently introduced. We herein report the first three cases of successful application of this device for distal pancreatectomy performed during cytoreductive surgery for ovarian cancer.

Key words: Ovarian cancer; Distal pancreatectomy; Linear stapler; Tissue reinforcement; Pancreatic leakage.

Introduction
Optimal cytoreduction at primary debulking surgery has been shown to be the most important prognostic factor in the management of ovarian cancer [1, 2]. Advanced ovarian cancer may involve the spleen and even into the pancreatic tail. Thus, distal pancreatectomy combined with splenectomy is necessary for optimal cytoreduction [3].

Pancreatic leakage is a major determinant of morbidity after distal pancreatectomy. In gastrointestinal surgery, the reported rates of pancreatic leakage are highly variable, ranging from 0-61% (21% on average) [4]. In the surgery performed for gynecologic cancer, Kehoe et al. reported that four of 17 patients who underwent a distal pancreatectomy developed pancreatic leakages and were managed with percutaneous drainage [3].

Prevention of the pancreatic leakage is crucial and many techniques have been developed for the closure of the pancreatic remnant. Simple closure using linear stapler devices has been introduced, with the hope that by utilizing techniques that are easily performed would improve the effectiveness and safety of the surgical procedures. This, however, has not yet been proven: the stapling technique is not necessarily safer than previous procedures, but it has been shown to be just as safe as a traditional hand-suture technique in terms of pancreatic leakage [4].

With the aim of less pancreatic leakage, some surgeons have proposed the addition of tissue reinforcement materials to the stapling line [5, 6]. In one such method, a biodegradable buttress mat is mounted on the facing surfaces of the cartridges of a linear stapler and is stapled onto both sides of the cutting edges during the firing. The reinforcement material supplies an anchor for the staples to compress and seal tissues edges firmly, and act as a scaffold for fibroblast-mediated wound healing.

A ready-to-use linear stapler preloaded with tissue reinforcement was recently released that allows a surgeon to apply the material by one-step firing. We herein report our experiences with the first three cases of ovarian cancer in which this device was used for distal pancreatectomy.

Case Reports
Three case are presented in which the distal pancreatectomy procedure with associated splenectomy using a Duet TRS Reload device (Covidien, Norwalk, CT) was carried out.

The newly introduced linear stapler, Duet TRS Reload, is preloaded and secured on the anvil and cartridge with synthetic absorbable reinforcement material for tissue reinforcement (Figure 1 A, B). This device places the reinforcement material on the both sides of the sealing line, and two triple staggered rows of staples are inserted while the tissues between the rows are simultaneously transected (Figure 1C).

Distal pancreatectomy combined with splenectomy was performed when a metastatic lesion of ovarian cancer was identified on the pancreatic tail, splenic hilus, or both. The spleen and pancreatic tail were mobilized, and splenic artery and vein were ligated and divided. Then, pancreatic parenchyma was simply transected using the Duet TRS Reload device (Figure 2). A drain was placed onto the pancreatic bed, and the amylase values of the drained fluid were measured postoperatively. Pancreatic leakage was suspected when the drained fluid contained elevated amylase greater than three times the upper normal serum value after postoperative day 3 [7]. The use of the device for distal pancreatectomy was approved by the Institutional Review Board.

Case 1
A 50-year-old female underwent primary surgery for bilateral ovarian tumors with upper abdominal disease. Her histopathological diagnosis was serous adenocarcinoma, and the clinical stage was IIIc. Extended surgery, including rectosigmoidec-
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tomy, diaphragmatic stripping, systemic paraaortic and pelvic lymphadenectomy, and distal pancreatectomy with splenectomy were performed to accomplish a visible residual tumor-free status. The patient’s postoperative course was uneventful without any evidence of pancreatic leakage. Oral feeding was resumed eight days after surgery.

Case 2
A 43-year-old female underwent primary surgery for a right ovarian tumor with extensive upper abdominal disseminated disease. The histopathological diagnosis of the ovarian tumor was serous adenocarcinoma, and the clinical stage was IIIC. Extended surgery, including rectosigmoidectomy, partial resection of the ileum, diaphragmatic stripping, systemic paraaortic and pelvic lymphadenectomy, and distal pancreatectomy with splenectomy were performed to accomplish a visible residual tumor-free status. The postoperative course was uneventful without any evidence of pancreatic leakage. Oral feeding was resumed 12 days after surgery.

Case 3
A 60-year-old female underwent primary surgery for Stage Ic ovarian cancer. Her histopathological diagnosis was clear cell adenocarcinoma of the left ovary. Eighteen months after the primary surgery, a metastatic lesion was demonstrated by a follow-up computed tomography scan at the splenic hilus, and a secondary cytoreductive surgery was performed, including distal pancreatectomy with splenectomy, in order to achieve a visible residual tumor-free status. Her postoperative course was uneventful without any evidence of pancreatic leakage. Oral feeding was resumed 14 days after surgery.

Discussion
A variety of attempts to avoid pancreatic leakage after distal pancreatectomy have been reported, including pancreatic duct ligation, ablative transection, use of fibrin glue, hand-sewn patches, stenting of the pancreatic duct, and use of stapling devices. However, a meta-analysis could not identify any technique that was significantly superior to the traditional hand-suture technique [4].

Recently, the application of tissue reinforcement for stapled transection lines was reported in a distal pancreatectomy in gastrointestinal surgery [5, 6]. Using this procedure, two pieces of bioabsorbable materials were placed over the anvil and cartridge, and stapled onto the cutting surfaces of the pancreas simultaneously during

Figure 1. — A: Close-up view of the standard linear stapler. Two triple staggered rows of staples (a and b) can be seen. A groove (c) between the two rows is for the transection knife placed on the anvil. B: A close-up view of the new linear stapler, Duet TRS Reload (Covidien, Norwalk, CT). A semi-transparent material for reinforcement is preloaded onto the anvil (arrowheads) and cartridge (arrows) for each side. An anchoring suture (d) keeps the reinforcement material flat and secure during manipulation. C: Transection lines produced using the standard stapler (left side) and the stapler with the reinforcement (right side). The sleeves (e) are made of two layers of a semi-transparent material at the cutting edge.

Figure 2. — Intraoperative photographs of Case 2. A: Identification of the disease involving the superior part of the pancreatic tail. B: The appearance of the pancreatic remnant closed with staple-line reinforcement.
The application of a newly developed linear stapler preloaded with tissue reinforcement for distal pancreatectomy in the etc.

The application of a newly developed linear stapler preloaded with tissue reinforcement for distal pancreatectomy in the etc. firing. Consequently, two layers of reinforcement material sandwich the soft pancreatic parenchyma and strengthen the cutting edges. This technique significantly decreased the pancreatic stump leakage rates compared to that without the reinforcement.

A drawback of this technique is the manual loading of the reinforcement material. Surgeons need to set the reinforcement material for both the anvil and the cartridge every time before use. Moreover, careful handling of reinforcement-mounted devices is necessary during the manipulation to avoid accidental displacement or slipping off of the reinforcement material. Compared to this technique, a new linear stapler, the Duet TRS Reload, is preloaded with reinforcement material that is securely anchored on the cartridge by a nylon string. This ready-to-use device enables one-step endostapling with tissue reinforcement.

The use of tissue reinforcement strengthens the cutting surfaces and enhances tension strength, and reduces bleeding from the pancreatic stump [6]. The absorbable reinforcement material serves as a 3-dimensional platform for wound healing. Fibroblasts migrate to the pancreatic stump and secret collagen fibers promoting tissue healing, and macrophages degrade the reinforcement material. The reinforcement material integrated into the Duet TRS Reload is the absorbable synthetic polymer, which is composed of glycolide (60%) dioxanone (14%), and trimethylene carbonate (26%). Thus, complications caused by long-standing foreign body materials, such as infection, migration, erosion, or fistula formation, are unlikely occur as a result of these biodegradable materials [5]. However, while the Duet TRS Reload is currently in use, its use has not yet been approved for pancreatic surgery.

We herein reported the successful application of the linear stapler preloaded with tissue reinforcement to distal pancreatectomy in the management of three patients with ovarian cancer. The device is convenient and simplifies the closure technique. It is potentially useful for gynecological surgeons to perform distal pancreatectomies. Further studies are needed to confirm the efficacy and safety.

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Malignant melanoma ovarian metastasis mimicking acute tuboovarian abscess

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Summary

Background: Metastases of malignant melanoma to the reproductive organs are occasionally encountered. They always represent a diagnostic challenge and they mimic various ovarian entities from primary ovarian malignancy to benign tumors. Case: A 35-year-old woman presented with bilateral ovarian metastases which had clinical features of an acute state mimicking a tuboovarian abscess. The diagnosis was established postoperatively. Conclusion: Sophisticated imaging methods may be necessary in cases of ovarian tumors in patients with a previous history of melanoma with possible metastatic dissemination. Urgent admittance and treatment of these patients with a range of clinical symptoms can be critical and may lead to a wrong diagnosis. Attentive monitoring of ovarian morphology in women with treated malignant melanoma is mandatory to detect rare but possible metastatic sites. Regardless of surgical and adjuvant therapy dissemination of malignant melanoma to the ovary has unfortunately a poor prognosis.

Key words: Malignant melanoma; Ovarian metastasis; Ovarian tumor.

Introduction

Malignant melanoma is an aggressive and fatal skin tumor. Epidemiologic analysis confirms that the incidence of this tumor is rising in comparison to other solid malignant tumors worldwide and that it occurs mostly in adults [1]. Early detection and surgical therapy is mandatory for the patient as well as an accurate staging according to the American Joint Committee on Cancer (AJCC) melanoma staging system that rates the level of invasion by Clark’s level and vertical thickness of tumor by Breslow’s measurement [2, 3]. Adjuvant postoperative therapy in terms of chemotherapy, immunotherapy, radiotherapy and biologic and gene therapy is still being developed by various research [4]. In spite of continuous development of diagnostic and therapeutic approaches this tumor is fatal for most patients [5].

Metastases of malignant melanoma involving the ovary are rare considering the literature and may mimic various ovarian entities from primary ovarian malignancy to benign tumors [5]. The majority of reported cases with abdominal pain and other various clinical features and symptoms that we found were in need of urgent admittance [6-9].

Case Report

We present a case of a 35-year-old woman admitted to our Clinical Hospital with acute abdominal pain, fever (39°C axillary body temperature), chills, fatigue, lack of appetite and nausea. These symptoms in a milder form had already been present a few days before and they were understood and treated as flu. The patient had no previous gynecologic illnesses or menstrual cycle irregularities. She had given birth to one child by that time and had no miscarriages. Five years before she had a skin mole excised from her upper back. The treatment was wide local skin excision with a tumor margin of 2 cm. The pathohistology after surgery revealed a malignant melanoma measuring 1.5 cm in diameter (Clarks level III/Breslow thickness III). No vascular invasion was seen and the lesion was completely excised. The patient had regular check-ups for the disease, the last one a year before. Pelvic bimanual exam revealed a palpable tender, painful, fixed adnexal tumor left of the uterus that was grapefruit size and shape. There was no vaginal bleeding or colored heavy discharge. Ultrasonography showed an 8 cm large multilocular, cystic, complex left adnexal mass with septations. Laboratory investigations showed elevated erythrocyte sedimentation rate and C-reactive protein, 60 and 61 mg/l, respectively. White blood cell was moderately elevated and CA 125 was in normal range. Her condition was diagnosed as acute tuboovarian abscess and she was admitted to the gynecologic department. Standard parenteral broad spectrum coverage therapy was introduced (clindamycin 1 g IV every 8 hours and gentamycin 120 mg IV every 12 hours). The following 24 hours the patient was briefly clinically stable. In spite of this treatment after 24 hours her temperature raised again, abdominal pain and other symptoms were in exacerbation and the patient started to vomit. The acute abdomen diagnosis was established and emergency surgical intervention was performed. Laparotomy findings were moderate ascites in the Douglas pouch, the left ovary was transformed to 9 x 7 x 6 cm in size and a large dark brownish, solid tumor with a smooth surface was seen. On the lateral side of the right ovary there was a 1 x 1 cm large dark cystic ovarian lesion otherwise normal in size and morphology. We
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found no other pathologic findings in the abdominal cavity. The pathohistological examination revealed a metastatic bilateral ovarian malignant melanoma. On the cut surface of the left ovary a solid, brownish, partially necrotic and hemorrhagic tumor was found. Morphologically large, anaplastic tumor cells with scanty cytoplasm, large nuclei and centrally placed nucleoli formed solid sheets (Figure 1a). Tumor infiltrated almost all the ovarian stroma. Scanty subcortical areas were free of tumor. The contralateral partially resected ovary also revealed the same tumor. Immunohistochemical analysis showed positive staining for S-100, melan A and HMB-45 in tumor cells (Figure 1b,d). Tumor cells were negative for CK7 and CK20. MIB was positive in 70% of tumor cells (Figure 1c). The omentum was free of tumor. Considering the patient’s age and her explicit wish before operative treatment we performed left salpingo-oophorectomy, omentectomy and right ovarian resection of the lesion. Postoperative recovery was satisfactory. By immediate additional examinations we found bone metastases (right tibia). The patient underwent palliative irradiation of the bone and seven cycles of dacarbazine (also termed DTIC every 3 weeks) chemotherapeutic protocol. A year later multiple intestinal and pulmonary metastases were diagnosed. The patient additionally underwent five cycles of Dartmouth protocol chemotherapy (DTIC, cisplatin, BCNU + tamoxifen) and three cycles of immunotherapy with interferon A (IFN 5 millions U). She died 15 months after laparotomy.

Discussion

Ovarian metastases of malignant melanoma are a conflicting and uncommon condition that according to researched literature in most cases is found during autopsy [10]. If found before, unlike other metastatic tumors, it almost always appears as a unilateral tumor resembling an ovarian primary malignancy which accompany various acute clinical features [5]. Even pathohistological findings could be misdiagnosed as they resemble ovarian primary tumors. Of all published case reports that we found and that were surgically treated after urgent admittance none was presented as suspected pelvic inflammatory disease or tuboovarian abscess by clinical appearance.

Metastases of melanoma represent distended disease with a poor prognosis [7]. Ovarian metastases should be surgically treated although there is no proven value of radical surgery in metastasis to the ovary of nongenital cancers [11]. Reviewing the literature, no specific state or protocol is established related to surgical approach to this rare extra-ovarian malignancy. Positron emission tomography (PET) scan has been established lately as sensitive enough and specific in differentiating metastases of malignant melanoma from other lesions in contrast to
other diagnostic methods [12]. According to the fact that
the majority of these patients in referred case reports are
in reproductive age, unilateral salpingo-oophorectomy
was the preferred surgical treatment if found as solitary
spread of the disease. The benefit of adjuvant postopera-
tive therapy in terms of prolonged survival is doubtful
[13, 14]. Various chemotherapy agents are used, including
dacarbazine (also termed DTIC), immunotherapy with
interleukin-2 (IL-2) or interferon (IFN)) as well as local
perfusion used by different centres. IL-2 (proleukin) is
the first new therapy approved for the treatment of
metastatic melanoma in 20 years [15]. A number of new
agents and novel approaches are under evaluation and
show promise [16]. One of the most promising current
experimental treatments is OncoVEXGM-CSF which is
currently in Phase 3 [17]. Additional evaluation and thor-
ough pursuit for local, regional and distant metastases is
advised as ovarian involvement can be the first evident
site after even long remission time [8, 14]. When there is
distant metastasis of malignant melanoma, the cancer is
generally considered incurable with five year survival rate
less than 10% [18]. The median survival time is 6-12
months. Treatment is palliative, focusing on life-exten-
sion and quality of life.

A tuboovarian mass is a common clinical feature in
reproductive age. Rising incidence of sexually transmit-
ted diseases increases the appearance of accompanied
clinical findings of pelvic inflammatory disease (PID)
and tuboovarian abscess (TOA). Palpable adnexal masses
with pelvic pain, fever and chills are the major and most
frequent clinical signs of TOA. Conservative treatment in
reproductive age either with antimicrobial regiments or
surgery are used in order to preserve reproductive organs.
Surgical intervention is inevitable in patients that do not
react to antibiotic therapy [19].

Our patient developed signs of acute abdomen. Surgery
was inevitable and mandatory in this case in revealing and
treating the real cause of her acute state. To our knowl-
dge this is the first presentation of ovarian metastatic
melanoma with clinical appearance mimicking TOA. We
found bilateral involvement of the ovaries but no extra-
ovarian spread intraoperatively. PET scan was not preoper-
alively made nor considered. Afterwards accurate investi-
gation of other systems and monitoring of the patient
before and during adjuvant therapies pointed out that the
disease had already progressed at the time of ovarian
metastatic site disclosure. Additional palliative treatment,
irradiation and chemotherapy did not achieve the desired
response. The patient died 15 months after surgery which
confirms, and is in accord with, the literature concerning
the inefficiency of applied adjuvant therapy.

It is elucidated that attentive monitoring of any pathol-
ogy of ovarian morphology in women with treated mali-
gnant melanoma is mandatory to detect an early and maybe
solely metastatic feature of the primary disease. Publicized
case reports and their analyses acknowledges relapse of the
disease after long remission time. Accurate screening using sophisticated diagnostic tools, particular-
ly up-to-date PET scan, could be used to monitor, detect
and differentiate latent or manifested spread of this dead-
ly disease [12].

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Isolated sigmoid colon metastasis from a primary fallopian tube carcinoma: a case report

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Summary

Isolated metastasis of primary fallopian tube carcinoma (PFTC) is extremely rare. We describe a case of a 41-year-old asymptomatic woman who was referred three years after the initial treatment for PFTC due to elevated serum CA-125 levels. The abdominal and pelvic CT scans revealed a pelvic mass near the top of the vaginal vault. On surgery, a sigmoid colon tumour was found and a sigmoidectomy was performed. On histopathology the tumour involved the bowel wall from serosa to submucosa, without involvement of the underlying mucosa. Immunohistochemical staining was positive for cytokeratin 7 and negative for cytokeratin 20, and the tumour was determined to be a metastatic müllerian neoplasm, consistent with the initial PFTC. Although this is the first reported case of colon metastasis of PFTC, the possibility of such an unusual site of metastasis should be kept in mind, as PFTC may recur as isolated bowel lesions even in the absence of peritoneal disease.

Key words: Fallopian tube carcinoma; Metastasis; Sigmoid colon.

Introduction

Primary fallopian tube carcinoma (PFTC) is an uncommon tumour accounting for approximately 0.1%–1.8% of female genital malignancies [1]. Although knowledge about the natural history and recurrence of PFTC is limited, distant metastasis is considered to be exceptional. Metastatic colorectal cancer on the other hand, occurs in only 1% of colorectal cancers and an isolated colonic metastasis is very rare [2]. To our knowledge this is the first reported case in the literature of PFTC with an isolated metastasis to sigmoid colon.

The patterns of spread of PFTC have long been considered similar to those of epithelial ovarian cancer (EOC), principally by the transcelomic exfoliation of cells that implant throughout the peritoneal cavity. In approximately 80% of patients with advanced disease, metastases are confined to the peritoneal cavity [1]. Tumour spread can also occur by means of contiguous invasion, transluminal migration, and haematogenous dissemination.

We present a case of PFTC in which an isolated sigmoid lesion limited to the serosa and muscularis propria was found without any evidence of mucosal involvement, three years after surgical debulking and platinum and paclitaxel-based combination chemotherapy.

Case Report

A 38-year-old Caucasian woman with a two-year history of primary infertility and no family history of cancer, was initially referred to our Department of Obstetrics and Gynaecology in March 2006 for treatment of progressively enlarging bilateral ovarian cysts, found during infertility investigation. The patient had already had seven unsuccessful intrauterine insemination cycles and three in vitro fertilization attempts, according to the short protocol of ovarian stimulation with GnRH agonist and gonadotrophins, but the pregnancy outcome was negative. Transvaginal (TVS) ultrasound as well as abdominal computed tomography (CT) scans showed bilateral adnexal masses; a right cystic mass (4.2 × 2.6 cm) and a left side complex mass (13 × 10 cm). The serum CA-125 and CA 15-3 concentrations were 600 U/ml and 32.6 U/ml, respectively (normal ranges < 35 U/ml, < 30 U/ml, respectively). The serum CA 19-9 and CEA were normal. The Papanicolaou cervicovaginal smear was negative.

Exploratory laparotomy at that time revealed bilateral adnexal masses. Frozen section evaluation of the left adnexal mass showed carcinoma. Staging laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy and retroperitoneal lymph node sampling were performed. There was no obvious tumour spread elsewhere in the abdominal cavity. Peritoneal cytology was positive. Pathologic examination revealed a grade 2, moderately differentiated right endometrioid PFTC. In the left ovary, an endometriotic cyst and metastatic implants from the contralateral PFTC were found. All 24 resected bilateral lymph nodes were free of disease. No evidence of neoplastic involvement of the uterus, the ovaries or the omentum was found. Estrogen and progesterone receptors were identified by immunohistochemistry (monoclonal antibody 6F11 for estrogens receptors and 1A6 for progesterone receptors, Novocasta, Newcastle, UK) in 40% and 10% of the neoplastic cells, respectively. The tumour was a FIGO Stage IIIC PFTC.

Surgery was followed by six cycles of combination chemotherapy using paclitaxel (175 mg/m²) and carboplatin (AUC 6) without significant complications. The patient had been followed-up with clinical examination and measurement of serum CA-125 levels, which have remained less than 15 U/ml for three years. A CT scan of the upper abdomen and pelvis, which was conducted biannually, showed no evidence of disease.

In January 2009, the patient while asymptomatic was referred...
abdominal or pelvic masses. At the time of this report, one year after the patient completed her chemotherapy, she remains asymptomatic. She is followed-up every three months with clinical examination and measurement of serum CA-125 levels, which up to now have been within the normal range.

Discussion

PFTC is a rare tumour that resembles EOC histologically, clinically, as well as in surgical staging, management, indications for adjuvant chemotherapy and recurrence pattern. The most common encountered spread pattern is intraperitoneal dissemination through the transcoelomic route to neighbouring organs and peritoneal surfaces. Despite this fact, most metastases are considered to be extrapelvic, and half or more of them are extraperitoneal, usually in combination with intraperitoneal recurrence [1]. Lymphatic and haematogenous dissemination is exceptional, found late in the course of the disease and presents as an inguinal lymph node [3], bone [4], or brain metastases [5]. To the best of our extensive literature search this is the first reported case of isolated sigmoid colon metastasis from a PFTC.

Given that all knowledge concerning colon metastasis comes from reports regarding EOC, it has been documented that the serosa is initially affected and then invasion extends from serosal and subserosal tissues into the muscularis propria and mucosa of the bowel wall. Reed...
et al. in their review of 77 autopsy records of patients with ovarian cancer, found metastasis to bowel serosa in only 86% and involvement to bowel mucosa in 36% of cases [6]. However, when mucosal involvement occurs, it may reflect either invasion from the serosal surfaces or haematogenous dissemination with infiltration of the submucosal capillary network. An atypical sigmoid metastasis from a high-grade mixed adenocarcinoma of the ovary has been reported, where the lesion was limited to the mucosa and muscularis propria without any evidence of serosal involvement [7]. More recently, Shibahara et al. reported a caecum metastasis in the muscularis propria and subserosa with only focal invasion of the colon mucosa and invasion of the retroperitoneum, which developed more than 20 years after the treatment of the primary bilateral ovarian cancers [8]. In the present case, the bulky tumour infiltrated the serosa extending to the colon mucosa. The pattern of metastasis was thought to have spread by the peritoneal route and one could expect the presence of advanced intraperitoneal tumour burden.

It is often difficult to distinguish between PFTC (especially the endometrioid and mucinous types) with sigmoid infiltration and primary gastrointestinal tract tumours. With regard to immunohistochemical staining which may be useful in the differential diagnosis, all the information comes from EOC. PFTC similar to ovarian carcinomas, other than those of mucinous type, are almost invariably positive for cytokeratin 7, while colonic carcinomas show noticeable positivity for cytokeratin 20 [9]. Loy et al. reported a cytokeratin 7 positive/cytokeratin 20 negative immunophenotype to be nearly 100% specific for an ovarian origin, and conversely a cytokeratin 7 negative/cytokeratin 20 positive immunophenotype was seen in 94% of the tumours of colonic origin [10]. Other tumour markers such as CEA and CA-125 can also be used; CA-125, estrogen receptors, and progesterone receptors are generally positive in ovarian and fallopian tube cancers, and CEA is generally positive in colorectal cancers [11]. In our case, the colonic tumour was positive for cytokeratin-7, CA-125, and estrogen receptors, and negative for cytokeratin-20, CEA, and progesterone receptors. This pattern was consistent with a müllerian rather than a colonic origin. In addition, a comparison of the patient’s PFTC with the colonic tumour revealed that the two tumours had similar histologic features.

In conclusion, we present the first case of PFTC with isolated sigmoid colon recurrence, diagnosed on the basis of increased serum CA-125 levels. The possibility of such an unusual site of metastasis should be kept in mind, even if the patient is asymptomatic and in a disease-free state. A high index of suspicion is needed, so that a colonoscopic evaluation – which was not performed in our case – could be considered as part of workup studies. Given that lack of peritoneal surface involvement does not exclude recurrence of PFTC, the treatment of choice for the solitary colon metastasis may be surgical, followed by adjuvant chemotherapy, while intensive surveillance is essential for an early diagnosis and appropriate treatment with the perspective of the best prognosis.

References


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Primary carcinoma of the neovagina: a case report

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Summary

We present a case of squamous cell carcinoma arising in the neovagina of a woman in whom we performed vaginoplasty 20 years before. To the best of our knowledge, this is the 23rd case of total carcinoma arising in the neovagina constructed because of vaginal agenesis, and the 3rd case of carcinoma arising in the neovagina performed without using a graft.

Key words: Vaginal agenesis; Vaginoplasty; Neovagina; Carcinoma.

Introduction

Congenital absence of the vagina is a very rare anomaly and it ranges from vaginal shortening in patients with androgen insensitivity to complete agenesis as part of Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome [1]. The treatment of partial or complete vaginal agenesis is surgical. A neovagina constructed by vaginoplasty does not have a zero risk of carcinoma. In this article, we present a case of carcinoma arising in a neovagina constructed without using a graft with dissection between the bladder and rectum because of vaginal agenesis due to MRKH syndrome. To the best of our knowledge, this is the 3rd case of carcinoma arising in a neovagina performed without using a graft, and the 23rd case of total carcinoma arising in a neovagina.

Case Report

In 1990, a 19-year-old white female was referred to the Gynecology Clinic of the University of Ondokuz Mayis for therapy of vaginal agenesis. In the patient diagnosed with MRKH syndrome, a neovagina was constructed by dissection between the bladder and the rectum, according to the method of Warthou, without using a tissue graft. An acrylic prosthesis of 10 cm in length and 3.5 cm in diameter was inserted into the neovagina following surgery. The patient was married and had satisfactory sexual activity; she was present at follow-up one year after surgery. She had no complications from the neovagina, except a persistent clear discharge. After the first year of the operation, the patient did not go to her control examinations.

In 2010, approximately 20 years after vaginoplasty, the patient presented to our outpatient clinic with complaints of bloody discharge and pelvic pain. In the years following surgery, she had a normal sex life and continued to insert the prosthesis into her neovagina each night for at least six hours for approximately 20 years. Pelvic examination revealed fragile granulation tissue of 3 x 4 cm in size in the apex of the neovagina. Pelvic ultrasound revealed a non homogenous mass of 40 x 23 mm in size in the neovaginal apex. Histopathological examination of the specimen taken from the granulation tissue in the neovaginal apex showed squamous cell carcinoma. There was no history of active or passive tobacco exposure, sexually transmitted diseases, radiotherapy application to the genital region or an operation due to genital malignancy previously. The patient underwent a series of diagnostic examinations including magnetic resonance imaging, cystoscopy and rectosigmoidoscopy. Tumor seemed to extend into the paravaginal tissues and to the pelvic sidewalls (Stage III tumor according to FIGO). The treatment was planned as intensity modulated radiation therapy (IMRT) + brachytherapy.

Discussion

As vaginal agenesis is a rare condition, carcinoma arising in the neovagina is also rare. In the literature, up to now, a total of 22 cases of carcinoma arising in the neovagina in patients who underwent vaginoplasty due to vaginal agenesis have been reported [1-7]. Of these, the information regarding ages of four patients at vaginoplasty, ages of three patients at carcinoma diagnosis, vaginoplasty technique and carcinoma type of two patients were not available [1-3]. Different kinds of materials have been used for vaginal reconstruction. The majority of operations have been performed using parts of intestines or skin grafts. Neovagina has been constructed without tissue transplantation in only two of the cases with reported neovaginal carcinoma in the literature [1]. The above-presented patient is the 3rd case with carcinoma arising in the neovagina without tissue transplantation. The primary malignancy of the neovagina appears to be related to the transplanted tissue except for two patients. Of these two patients, the one in whom a skin graft was used for the vaginal reconstruction had adenocarcinoma, the other in whom a urinary bladder flap was used had squamous cell carcinoma (Table 1).

Optimal treatment of the malignancies arising in the neovagina has not yet been determined, and every patient should be reported in detail with follow-up so that therapy can be evaluated. Like carcinoma in a natural vagina, survival may be related to the extent of disease at diagnosis. Nine of the patients reported were treated primarily with radiotherapy (7 with radiotherapy only, 1 with radiotherapy followed by posterior exenteration, 1 with radiotherapy followed by chemotherapy); nine with primary surgical therapy (1 with posterior exenteration, 1 with posterior exenteration followed by radiotherapy, 4
with total exteration, 2 with vaginectomy, 1 with vaginectomy followed by radiotherapy). The information regarding the treatment methods of four patients was not available [1-7].

It appears that no vaginoplasty has a zero risk of carcinoma. Moreover, the absence of transplanted tissue does not seem to protect the woman from the risk of carcinoma. Mechanical irritation from a prosthesis can add to other carcinoma risk factors, such as viral infection. Therefore, patients with neovagina, whatever the construction technique is, need to be followed up regularly. Additional case reports and prospective clinical studies are needed to determine optimal treatment options to improve patient prognosis.

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Uterine sarcoma with abdominal wall metastasis following laparoscopy: case report

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Summary

Purpose: This work aimed to prevent artificial implantation in laparoscopic surgery for gynecological tumors. Methods: A case of uterine sarcoma with abdominal wall metastasis following laparoscopy was analyzed for clinical features. Results: A diagnosis of uterine sarcoma was made in Stage IV and the previous laparoscopic surgery had caused artificial abdominal wall metastasis. Conclusions: We need to protect the puncture port in laparoscopic surgery of gynecological tumors to prevent artificial implantation.

Key words: Uterine sarcoma; Laparoscopy.

Introduction

Uterine sarcoma is rare and has a high degree of malignancy. Laparoscopy is one of the most advanced therapeutic methods for gynecological surgery with the extensive development of laparoscopic surgery, and the complications of this form of surgery have been gradually recognized. A patient with uterine sarcoma and abdominal wall metastasis following laparoscopy presented at our hospital. The clinical features of the case are analyzed.

Case Report

A 37-year-old woman was admitted to Shenzhen Nanshan Hospital on April 6, 2010 after a physical examination revealed clumps in her pelvic cavity. The patient had undergone laparoscopic resection for a hysteromyoma at another hospital in May 2009. Physical examination revealed three scars (length 1 cm each) from the previous laparoscopic surgery in the hypogastric and umbilical regions. The surgery scar in the right lower quadrant had significantly expanded, and a clump (6 × 8 cm) could be detected under the scar on palpation. Magnetic resonance imaging (MRI) examination revealed a space-occupying lesion in the uterus and its periphery along with invasion of the right lower abdominal wall by the lesion. The patient underwent exploratory laparotomy on April 12, 2010. We observed that the surfaces of hysterauxesis, peritoneum and intestinal canal were covered with white nodules of various sizes. The bilateral adnexa appeared normal and the swollen clumps were scattered in the pelvic cavity. The peritoneum around the scar in the right lower quadrant revealed irregular intumescence; its surface showed small white nodules. The masses were obtained and frozen for pathological examination. All masses were considered to be malignant tumors. The patient decided that she wanted to retain at least one ovary. Therefore, we performed resection of the whole uterus, right adnexa, and left oviduct. The findings of the postoperative pathological examinations are as follows: poorly differentiated endometrial stromal sarcoma with gonadal stromal differentiation (Figure 1). A diagnosis of uterine sarcoma was made in Stage IV.

Discussion

As the patient could not provide any specific condition for the previous surgery nor a detailed pathological diagnostic report, we believe that hysteromyoma was an erroneous diagnosis. The pathological diagnosis in this surgery indicated that the patient’s pathological state of the uterus was totally in accordance with the pathological state of abdominal wall metastasis. Moreover, the tumor position for abdominal wall metastasis was located just in the periphery of the puncture port of the right lower quadrant from the last surgery. Based on these features, we conclude that some tissue of uterine sarcoma

Revised manuscript accepted for publication February 22, 2011
remained in the puncture port of the abdominal wall while obtaining the specimen during the first surgery, thereby artificially inducing abdominal wall metastasis. Previous studies [1-3] have reported that tumor fragments that remain in the abdominal cavity after pulverization during laparoscopic resection of a hysteromyoma could directly get implanted in the peritoneum. The case indicates that during laparoscopy, the puncture port needs to be protected.

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Gestational choriocarcinoma arising in a tubal ectopic pregnancy: case report

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Introduction

Ectopic pregnancy is one in which the site of implantation occurs other than the endometrial cavity. Its incidence is reported as 1.3-2% [1]. Gestational choriocarcinoma associated with ectopic pregnancy is an extremely rare event with a reported incidence of approximately 1.5 per 1,000,000 births [2]. We report a case of a primary tubal choriocarcinoma.

Case Report

A 38-year-old, gravida 4, parity 3, patient was admitted to the emergency room with the complaint of abdominal pain. Vital signs were in normal ranges. Peritoneal irritation signs were present and serum hCG level was found to be greater than 15000 mU/l. Transvaginal ultrasound images were compatible with ruptured tubal ectopic pregnancy. Hemoperitoneum and ruptured tuba were found at laparotomy and a right salpingectomy was performed. The histopathological evaluation reported the lesion as primary tubal choriocarcinoma. The patient was referred to a tertiary care center for treatment and follow-up. Conclusion: Adequate monitoring of β-hCG titers and careful examinations of pathologic specimens are important to avoid misdiagnosis of ectopic gestational trophoblastic disease.

Key words: Choriocarcinoma; Ectopic pregnancy; Gestational trophoblastic disease.

Discussion

Choriocarcinoma is one of the most serious forms of gestational trophoblastic neoplasia (GTN). Although most cases develop following molar pregnancy, these tumors may follow term pregnancies, spontaneous abortions, pregnancy termination or ectopic pregnancy. Clinical presentation of ectopic GTN is similar with ectopic pregnancy. Gillespie et al. determined the clinical presentation, treatment, and outcome of women diagnosed with ectopic gestational trophoblastic neoplasia [2]. This study concluded that the presentation of ectopic gestational trophoblastic disease is similar to that of ectopic pregnancies. Also, Muto et al. reported that patients with tubal gestational trophoblastic disease including partial and complete hydatidiform mole, invasive mole, choriocarcinoma, and placental site trophoblastic tumor cannot be distinguished from patients with tubal pregnancies by means of presenting signs, symptoms, or laboratory tests [3].

The rate of ectopic pregnancy and mean maternal age has increased and more conservative treatment options have become more acceptable. Medical therapy is preferred by most as an alternative treatment. Only methotrexate has been extensively studied as an alternative to surgical therapy [4]. The treatment is initiated without histopathologic determination. Bakri et al. stress that appropriate monitoring of β-hCG titers is essential to determine the need for surgical treatment and to avoid missing ectopic gestational trophoblastic disease [5].
In conclusion, to avoid misdiagnosis of ectopic gestational trophoblastic disease, adequate monitoring of β-hCG titers and careful examinations of pathologic specimens are important.

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Rare metastases of carcinoma of uterine cervix

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Summary
This paper describes a case of cancer of the uterine cervix metastasizing in the spleen two years after the primary carcinoma was diagnosed and treated. After detailed diagnostics, the patient was subjected to surgery. Histopathological examination after splenectomy confirmed a very rare case—presence of metastases of planocellular carcinoma of the uterine cervix. Over the last ten years, references cite isolated cases of metastases of adenocarcinoma of the colon, stomach and breast metastases to the spleen as well as lung carcinoma and malignant skin melanoma. Until now cases of uterine cervix carcinoma metastasizing to the spleen have been published as micrometastases detected in autopsy material.

Key words: Metastases in the spleen; Uterine cervix carcinoma.

Introduction
Secondary deposits in the spleen are extremely rare. Over the last ten years, references have described only isolated cases of adenocarcinoma of the colon, stomach and breast metastases to the spleen [1-4]. Such metastases of lung carcinoma and malignant skin melanoma in the spleen are somewhat more frequent, while planocellular carcinoma metastases are extremely rare [5-7]. A case of planocellular carcinoma of the lower third of the esophagus metastasizing to the spleen and the tail of the pancreas has been reported [8]. As far as metastases of carcinoma of the uterine cervix to the spleen are concerned, published studies performed on autopsy material show that cervical carcinoma rarely metastasizes to the spleen—micrometastases of this carcinoma in the spleen have been found in 1.6% cases of untreated patients and 1.2% cases of patients diagnosed with cervical carcinoma [9, 10]. Cases of patients with diagnosed and histopathologically confirmed metastases (after splenectomy) of this carcinoma in the spleen during the survival period are isolated and rare [11].

Case Report
This paper describes a case of planocellular uterine cervix carcinoma metastasizing to the spleen two years after being detected and treated. At the moment the primary tumor was detected the patient was 40 years old. Colposcopic examination detected a polypoid formation on the uterine cervix which bled on contact and was immediately subjected to biopsy. The biopsy was more complicated due to profuse bleeding, causing the patient to be rushed to the University Clinic of Gynecology and Obstetrics where the bleeding was taken care of. Invasive planocellular carcinoma of the uterine cervix in clinical Stage Ib according to FIGO was verified. Radical hysterectomy according to Wertheim-Meigs was performed without operative and postoperative complications. Definite postoperative histopathological findings verified planocellular uterine cervix carcinoma FIGO Stage Ib, histological grade G2NG2, without lymph and vascular invasion and without metastases in the removed lymph nodes. Considering the patient’s age and tumor histological grade, oncological treatment was continued by administration of radiation therapy for a month, transvaginally and transcutaneously according to a suitable protocol. Undesired effects of radiation therapy were present: gastrointestinal discomfort, dermatitis and colpitis.

The patient underwent regular quarterly check-ups and was without signs of disease during the next two years. Exactly two years after surgery, Color Doppler ultrasound examination of the abdomen revealed two hypoechochogenic round lesions in the spleen 25 and 30 mm in size (Figure 1). Doubt was raised about the presence of secondary deposits. The patient thus underwent computerized tomography (CT) examination, but also this method was not able to give an accurate diagnosis. Nevertheless, during this diagnostic period which lasted about one month, the patient started to complain about pain under the left ribs which spread to the left part of the dorsum, initially weak, but growing stronger, accompanied by irregular bowel movements and rice water stools. Finally, surgery was performed and the presence of metastases in the spleen was detected. Secondary malignant disease had perforated the spleen capsule in two areas on the outer side of the spleen (Figure 2).

Splenectomy was performed according to the standard surgical procedure. Based on abdominal cavity exploration it was ascertained that the malignant disease was in advanced stage. Secondary deposits affected the iliac cavities, extending towards the femoral region and completely surrounding the large blood vessels. Histopathological results confirmed existence of metastases of a very weakly differentiated planocellular carcinoma in the spleen.

The patient recovered well one month after surgery. However, during the second month after surgery the patient’s condition progressively worsened. The gastrointestinal discomfort kept intensifying, causing general weakness and exhaustion. One month later exitus letalis occurred.

Discussion
According to data from the literature, secondary deposits of various malignant tumors in the spleen are found in 0.002% of cases. They are more frequent in men.
Analysis of malignant tumors which metastasize to the spleen concluded that the most frequent are lung carcinoma (24.6%), followed by malignant skin melanoma (15.8%) and breast carcinoma (12.3%) [9]. Colorectal carcinoma, stomach carcinoma, hepatocellular carcinoma are next in frequency [12-14]. Metastases of carcinoma of uterine cervix have been described in material obtained during autopsy as micrometastases, while individual cases discovered during the survival period are extremely rare [5]. Only few such cases are known - most often the disease progression takes place two to three years after surgical treatment followed by radiation therapy in patients whose disease was in clinical Stage II when it was discovered.

All data published until now show that appearance of metastases in the spleen is the sign of an extremely poor prognosis. Average survival after splenectomy in all cases of surgically diagnosed metastases equalled approximately three months.

Diagnosing metastases can be a difficult issue [15-18]. Thus it requires the use of modern equipment, CT, magnetic resonance imaging and even positron emission tomography which has been described in the literature as the most precise method for detecting secondary deposits in the spleen. For the patient, the main problem is the time which passes before clinical diagnostics and a decision about further treatment, considering the fact that metastases to the spleen are signs of advanced disease, i.e. of an extremely poor prognosis.

Another problem related to metastases in the spleen is possible rupture of the spleen and possible thrombosis of the lineal vein and all complications deriving from these two states. Figure 3 depicts rupture of the spleen in the case presented in this paper (Figure 3).

Rupture of the spleen has been described in several cases of lung, colorectal and breast carcinoma metastases [19, 20].

In recent years great importance has been ascribed to prevention, detection and timely treatment of asymptomatic lesions because this is the most efficient way of fighting against malignant diseases of the uterine cervix. This goal is best achievable by vaccination and systemic screening of the female population.

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Angiokeratoma of the vulva

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Introduction

Angiokeratoma of the vulva is an uncommon benign cutaneous lesion [1, 2]. Its etiology and pathogenesis remain unclear. Perhaps it is the result of dilation of ectatic thin-walled blood vessels and congested capillaries in the subdermal layer [3].

It generally occurs on the labia majora and rarely on the clitoris [1, 2]. It is easily confused with other benign and malignant tumors from which they must be differentiated by histological examination [1, 2]. We present two cases of angiokeratoma of the vulva and review the literature.

Case Report

Case 1

The patient, a 65-year-old, gravida 1, para 1, postmenopausal Greek woman presented with the complaint of vulvar pruritus. Her past surgical history was unremarkable. Her family history revealed no evidence of cancer among the first-degree relatives.

On gynecologic examination there was a bluish globular lesion 1.1 cm involving the left labia major. There were no palpable inguinal lymph nodes and the rest of pelvic examination was normal.

The patient underwent wide local excision of the lesion. Histopathology revealed angiokeratoma of the vulva.

Follow-up 48 months after initial surgery showed no evidence of recurrence.

Case 2

The patient, a 69-year-old, gravida 2, para 2, postmenopausal Greek woman presented with the complaint of vulvar pruritus. Her past surgical history was unremarkable. Her family history revealed no evidence of cancer among the first-degree relatives.

On gynecologic examination there was a cherry red papular lesion 0.7 cm involving the right labia major. There were no palpable inguinal lymph nodes and the rest of pelvic examination was normal.

Follow-up 32 months after initial surgery showed no evidence of recurrence.

Discussion

Angiokeratoma is a benign vascular lesion, characterized by ectatic dilatation of preexisting vessels of the papillary dermis accompanied by a hyperkeratotic epidermis [4]. Angiokeratoma of the vulva is relatively uncommon [1, 2]. It may affect women between 20 and 40 years of age (range 15-58 years) [1, 2]. There is no racial distinction [2]. It has been observed in both white and black women [1, 2, 5, 6].

Its etiology and pathogenesis remain unclear. Embryologically the labia majora and scrotum are derived from the labioscrotal swellings [2]. As they are homologues, the pathophysiology of vulvar and scrotal angiokeratoma is thought to be the same [1, 2, 7, 8].

Angiokeratoma of the vulva perhaps is the result of dilation of ectatic thin-walled blood vessels and congested capillaries in the subdermal layer [3]. Degenerative changes in the elastic tissue of the blood vessels appear to be important in the pathogenesis [1, 2]. These changes could result from a primary (congenital, idiopathic) or a secondary process (decreased nonstriated muscle support, increased venous pressure, chronic inflammation) [1, 2]. Pregnancy, hysterectomy, vulvar varicosities, hemorrhoids, inflammation and radiation have been presumed to be predisposing factors [1, 2, 7, 9, 10]. In our patients we could not find any predisposing factors.

It generally occurs on the labia majora and rarely on the clitoris [1, 2]. In most cases it is unilateral and located on the left side of the vulva [1, 2]. The lesions may be single or multiple (maximum 24 lesions) [1, 2, 11]. In our patients, the lesion was single and located on the labia majora.

The lesions usually measure between 2 mm and 10 mm in diameter and may assume a papular, globular or warty...
appearance [1, 2, 7, 11]. The earlier lesions are cherry red in color which become bluish or brownish as they increase in size and duration [1, 2, 7, 11, 12]. In our cases, one patient had a bluish globular lesion 1.1 cm and one patient had a cherry red papular lesion 0.7 cm in size.

Angiokeratoma of the vulva is usually asymptomatic [1, 2, 11]. The most common symptoms are intermittent bleeding (25%), vulvar pruritus (11%) and pain (9%) [1, 2, 6]. Frequently, patients complain of blood-stained underwear [1]. Patients with symptoms often seek medical attention sooner than those with asymptomatic lesions [1, 2]. Our patients presented with a complaint of vulvar pruritus.

Because of the varied clinical presentation, angiokeratoma of the vulva should be clinically differentiated from infectious (bacterial, viral), inflammatory, vascular and epithelial (benign, malignant) lesions [2, 7, 9]. In all patients the diagnosis must be confirmed by biopsy [2, 7, 13]. For patients with asymptomatic lesions reassurance with periodic follow-up is an adequate approach [2]. For patients with symptomatic lesions the therapeutic options are surgery (local excision, vulvec- tomy), electrosurgery and laser [2, 5, 7, 12-15]. Laser therapy has recently become the treatment of choice because it is less painful, causes minimal blood loss and cosmetically is much better, though the disease may recur more often compared to surgical excision [2, 12, 14, 15]. In our patients we performed wide local excision of the lesion.

Although it is a rare disease, angiokeratoma of the vulva should be included in the differential diagnosis of a vulvar tumor.

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