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EUROPEAN JOURNAL OF GYNAECOLOGICAL ONCOLOGY (ISSN 0392-2936) publishes original peer reviewed works in the fields of female genital cancers and related subjects and also proceedings of gynecologic oncology society meetings all over the world. The Journal is covered by CURRENT CONTENTS, SCISEARCH, RESEARCH ALERT, INDEX MEDICUS, MEDLINE, EMBASE/Excerpta Medica, CURRENT ADVANCES IN CANCER RESEARCH, BIOSIS.
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An improved, disposable indwelling intrauterine tube ("Smit Sleeve") not requiring retaining stitches for brachy-radiotherapy for carcinoma of the cervix

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Summary

Objective: The objective was to improve the design of the indwelling-intrauterine tube (IIUT) for brachy-radiotherapy of cervical cancer or sleeve, specifically one that would not require stitching to retain it properly in the uterus for periods of one to two weeks and to ensure hygiene by making them disposable, thinner, lighter, more economical, as well as more user-friendly for doctor and patient alike, and to satisfy new developments in terms of computed tomography (CT) and magnetic resonance imaging (MRI) compatibility. Materials and Methods: Injection moulding of carefully-selected medical grade polymers enabled ten improvements to the original sleeve; some were impossible to achieve with lathe turned items. The most important innovation was the addition of two delicate and very soft "wings" to the sleeves near the tips. The sleeves were used in 50 consecutive patients with advanced carcinoma of the cervix. Metal markers could be eliminated by adding barium to the polymers. Results: Not a single sleeve fell out in any of the 50 patients. No complications related to the use of the sleeves were observed. These sleeves are now used exclusively in this clinic. Conclusions: The improvements were very successful; none fell out and no suturing was required, which made them still more cost-effective and more comfortable to patients.

Key words: “Smit Sleeve”; Brachy-radiotherapy; Cervical Carcinoma.

Introduction

The indwelling intrauterine tube (IIUT) was first described in 1989 [1] and showed that the clinical and pathological results obtained in 52 patients with Stage IB cervical cancer treated with a course of 8, 12, or 16 fractions of high-dose rate remotely-controlled brachy-radiotherapy (HDRBRT), unheard of at the time, was comparable to the results in 34 patients with Stage IB treated with low dose-rate radium. The intracavitary therapy in Stage IB patients with cervical cancer preceded a Wertheim-Meigs hysterectomy. The article showed for the first time that the IIUT enabled the easy and safe administration of multiple fractions of HDRBRT, satisfying the radiobiological demands for adequately fractionated high-dose rate (HDR) radiotherapy, eliminating the need for multiple anaesthetics simultaneously. The multi-fractionated treatments could be given on an outpatient basis, greatly reducing costs and greatly improving patient comfort. Further details were supplied later [2, 3]. An analysis of 732 patients with Stage III cancer of the cervix affirmed the long-term safety and efficacy of the method and modality [4]. There were however, minor problems with the older sleeves, mainly the high cost of producing the original sleeves on a lathe, the tendency of sleeves to fall out and to be lost, and the need for cleaning, re-sterilizing, and re-packaging, not ideal in an age where HIV/AIDS infections are rampant. Besides the radiobiological advantages of the IIUT [5, 6], it also prevented accidental perforation of the uterus by the source guide tubes (SGTs) and acted as a drainage tube, for example in cases of pyometra; this feature stopped delays in treatment. All the positive attributes of the original sleeve were retained. The sleeves are recommended for routine use by the Royal College of Radiologists [7].

Materials and Methods

Injection moulding enabled the addition of very delicate "wings" to the shaft to retain the sleeves in utero without suturing and the sleeves could be made disposable: features which were impossible before; altogether ten improvements resulted. The sleeves were used in 50 consecutive patients and none fell out. The injection moulded sleeves are now used exclusively in this busy clinic.

Results

Ten improvements could be identified: the addition of two delicate "wings" to the shaft of the sleeve (Figure 1) The wings are just sturdy enough to support the weight of the sleeves. The wings were designed so that they fold during insertion and extraction of the sleeve without causing any trauma. The wings "catch" the sleeve in the narrowing portion of the uterine cavity before the internal os. For the very short sleeves (30 mm), the wings do not reach beyond the internal cervical os, but catch in the widest point of the cervical canal between the internal and external openings, and the external os acts as a carrier for the sleeve. The "wings" are very slender, flexible, and soft projections 5.5 mm long x two mm wide x one mm thick with rounded, non-traumatic edges.

Barium sulfate could be mixed in with the polymer granulate, thus rendering the sleeves opaque to X-rays, including CT scanning and eliminated the need for metal markers, which also make them suitable for imaging by

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used, sleeves have open ends so that any length of SGT can be
50 mm, with 4.5 inner canal that would enable the use of
tumor in each sterilized packet.

Intervals and are immediately available to the radiation
sleeve lengths vary from 30 mm to 80 mm long in one cm
end could be only made with a 5.4-mm diameter The
walls could be made thinner, thus demanding lesser dilatation of the
cervix should be about six mm for the short sleeves (< 50 mm) and seven to eight mm for the very long
sleeve (80 mm) or about 1.0 mm more than the outside diameter
of the thickest section of the sleeve shaft.

Figure 1. — Shows the modified intra-uterine sleeve in position
in the uterus. The delicate ‘wings’ are sturdy enough to support
about ten times the weight of the sleeve. On insertion or extrac-
tion of the sleeve, the soft wings simply fold away without
causing trauma. The thin front end makes insertion easier.
Dilatation of the cervix should be about six mm for the short
sleeves (< 50 mm) and seven to eight mm for the very long
sleeve of the new design fell out, nor was there any evi-
dence of trauma, infection, discomfort or any untoward
reaction. The sleeves have now been in use in this busy
clinic for more than 27 months from May 2010 of August
2012. It needs to be noted however, that the wings are
there purely to keep the sleeve in the uterus—it is not a
strong physical anchor, and care needs to be taken not to
dislodge the sleeve when removing the SGT; gentle
contra-pressure is needed on withdrawal. A special instru-
ment for this is being designed.

Normally around 15% of the older sleeves dislodged
and fell out, which implies a treatment delay, while a
second placement under anaesthesia is scheduled. The
new sleeves therefore promise to be a substantial cost
saver by eliminating cleaning, re-packing, and re-steriliz-
ing the used sleeves, and by avoiding second forays to the
operating room/theater. Lost sleeves of the older type was
a major cost factor, now eliminated by the new more
effective sleeves.

Conclusions
None of the basic benefits of the older generation
sleeves were sacrificed, a major gain was the elimination
for the need for suturing the sleeves in place, making them
MRI compatible and more hygienic. The new alterations
will make the sleeves even more user-friendly, cost-effec-
tive, and safe – to the operator, theatre staff, hospital, and
patient. Figure 1 illustrates features of the new sleeve.

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uterine tube to facilitate intra-cavitary radiotherapy of carcinoma of the
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Impact of multimodal therapy on the survival of patients with newly diagnosed uterine carcinosarcoma


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Summary

Purpose: To investigate treatment outcomes of uterine carcinosarcoma (CS) patients who underwent complete surgical resection of all visible disease and platinum-based adjuvant chemotherapy (multimodal therapy). Materials and Methods: The authors reviewed 127 uterine CS patients treated at this institution from 1990 to 2010. They operated 123 patients in clinical Stages 1-3, 97 of which underwent complete resection and systemic lymphadenectomy. Results: A total of 97 patients (FIGO 2008: Stage 1 in 50 patients, Stage 2 in six, Stage 3 in 37, and Stage 4 in four) underwent surgical staging, 74 of which were administered five cycles (median) of platinum-based adjuvant chemotherapy. The median overall survival (OS) associated with multimodal therapy 50.6 months compared with 34.9 months incomplete multimodal therapy. After multimodal treatment, 32.9% (32/97) patients showed recurrence (24/32 hematogenous). Conclusion: Multimodal therapy increased survival among uterine CS patients, but the recurrence rate remained high. Further consideration of treatment options for uterine CS is required.

Key words: Uterine carcinosarcoma; Multimodal therapy; Prognostic factor.

Introduction

Uterine carcinosarcoma (CS) is a rare but aggressive malignancy. It has a propensity for hematogenous and lymphogenous spread, resulting in poor overall survival [1]. Since 2008, CS have been classified according to the International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial adenocarcinoma. It is currently unclear whether it is best to perform complete surgical resection with systemic lymphadenectomy and to administer postoperative adjuvant chemotherapy, and there is no established procedure [2]. Limited data suggest that survival is improved in CS patients with complete resection of disease, but these data have not been evaluated in the setting of contemporary risk factors for recurrence or recent chemotherapeutic options. Few prospective trials have evaluated therapeutic strategies for uterine CS independent of other uterine sarcomas [3]. The strategy of lymphadenectomy for staging purposes is a possibility to reducing the recurrence, resulting in the removal of micro-metastatic foci and target tissue. Adjuvant chemotherapy may also reduce hematogenous distant metastases. The authors performed this retrospective review to investigate the treatment outcomes of patients with CS in terms of survival and disease recurrence and attempted to identify factors predictive of survival. This study aimed to determine whether complete surgical resection of all visible disease with systemic lymphadenectomy and adjuvant chemotherapy had an impact on the survival outcome of uterine CS.

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Materials and Methods

This was a retrospective case-control trial. Following institutional review board (IRB) approval, 127 uterine CS patients who were treated at the Cancer Institute Hospital (CIH) between January 1, 1990, and December 31, 2010, were identified. Multimodal therapy was defined as complete surgical resection of all visible disease followed by at least three cycles of platinum-based adjuvant chemotherapy. Four patients were excluded if they had incomplete medical records or other pathology. All surgico-pathological information, including the history (homologous or heterologous), tumor size and location, uterine variables, lymph node metastasis, other organ involvement, demographics, FIGO stage, surgical outcome, and survival were identified from medical records and reviewed. The histological subtypes of the uterine tumors were determined according to the 2003 World Health Organization (WHO) classification of tumors. Tumors were diagnosed as CS if both malignant epithelial and mesenchymal elements were evident. Histological slides were reviewed by one of the investigators who is a pathologist. These data were used to update the disease Stage based on the FIGO 2008 staging for endometrial carcinoma. All of the patients underwent surgery performed by gynecologic oncologists. Surgical staging comprised of an abdominal extrafascial hysterectomy or modified radical hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and systemic lymphadenectomy for surgical staging. After surgery, the only adjuvant therapy administered was chemotherapy, and no patient underwent radiation therapy. Before 2005, the patients received ifosfamide-cisplatin-epirubicin combination chemotherapy. An alternative regimen of carboplatin-paclitaxel therapy was used for uterine CSs from 2006 to 2010. The authors aimed to administer six cycles of chemotherapy with a schedule of cisplatin at 15 mg/m2 for five days plus ifosfamide at one gram for four days, with mesna plus 50 mg/m2 epirubicin on day five approximately every three weeks. Paclitaxel at 175 mg/m2 (administered as a three-hour intravenous infusion) and carboplatin AUC6 were administered for six cycles approximately every three weeks (Figure 1).
Statistical analysis

Progression-free survival (PFS) was defined as the interval from the date of primary surgery to the date of the first documented recurrence based on a measurable lesion identified by computed tomography (CT) or positron emission tomography-CT (PET-CT). Overall survival (OS) was defined as the interval from the date of primary surgery to the date of death or last follow-up. The OS and PFS rates were determined for all patients, and the rates were calculated using the Kaplan-Meier method. Factors such as the presence of lymph node involvement, lymphovascular space invasion (LVSI), depth of tumor invasion, adnexal invasion, tumor size, washing status, and histology were also analyzed. Univariate and multivariate Cox regression analyses were performed to identify factors predictive of survival outcomes and to estimate hazard ratios. The statistical significance level was set at 0.05. All statistical analyses were performed using SPSS version 18.

Results

Procedures for determining survival

A total of 123 patients underwent primary surgery for clinical Stages 1-3 uterine CS at CIH. Of these patients, 97 underwent complete resection of all visible disease with staging laparotomy including lymphadenectomy. After complete surgical resection, 74 patients received more than three cycles of total platinum-based adjuvant chemotherapy. The remaining 23 patients underwent complete resection and less than two cycles of platinum-based adjuvant chemotherapy. Multimodal therapy was thus achieved in 74 of the 97 patients. A total of 76.3% (74/97) of the patients received adjuvant chemotherapy. Twelve patients rejected additional treatment, and 11 could not receive sufficient adjuvant chemotherapy because of disease progression. Among the 26 patients with incomplete resection (residual disease), 76.9% (20/26) received adjuvant chemotherapy. Adjuvant chemotherapy was not administered or was administered over an insufficient number of cycles because of early disease progression in six patients. The median OS for the entire cohort was 44.5 months. The median OS in patients who underwent complete resection was 50.6 months, compared with 34.9 months in the patients who underwent incomplete resection. There was thus a trend toward improved OS in the patients who underwent complete resection (50.6 vs 34.9 months) (Figure 2).

Patient and tumor characteristics

Prognostic factors were evaluated to determine whether there was an association between OS and PFS among 97 patients who underwent complete surgical resection of all visible disease (Table 1). The FIGO 2008 Stages in these patients were as follows: 50 patients (51.5%) had Stage 1; six (6.1%) had Stage 2; 37 (38.1%) had Stage 3; and the remaining patients had Stage 4 (4.1%). Of the four patients with Stage 4, two had peritoneal dissemination, one had omental metastasis, and two had direct intestinal invasion. All of the patients underwent hysterectomy: total abdominal hysterectomy (28 patients), modified radical hysterectomy (60 patients),
Impact of multimodal therapy on the survival of patients with newly diagnosed uterine carcinosarcoma

and radical hysterectomy (nine patients). In addition, all patients underwent bilateral salpingo-oophorectomy and systematic lymphadenectomy, including pelvic lymphadenectomy. Seventy-three (75.2%) patients also underwent para-aortic lymphadenectomy. The median number of lymph nodes collected from the pelvic and para-aortic regions was 49 (range 21-113), which was an acceptable number. If the patients had peritoneal dissemination or metastatic disease in other organs at the time of surgery, additional surgical procedures were performed in cooperation with the surgical oncologist. Additional extensive surgical procedures were performed in 19 patients including the following: omentectomy (19 patients), bowel resection (two patients), and peritoneal resection (two patients). Multimodal therapy was administered to 76.3% (74/97) of patients and included at least three cycles of postoperative platinum-based chemotherapy (median five cycles, range three to seven cycles) after complete surgical resection. Twenty-three patients did not complete the prescribed course of postoperative chemotherapy because of death or disease progression (11 patients) or intolerance and refusal to continue treatment (12 patients). The ifosfamide-cisplatin-epirubicin combination chemotherapy regimen was administered to 52.7% (39/74) of the patients. The carboplatin-paclitaxel combination chemotherapy regimen was administered to 43.2% (32/74) of patients, and another platinum-based chemotherapy regimen was administered to 4% (3/74) of patients.

Risk factors for recurrence and prognostic factors predictive of survival

At the time of analysis, 32.9% (32/97) of the patients had experienced disease recurrence and 27.8% (27/97) had died. The median follow-up period was 49.3 months. The following prognostic factors were not associated with the risk of recurrence or death: age, surgical procedure, histological type, cervical or adnexal invasion, LVSI, washing status, and tumor size. Adjuvant chemotherapy, lymph node metastasis and myometrial invasion were associated with PFS in the multivariate analysis. Although adjuvant chemotherapy was not significant in the univariate analysis. Clinically, this factor was thought to be very important, and it was therefore included in the multivariate analysis. The presence of adjuvant chemotherapy, lymph node metastasis and myometrial invasion were associated with PFS in the multivariate analysis. Although adjuvant chemotherapy had no influence on OS.

Table 1. — Patients and tumor characteristics.

<table>
<thead>
<tr>
<th>Demographics</th>
<th>No.</th>
<th>Median age (range) 59.0 [27 - 79]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological Stage (FIGO 2008)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Surgical procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLX + PALX</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>PLX only</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homologous</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Heterologous</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Lymph vascular space invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth &lt; 1/2</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Depth ≥ 1/2</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>Cervical invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Adnexal invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>83</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Washing status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>


Table 2. — Univariate and multivariate analyses of factors associated with progression-free survival (PFS), and overall survival (OS) in uterine carcinosarcoma.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
<th>Overall Survival Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median PFS (months) (95% CI)</td>
<td>Hazard Ratio (95% CI)</td>
<td>Median OS (months) (95% CI)</td>
</tr>
<tr>
<td>Lymph node</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>50.1 (45.5 - 54.8)</td>
<td>1</td>
<td>52.1 (47.9 - 56.2)</td>
</tr>
<tr>
<td>Positive</td>
<td>34.4 (25.8 - 42.9)</td>
<td>0.005</td>
<td>3.15 (1.28 - 7.75)</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1/2</td>
<td>54.8 (49.9 - 59.6)</td>
<td>1</td>
<td>55.8 (51.7 - 59.9)</td>
</tr>
<tr>
<td>≥ 1/2</td>
<td>39.1 (33.1 - 44.1)</td>
<td>0.004</td>
<td>3.42 (1.12 - 10.4)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3 cycles</td>
<td>50.9 (47.0 - 54.9)</td>
<td>1</td>
<td>51.2 (47.2 - 55.2)</td>
</tr>
<tr>
<td>0-2 cycles</td>
<td>46.2 (37.3 - 55.0)</td>
<td>0.117</td>
<td>3.67 (1.46 - 9.22)</td>
</tr>
</tbody>
</table>

Factors without a survival association: age, surgical procedure, histological type, cervical or adnexal invasion, lymph vascular space invasion, washing status, and tumor size.
Table 3. — Site of first recurrence in 32 patients.

<table>
<thead>
<tr>
<th>Number of sites</th>
<th>Single</th>
<th>Multiple</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of recurrence</td>
<td>Pelvis</td>
<td>Vagina 6</td>
</tr>
<tr>
<td></td>
<td>Pelvic tumor</td>
<td>5</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Liver</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Omentum</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal tumor</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Peritoneum</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
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<td>Distant metastasis</td>
<td>Lung</td>
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<td>Bone</td>
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<td>Mode of metastasis</td>
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<td>Lymphogenous</td>
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<td>Disseminated</td>
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<td></td>
<td>Local recurrence</td>
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Recurrence

Of the 97 patients, 32 (32.9%) experienced disease recurrence within five years. The median follow-up period for the surviving patients without recurrence was 44.5 months (95% CI: 40.1-49.0 months). The site of first recurrence was classified as pelvic, abdominal, and distant. Multiple sites of first recurrence were counted once for each site. The site of recurrence and mode of metastasis were duplicated. A total of 65% of the patients had multiple sites of recurrence when the relapse was diagnosed. Hematogenous metastasis appeared to be more common and affected 23 patients. The most common site of recurrence was in the lungs (14 patients). Metastases were also identified intra-abdominally in 13 cases, in the liver in three, in the omentum in two, and in the spleen in one case. Five patients had bone recurrence. Only five patients had lymphogenous metastasis, three of whom had metastasis in an extra-lymphadenectomy region, such as the inguinal or mediastinal lymph nodes. Four patients had disseminations identified in the peritoneum and six patients had local recurrence in the vagina (Table 3).

Discussion

CS is an aggressive uterine cancer with a propensity for hematogenous and lymphogenous spread resulting in a poor survival rate. Despite multimodal treatment, the five-year DFS in various reports has ranged from 33% to 39% [4, 5]. This study assessed a relatively large cohort of patients treated at a single institution who were followed over a 20-year period. Ninety-seven patients who underwent complete surgical resection of all visible disease were eligible for analysis. Surgical factors predicting survival were also evaluated. Complete surgical resection with systemic lymphadenectomy was associated with a 24-month improvement in OS over those following surgical procedures for residual disease (73.2% vs 30.2%, respectively; \( p < 0.001 \)). The actual therapeutic effect of radical surgery, which is the complete surgical resection of all visible disease with systemic lymphadenectomy, appears to be an important predictor of survival for this rare uterine malignancy. Similar results have also been reported in the majority of published studies [6]. As a first step, an attempt toward complete resection of uterine CS may be reasonable given the poor prognosis [7]. In the present study, complete resection and surgical staging, including pelvic and/or para-aortic lymphadenectomy, were performed under the same procedure at a single institute; therefore, physician bias can be considered to be minimal. Temkin et al. [8] stated that the dissection of 21-25 lymph nodes is required to assess the extent of lymph node metastasis. In this study, the average number of lymph nodes collected from the pelvic and para-aortic regions was 49 (range 21-113), which is considered to be an adequate number. A total of 31.9% (31/97) of patients demonstrated lymph node metastasis. The incidence of lymph node metastasis also influenced the prognosis (HR = 2.80, 95% CI 1.15 - 6.84 for OS and HR = 3.15, 95% CI 1.28 - 7.75 for PFS). The present results indicate that systemic lymphadenectomy may contribute to the reduction of recurrence risk with a combination of micro-metastatic foci and “target tissue” removal, thereby acquiring therapeutic importance in uterine CS. Even when systemic lymphadenectomy with complete resection of all visible disease was performed with aggressive adjuvant chemotherapy for the purpose of controlling invisible micro-metastatic foci, 32.9% (32/97) of the patients experienced disease recurrence. Five of these patients experienced lymph node recurrence. However, this occurred outside of the range of systemic lymphadenectomy, e.g., in the inguinal or intestinal membrane lymph nodes. These results indicate that this therapy has the potential to prevent lymph node recurrence. An attempt towards complete resection of all visible disease with systemic lymphadenectomy in uterine CS may be a reasonable treatment option; however, further investigation is required. The most effective adjuvant chemotherapy regimen for uterine CS has yet to be established. In this study, platinum-based chemotherapy was administered. Cisplatin is the most active and widely-used agent in the treatment of uterine CS [9]; however, it is unclear whether platinum-based adjuvant chemotherapy is actually effective. Previously, trial combination regimens have been reported to be superior to single agents. For example, higher objective response rates in advanced or recurrent CS have been reported with cisplatin plus ifosfamide (54%) [10, 11] and paclitaxel plus ifosfamide (45%) [12]. At present, despite the paucity of data, paclitaxel and carboplatin regimens are commonly used to treat uterine CS [13]. This institution’s policy before 2005 was to administer ifosfamide, cisplatin, and doxorubicin regimens. After 2005, paclitaxel and carboplatin regimens were administered in uterine CS patients. The efficacies of these regimens were acceptable given the existing trial results. In this study, the administration of adjuvant chemotherapy after complete resection was significantly associated with survival. The beneficial effect of adjuvant chemotherapy on survival may be confounded by the fact that most patients could not receive adjuvant chemotherapy because of rapid progression. Seven patients could not receive additional treatment because they were very ill. Their disease had progressed quickly, and it was decided on best supportive care rather than on chemotherapy. Ad-
juvant chemotherapy was significantly associated with survival, but the true benefit of adjuvant chemotherapy in uterine CS patients remains unclear. Adjuvant chemotherapy reduces the possibility of distant micro-metastasis. The disease will no longer be local, and considering its propensity for hematogenous spread, only systemic adjuvant chemotherapy may improve the chance of survival. In fact, hematogenous recurrence appeared to be common, occurring at a rate of 71% (23/32). The sites of hematogenous recurrence in the 23 patients were as follows: lungs (14 patients), abdomen (three patients), liver (three patients), bone (five patients), and spleen (one patient). At the time of suspected recurrence, the patients suffered recurrences at multiple sites. Even with the authors’ strategy of controlling local disease by surgical resection and preventing distant recurrence by aggressive systemic adjuvant chemotherapy, they could not control hematogenous distant recurrence. Surgical resection, including systemic lymphadenectomy, may influence local disease control. Despite systemic chemotherapy, 32.9% (32/97) of the patients relapsed. This indicates that the chemotherapeutic regimen for uterine CS requires further consideration. Although the optimal treatment for this disease remains unknown, systemic chemotherapy with molecularly targeted drugs that interfere with tumor angiogenesis may be a viable treatment strategy for this rare malignancy [14]. In the present study, the median follow-up period for surviving patients treated with multimodal therapy was 49.5 months (95% CI: 45.7-53.2 months). The median five-year OS for the entire cohort was 72.2%. According to each FIGO Stage, the median five-year OS rates were the following: 80.4% (Stage 1), 66.7% (Stage 2), 61.1% (Stage 3), and 50.0% (Stage 4). The existing data on this rare tumor indicate that the five-year OS rates according to Stage are 54%, 31%, 13%, and 0% for Stages 1, 2, 3, and 4, respectively [15]. The present results suggest a relatively favorable prognosis and should be interpreted with caution. However, this study was limited by the inherent deficiencies of a retrospective study, including patient selection bias. The authors advice that prospective and randomized studies are required in order to establish the usefulness of adjuvant chemotherapy regimens in patients with no residual disease after surgery. In conclusion, complete surgical resection followed by aggressive platinum-based adjuvant chemotherapy (multimodal therapy) increased survival among uterine CS patients, but the recurrence rate remained high. Further consideration of treatment options for uterine CS is required.

References


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Clinical outcome of patients with microinvasive adenocarcinoma of the uterine cervix

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Summary
Background: The objective of this analysis was to present the clinical outcome of patients with microinvasive adenocarcinoma (AC) of the uterine cervix treated at the Department of Obstetrics and Gynecology between 1999 and 2010. Materials and Methods: The authors analysed 125 patients with microinvasive AC. The analysis involved the following parameters: women’s age at surgery, type of surgery, number of positive lymph nodes, and patient’s survival. Additionally, a questionnaire regarding history and symptoms before diagnosis and postoperative follow-up was developed and analysed specifically for this study. Results: The mean women’s age at surgery was 40.58 ± 9.58 years. In 70 women (56%), the performed treatment was conization, 34 women (27.2%) underwent simple hysterectomy, and 24 (19.2%) women had radical hysterectomy. In 14 (11.2%) women, the margins of the cone were not disease-free, in nine of them the authors later performed radical hysterectomy. From 14 women who became pregnant after treatment, 13 (16.9%) of them gave birth. One of the 125 patients diagnosed with microinvasive AC died and the cause of death was rectal carcinoma. Conclusion: The authors may conclude that conservative management of patients with microinvasive AC is safe when exact evaluation of tumor extension and surgical margins of the cone are considered, and results in very low risk of recurrence, lymph node disease, and death caused by cancer.

Key words: Microinvasive adenocarcinoma; Cervical cancer.

Introduction
The term microcarcinoma was introduced by Mestwerdt [1] in 1947 and since then there has been an ongoing debate regarding the definition and management of microinvasive carcinoma of the uterine cervix. The International Federation of Gynecologists and Obstetricians (FIGO) have modified the staging system several times since 1960. FIGO Stage IA1 cervical cancer encompasses stromal invasion with a depth of 3.0 mm or less and an extension of 7.0 mm or less, and Stage IA2 is defined as cervical carcinoma confined to the uterus with stromal invasion of more than 3.0 mm, but not more than 5.0 mm, and a horizontal spread of 7.0 mm or less [2]. The Society of Gynecologic Oncologists (SGO) does not include the extension of the tumor and limits its invasion to a depth of 3.0 mm or less below the basement membrane. Additionally, the SGO excludes all patients with lymphovascular space invasion (LVI) from this definition [3].

Squamous cell carcinomas (SCC) account for approximately 80% of the carcinomas of the cervix, whereas adenocarcinomas (AC) account for 15%. Microinvasive AC of the cervix account for only 12% of all superficially invasive tumors [3]. Microinvasive SCC is now a well-accepted entity where conservative management is safe when exact evaluation of tumor extension and surgical margins of the cone are considered, and results in very low risk of recurrence, lymph node disease, and death caused by cancer [4].

Less is known regarding microinvasive AC and the pathological classification of microinvasive AC is more complex than that of microinvasive SCC [3, 5]. The optimal treatment for microinvasive cervical AC is controversial. Although curative therapy is pivotal, preservation of fertility is an important issue and therefore influences the choice of therapeutic strategy. The different strategies vary in radical hysterectomy with pelvic lymph node dissection to conization of the cervix. There are several reasons for the fact that there is no international consensus regarding treatment in early cervical carcinoma and the optimal therapeutic strategy is not known. One of them is because the definitions of the FIGO and the SGO of early cervical carcinoma are different and another problem is because the suggestion that cervical AC behaves more aggressively than SCC and therefore AC should be treated in a different way [6, 7]. There is also a lack of prospective randomized trials comparing conservative vs radical treatment in cervical AC due to the rarity of this carcinoma type. Several studies have shown a comparable prognosis for microinvasive AC compared with microinvasive SCC, leading to the adoption of a more conservative approach, especially where childbirth is desired [3, 8-11].

The objectives of this analysis were to present the clinical outcome of the patients with microinvasive adenocarcinoma treated at the Department of Obstetrics and Gynecology, University Medical Centre Ljubljana, from 1999 to 2010 and to contribute to the achievement of the international consensus concerning the treatment of microinvasive AC.
Materials and Methods

The authors performed a retrospective cohort study at the University Medical Centre in Ljubljana. They analyzed the data of all the patients (n = 147) treated at the Department from 1999 to 2010 for microinvasive AC regarding the type of treatment and its outcome. Pathology reports were reviewed, and patients with microinvasive AC on Papanicolaou (Pap) smear, cervical biopsy, cervical abrasion or conization specimen, were included in the study. Patients were excluded if microinvasive AC was found in coexistence with invasive carcinoma (in 11 women) or if no detailed pathology data were available. The authors also excluded 11 patients who came to this Institution for surgical treatment only from neighboring countries; the postoperative controls were implemented in their country. Finally the authors analyzed data from 125 patients. All the women were followed up at this hospital every three months for two years, every six months up to five years, and annually thereafter. The mean and median duration of their follow up was 20 and 18.78 years, respectively and there were no defaulters. The analysis involved the following selected parameters: women’s age at surgery, type of surgery, number of positive lymph nodes, and patient’s survival. The diagnosis of microinvasive AC was always made on the basis of histological examination of serial sections from cone biopsy specimens. The evaluation of cone margins was made by examination of an extensive number of histological step sections at least 200 to 400 apart.

Additionally, a questionnaire developed specifically for the present study was sent to patients to obtain information regarding history and symptoms before diagnosis and follow-up after operation, such as course of pregnancy and delivery, as well as postpartum outcome.

Results

The analysis involved 125 patients. The mean patient age at surgery was 40.58 ± 9.58 years; the mean age of the patients who had undergone conization was 37.69 ± 7.91 years. The types of surgical treatment applied are shown in Table 1.

There was no radical trachelectomy performed among the patients. In 70 women (56%), the authors performed conization, 34 women (27.2%) had simple hysterectomy, and 24 (19.2%) had radical hysterectomy. The margins of the cone were disease-free in 47 (37.6%) women, and in 14 (11.2%) women they were with disease. Histologically, microinvasive AC was found in all of these specimens; nine of these patients underwent radical hysterectomy. Of the 125 patients, 22 (17.6%) had lymphadenectomy and all of the removed pelvic nodes were invariably free of cancer. The mean number of removed nodes was 18.55 per women. In two women conization was the sole treatment; in one of these the margins of the cone were free of disease and in the other one the margins were histologically positive, hence the authors performed reconization.

The average age of women with simple hysterectomy was 44.67 ± 10.58; that underwent cold knife or large loop excision of transformation zone (LLETZ) were significantly younger with an average age of 37.69 ± 7.91 years (p = 0.00031).

One of the 125 patients diagnosed with microinvasive AC died because of rectal carcinoma. She was surgically treated at 45 years of age with radical hysterectomy without lymphadenectomy. She died six years later from rectal carcinoma.

In 2011, the survival rate of the 125 analyzed patients with microinvasive AC was 99.2%, whereas the survival rate of the 70 patients treated by conization was 100%.

Together, 77 (61.6%) women responded to the questionnaire. Data are presented in Table 2. From those women who did not give birth before the diagnosis of microinvasive AC, six (54.55%) women conceived and gave birth after the treatment, two women underwent a hysterectomy, and three did not conceive. After treatment for microinvasive AC, 14 (18.2%) women conceived, 30 (39.0%) did not conceive, and 33 (42.8%) women underwent a hysterectomy. In 14 women who became pregnant after treatment, 13 (16.9%) gave birth. In 14 women who became pregnant, seven women had gestational complications in the form of bleeding and other issues, while only one had a miscarriage.

Discussion

The incidence of AC of the cervix is increasing and it is thus accounting for a greater percentage of cervical cancer cases overall [12]. With increasing awareness of cervical cancer and improvement of detection modalities, lesions are now more commonly being identified in early stages. This along with the trend of women delaying childbirth until later in life renders it even more important to identify which lesions are amenable to conservative management [13].

In contrast to SCC, a human papillomavirus (HPV) associated disease of young and sexually active women, AC has been typically referred to as a disease of postmenopausal women, who show a higher incidence of nulliparity, diabetes mellitus, and hypertension [14-19]. However, many of these earlier epidemiological and clinical studies suffer from the lack of a normal control population, which may lead to underestimation of the
importance of the sexual risk factor of cervical AC. Recent surveys on cervical AC show the increase in its incidence and appearance of the disease in younger age groups [14-20]. This increasing trend in the relative proportion of AC has been evidenced in the present clinic as well. Accordingly, the relative proportion of AC in 1976 was 4.3%; ten years later (1986) it was 13.1% and from 1996 - 2006, up to 20.5% [14]. However, much of this increase may be only relative, and explained by significantly improved methods of early diagnosis and reduced incidence of cervical SCC by organized screening in many of the developed countries [4, 14, 15, 18, 20]. The mean age of the patients in this study was 40.58 ± 9.58 years; however the mean age of the patients who had undergone conization was 37.69 ± 7.91 years. The present data are consonant with the recently suggested increase in the incidence of AC among younger age groups [4, 14, 15, 18, 20].

Although one could argue that microinvasive AC should be staged and treated in the same way as microinvasive SCC, in clinical practice, AC tends to be managed more aggressively than its squamous counterpart.

In this Department, a conservative surgical approach to microinvasive cervical carcinoma (MIC) (both AC and SCC) was adopted in 1979, when the Rainer’s scoring system based on the evaluation of morphological criteria and exact estimation of the tumor size was implemented [21]. From 1973 to 2010, the rate of conization with/without pelvic lymphadenectomy as the sole mode of treatment of MIC (also Stage IA2), increased continuously and was the definitive treatment for almost 75% of all patients at the end of the observation period [22]. When the resection margins were not disease-free or lateral clearance was not adequate, the suggested treatment was hysterectomy if fertility was not desired, to avoid late recurrence. In spite of this, the frequency of Wertheim radical hysterectomy and simple hysterectomy had been declining; Wertheim radical hysterectomy was performed only in 9.0% of cases, mostly due to incorrect preoperative diagnosis of invasive carcinoma, based on scanty biopsy material [22].

In the present study, in 56% of the patients with microinvasive AC, the authors performed conization, 27.2% had simple hysterectomy, and 19.2% had radical hysterectomy. They observed no cases with lymph node metastasis, and no recurrences in this cohort of 125 women with microinvasive AC.

Besides the current study, few other studies only reported data regarding childbearing after conservative treatment by conization only [23-25]. After treatment for microinvasive AC, 14 women (18.18%) conceived, and 13 (16.88%) gave birth. Although these data suggest that childbearing after conization seems safe, more studies are needed. The present study does have its limitations: it is a retrospective and observational review. Because microinvasive AC is such a rare entity, the observational period required to collect a meaningful number of cases at this Institution was quite long (12 years). Despite this limitation, based on the literature to date, it appears that historically microinvasive AC of the cervix has been overtreated [11, 13, 23-27]. The radicality of surgery has no effect on rate of recurrence. The presence of LVSI does not correlate with lymph node metastasis [13]. Thus, the authors conclude that microinvasive AC of the cervix can be adequately treated with non-radical surgery and without routine evaluation of the regional lymph nodes.

Conclusion

The authors suggest that the treatment of microinvasive AC might be less radical, particularly in young women who opt to preserve their fertility and anatomical integrity, especially in histologically negative surgical margins and in the absence of LVSI.

The authors also suggest that conization or radical trachelectomy with/without laparoscopic pelvic lymphadenectomy might be the appropriate treatment for microinvasive AC, especially if LVSI is present and fertility is desired. When surgical margins are histologically positive and fertility is desired, more extensive follow up is recommended rather than prompt re-conization.

References

Clinical outcome of patients with microinvasive adenocarcinoma of the uterine cervix


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Photodynamic therapy effectively palliates gynecologic malignancies

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Summary

Background: There is a need for novel therapies for women with recurrent gynecologic malignancies. In this paper, the authors report their experience with photodynamic therapy (PDT). PDT involves administering a systemic injection of Photofrin II, a selective tumor photosensitizer hematoporphyrin derivative, followed by exposure of tumor tissue to visible light at 630 nm. The photodynamic destruction of tumor exhibits both cytoidal and vascular effects that may contribute to the tumoricidal effects observed. Materials and Methods: Patients were injected intravenously with two mg/kg Photofrin II. Approximately 48 hours post-injection, the tumor was exposed to red light (wavelength 630 nm ± 2 nm) from a laser through a flexible 400-µm quartz fiber with an attached microlens to produce a spot of uniform intensity and/or diffuser tip fiber to uniformly illuminate the cavity. Results: Thirty-two patients with recurrent gynecologic malignancies were treated with photodynamic therapy using Photofrin II dye and laser. A total of 45 PDT treatments were given; 25 patients received only one treatment, five patients received two treatments, two patients received three treatments, and one patient received four treatments. There were nine cervical, six vulvar, six vaginal, five ovarian, five endometrial carcinomas, and one recurrent pagets of the anal canal. Nine out of 11 (82%) patients with metastatic cutaneous lesions had a complete response. Five out of 21 patients (24%) with vaginal, cervical or anal recurrences had a complete response to therapy with median response time of 28 months. Toxicity associated with treatment was limited to burning sensation, pain, and edema at treatment site. There were no treatment related deaths. Conclusions: PDT is an effective therapy in patients with recurrent gynecologic malignancies and limited treatment options. PDT is an alternative therapy that offers the possibility of complete response in select groups of patient populations. Specifically, it provides palliation for superficial recurrent lesions of skin, cervix, vagina and vulva, in the absence of distant disease.

Key words:...

Introduction

Brief history

While the concept of destroying paramecium using certain dyes and light has been known since the early 1900’s, there have been a few aborted attempts to use this technique to destroy cancer in humans. The concept of using a photosensitizer, activated by an appropriate wavelength of visible light in the presence of endogenous oxygen (known as the photodynamic effect), was examined as a general way to destroy cancer cells and cancer tissue by researchers at Roswell Park Cancer Institute (RPCI) [1].

The use of photodynamic therapy (PDT) represents a novel approach in the treatment of recurrent gynecologic malignancies with metastasis to the genital area. The application of PDT to treat primary malignancies of the skin as well as gynecologic tumors, has previously been demonstrated with considerable success [2-4]. The targets of PDT include tumor cells, microvasculature supplying tumor cells, and inflammatory and immune systems of the host. The cumulative effect of PDT produces many different responses, specifically by direct cytotoxic effect by a combination of oxidative stress-initiated and anti-tumor activity of pro-inflammatory cells [5].

PDT involves the application of a photosensitizing agent that subsequently becomes activated by light of specific wavelength and intensity [6]. This produces a photodynamic reaction (PDR), as the photosensitizer accumulates in the cellular membrane of the cell and subsequently induces singlet oxygen (an excited state of molecular oxygen generated photochemically) which causes both cellular and vascular necrosis. This drug-light-reaction has moved photodynamic therapy to the forefront of treatment for malignant cutaneous lesions.

PDT is a localized treatment used for both palliative and curative intent in gynecologic malignancies that have manifestations in the vagina, perineum, anus and skin. Specifically in gynecologic malignancies, PDT has been previously used in Paget’s disease, vulvar and vaginal carcinoma, and adenocarcinomas of endometrial or ovarian origin. The present group and others have previously published on the use of PDT in recurrent gynecologic malignancies [4, 7-9].

Locoregional recurrences of gynecologic malignancies are common and often patients have co-morbidities that limit treatment options with traditional modalities or they have exhausted traditional treatment options (i.e. surgical resection, radiation or chemotherapy). As a result, alternative methods of treatment and palliation have been studied. The objective of this study was to identify patients with gynecologic malignancies that had received PDT therapy and report the response to therapy and evaluate associated toxicity that may limit its use.
Materials and Methods

After institutional review board approval, 32 patients with varied gynecologic malignancies including ovarian, endometrial, vulvar, cervical, and Paget’s disease of the anal canal were identified that were treated with PDT at RPCI from 1985 to 2011. These patients had failed conventional therapies, declined further chemotherapy or radiation or had significant co-morbidities with prohibited standard therapy. Patients were treated using Photofrin II, a photo sensitizing agent, and the application of a red light with a dye laser. All patients had biopsy-proven disease.

Patients were injected intravenously with standard dose of two mg/kg Photofrin II, previously developed protocol at RPCI. Approximately 48 hours post-injection, the tumor was exposed to red light (wavelength 630 nm ± 2 nm) from a laser through a flexible four-quartz fiber with an attached lens to produce a spot of uniform intensity and/or diffuser tip fiber to uniformly illuminate the cavity. An argon pump dye laser emitted up to four W at length of 630 ± 2 nm. Surface illuminations were also accomplished, depending on the specific area, using another quartz fiber equipped with a cylindrical diffuser, which emitted light laterally over a length of one to four cm. Most patients were treated once to the affected area or additional treatments if indicated.

Complete response (CR) was defined as a lack of detectable lesions within the area of treatment. Partial response (PR) was defined as at least 50% reduction in lesion diameter. No response (NR) or stable disease (SD) was defined as a decrease in tumor size less than 50% or no change in tumor parameters and appearance of no new lesions. Progressive disease (PD) was defined as increase in the size of the tumor mass.

Results

Thirty-two patients with recurrent gynecologic malignancies were treated with photodynamic therapy using Photofrin II dye and laser. A total of 45 PDT treatments were given; 25 patients received only one treatment, five patients received two treatments, two patients received three treatments, and one patient received four treatments. There were nine cervical, six vulvar, six vaginal, five ovarian, five endometrial carcinomas, and one recurrent Paget’s disease of the anal canal. Two patients received intraoperative PDT therapy after tumor resection. The two patients who received intraoperative PDT were not evaluated for response because one patient died postoperatively from sepsis and the other patient had incomplete clinical data.

Nine out of 11 (82%) patients with metastatic cutaneous lesions had a CR. Five out of 21 patients (24%) with vaginal, cervical or anal recurrences had a CR to therapy with median response time of 28 months. There were no significant differences in responses based on primary disease type identified.

All the patients were instructed not to expose themselves to sunlight and no skin burns were identified. Nine patients with skin lesions experienced a moderate to severe burning sensation, pain and edema at the treatment site requiring narcotic pain, medication, and supportive care. Pain related to treatment site resolved within two months of treatment. Patients with vaginal and cervical recurrences also had moderate to severe burning sensation, with maximum treatment for three weeks. There were no fistulas secondary to tumor necrosis in any of the patients and no treatment-related deaths were recorded. No alterations in renal or hepatic function were identified. Toxicity associated with treatment was limited to burning sensation, mild to severe pain, and mild to moderate edema at treatment site and surrounding tissue.

Discussion

Since 1985, this department has selectively employed the use of PDT in the treatment of loco-regional recurrence in gynecologic malignancies. In this report, 32 patients with gynecologic malignancies were identified and treated with PDT. Patients with cutaneous lesions had the best response to PDT, with nine out of 11 patients having a CR to therapy. PDT represents an attractive treatment modality in patients that cannot tolerate other forms of traditional therapy in the recurrent cancer setting.

Establishment of PDT as an effective therapy began in the early 1960’s by R.L. Lipson and S. Schwartz at the Mayo Clinic [14]. Using rudimentary preparations of hematoporphyrin led to the identification of fluorescence of neoplastic lesions visualized during surgical debulkings (Lipson Photodynamic therapy 1992). The first documented delivery of a PDT to gynecologic malignancies was given by Ward et al. and Forbes et al. in the early 1980’s [10, 11]. Forbes reported on 27 patients treated with a hematoporphyrin derivative. Hematoporphyrin derivative was activated by light at a 630-nm wavelength, which was delivered to cutaneous tumors. A CR was observed in five patients and PR was observed in 14 patients. The only significant side-effect was temporary cutaneous photosensitivity [10].

Rettenmeir treated seven gynecologic tumors with three out of the seven patients having a CR or PR to therapy [12]. Lobraico et al. reported on results of treatment on 45 different cutaneous lesions in seven people [13]. They showed a CR in 76% and PR in 18% after three months. More recently, Corti et al. reported on 26 cases of gynecologic malignancies treated with PDT [7]. In the palliative treatment group, a 66.6% response rate 60 days after treatment was observed. In the curative intent group, the CR rate was 71%. They did not have any major side-effects.

The use of PDT in urologic malignancies has also increased. Nseyo et al. reported on 58 patients to assess the long-term role of PDT in the management of resistant superficial transitional cell carcinoma (TCC) including Ta, T1, and refractory carcinoma in situ (CIS) of the urinary bladder [2]. These 58 patients underwent a single PDT treatment with 2.0 or 1.5 mg/kg of Photofrin and 10-60 J/cm² light (630 nm). At three months, CR rates were 84% and 75% for residual resistant papillary TCC and refractory CIS, respectively; and 90% of patients treated prophylactically had not had a recurrence [2].

This report represents the largest series of patients with gynecologic malignancies treated with PDT. The authors previously have published on a smaller subset of patients at RPCI with modest results [4]. In the original series reported, 21 patients with recurrent gynecologic malignancies were treated with PDT. Seven of 21 patients with
cutaneous lesions had a CR to therapy. Two of the patients with CRs continued to be disease-free for 28 and 36 months of follow-up.

The use of this innovative treatment for metastasis of gynecologic malignancies could provide patients with both palliation of symptoms and curative treatment for selected cases. This novel approach can easily be adopted by most major cancer centers and provide an alternative option for treatment of patients who have failed or declined traditional therapies. Photodynamic therapy is effective in certain cases and of value in the treatment of recurrent gynecologic malignancies with excellent response rates. PDT also represents an alternative therapy for patients in whom surgical resection or chemotherapy cannot be tolerated or is contraindicated. PDT can be used in the palliative setting with limited toxicity.

References

Development of antiangiogenic therapies for ovarian cancer

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Summary

Angiogenesis is a dynamic process which leads to a development of cancer and metastases. The most recognized and dominant prognostic factor is vascular endothelial growth factor (VEGF) and its receptors. VEGF was identified in 1989. There are three receptors for VEGF: VEGFR1 (VEGF receptor 1) and VEGFR2 that play the role in angiogenesis and development of ascites, and VEGFR3 is critical for lymphangiogenesis. There is bevacizumab – a new drug, monoclonal antibody that can block connection VEGF to its receptors. The first notification of activity of bevacizumab in ovarian cancer was in 2005. The aim of the article is to show some clinical trials in ovarian cancer and their results. The bevacizumab was registered in November 2011 in first line with standard chemotherapy in ovarian cancer. There is a new weapon against this disease.

Key words: Ovarian cancer; Angiogenesis; Bevacizumab.

Introduction

Angiogenesis is a critical, multistage, complex, dynamic process in tumor growth, invasion, and metastasis. Vascular endothelial growth factor (VEGF) family and its receptors are the best-researched and dominant proangiogenic factors. VEGF was identified in 1989, its gene was mapped on chromosome 6p21.3, and soon after its molecular and biological properties were described [1-3].

VEGF became a research objective for the inhibitors of its manifold activity in numerous cancers, including ovarian cancer in relation to its overexpression and role in the development of ascites [4-8].

There are five members of the VEGF family: VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E, the most important being VEGF-A, composed of over ten isoforms, of which VEGF165 and VEGF121 seem to be the most active [3]. VEGF-A (henceforth referred to as VEGF) binds with VEGFR1 (flt-1), VEGFR2 (KDR/flk-1) and VEGFR3 (flt-4) receptors containing an intercellular domain that has tyrosine kinase activity. The two first receptors: VEGFR1 and particularly VEGFR2 play a role in promoting angiogenesis and VEGFR3 is critical for lymphangiogenesis.

The activation of receptors is associated with their phosphorylation, which is necessary in the initiation of angiogenic and lymphangiogenic processes [9].

The review by Matei and Schmitt discusses some promising phase II clinical trials for recurrent ovarian cancer that aim to block phosphorylation – and consequently biological activity, mainly VEGF and PDGF (platelet-derived growth factor). However, they did not yield expected results and were not registered as ovarian cancer treatments. These are as follows: sunitinib, cediranib, sorafenib, pazopanib, and BIBF1120 [10].

Another antiangiogenic mechanism is a specific blocking of VEGF binding to its receptors via antibodies; bevacizumab demonstrates such activity. It is a recombinant humanized monoclonal antibody, composed of 93% of human IgG1 and seven percent mouse components, which blocks the bindings of all VEGF isoforms to its receptors. This prevents new vessels from forming, normalizes existing vessels, as well as decreases tumor pressure and boosts drug delivery [10].

Bevacizumab activity was first reported by Monk et al. [11] in advanced platinum-resistant ovarian cancer in 2005, who also indicated the need for effective trials in patients with ovarian cancer. Since 2007, study results of bevacizumab for recurrent ovarian cancer in monotherapy in different groups of women have been presented: Cannistra et al. [12] a study of 44 women, Burger et al. [13] of 62 women, and Garcia et al. [14] with 70 women treated in combination with cyclophosphamide. The obtained therapeutic benefit varied from 16% to 24%. Micha et al. [15] administered bevacizumab in combination with paclitaxel and carboplatin as first-line therapy for ovarian cancer in 20 women and the therapeutic benefit was estimated to be 80%.

During the 2010 Annual American Society of Clinical Oncology (ASCO) Congress, the results of a multicentre phase III trial in ovarian cancer, primary peritoneal cancer and fallopian tube cancer were presented that were included in the GOG-218 (Gynecologic Oncology Group) study [16, 17]. The study enrolled 1873 women with Phase III (74% of patients) or Stage IV (26% of patients), most of whom underwent suboptimal cytoreduction (66% of patients). The double-blinded and randomized trial included three arms. In each arm patients received the same chemotherapy: carboplatin AUC6 and paclitaxel 175 mg/m²:

- In the first arm, placebo was added to the chemotherapy in cycle two and continued throughout next 16 cycles (up to 15 months).
- In the second arm, 15 mg/kg of bevacizumab was administered in cycles two through six, followed by placebo through next ten cycles (up to 15 months).
• In the third arm, 15 mg/kg of bevacizumab was administered in cycle two and as maintenance therapy until the 16th cycle (up to 15 months). Administration was added in the second cycle to ensure proper postoperative wound healing.

The endpoint was PFS (progression-free survival), where progression was defined by RECIST (response evaluation criteria in solid tumors) criteria as well as serum levels of the CA-125 marker.

Due to adverse effects, the therapy was discontinued in ten patients (four in the first arm, one in the second arm, and five in the third arm). Comparing results of the three groups under study, a significant extension of PFS was found in the third arm (bevacizumab in courses two to six, and as maintenance therapy throughout 16 cycles up to 15 months of treatment) in relation to the first arm, that is the control group (14.1 to 10.3 months). The PFS benefit was 3.8 months \( (p < 0.0001) \); reduction in the risk of progression in the third arm (bevacizumab throughout 15 months) decreased by 28%. The 15-month period was chosen to exceed the median PFS for the population under other trials to date, and this is where the PFS difference between groups was most prominent. The overall survival (OS) analysis did not yield any significant differences in the three arms under study (first arm: 39.3, second arm: 38.7, third arm: 39.7 months).

Results of the data updated in 2011 after 47% of the women had died were consistent with analyses from 2010. A comparison of PFS in the first and third arms without analysis of changes in serum CA-125 levels showed a six-month extension of PFS in the third arm.

Results of ICON7 (International Collaborative Ovarian Neoplasm) of a phase III trial, were presented during the 2010 European Society for Medical Oncology (ESMO) congress [18].

ICON7 is a two-arm, open-label trial of 1,528 patients with ovarian cancer, primary peritoneal cancer or fallopian tube cancer who had had primary surgery for the following FIGO Stages I-IIA (G3 or clear cell carcinoma) or IIB-IV (G1-G3, all histological subtypes).

Patients in both trial arms received paclitaxel and carboplatin AUC 5 or 6; the research arm additionally 7.5 mg/kg of bevacizumab initiated at cycle two, every 21 days for 18 courses (12 months). The analysis showed an improvement in PFS in the bevacizumab group – extended PFS (19.0 vs 17.3 months) – a benefit of 1.7 months \( (p = 0.00410) \). The benefit of prolonged PFS was estimated at 15%. Data analysis of patients from high-risk group (suboptimal cytoreduction in patients with FIGO Stage III disease and patients with FIGO Stage IV disease - 30% women) showed the greatest improvement in PFS in the bevacizumab group – the PFS increased by 5.4 months compared to the control group.

Initial OS analysis did not differ among all patients from the control and study groups.

During the 2011 ASCO Congress, the PFS and OS analyses were updated [19]. The PFS increased by 2.4 months in the study group compared to the control group (19.8 vs 17.4 months) – statistical significance \( (p = 0.039) \). OS benefit for high-risk group patients (FIGO Stage III debulked > 1 cm or FIGO Stage IV) was 7.8 months (36.6 vs 28.8 months) - statistical significance \( (p = 0.002) \). OS analysis according to different risk groups confirmed the benefit for high-risk patients receiving bevacizumab compared to control group. Such difference was not observed in the low-risk patients. Final results are due in 2013.

In conclusion: bevacizumab in first-line treatment resulted in statistically-significant improvement in PFS and high-risk patients are most likely to benefit from bevacizumab treatment; the final analysis will be available in 2013. The treatment was well-tolerated, main adverse effects included grade ≥ 2 hypertension and digestive tract events [16].

These findings formed the background to the decision issued by the European Medicines Agency (EMA): in November 2011 bevacizumab was registered as first-line treatment for patients with advanced ovarian, fallopian tube, and primary peritoneal cancers (FIGO Stages IIIB, IIC, and IV) in combination with carboplatin and paclitaxel for a maximum of six cycles, followed by monotherapy until disease progression, or up to a maximum of 15 months, or until unacceptable toxicity occurred at a dose of 15 mg/kg, once every three weeks.

Results of Ovarian Cancer Evaluation of Bevacizumab and Safety (OCEANS), a double-blinded phase III trial for recurrent platinum-sensitive ovarian cancer, were presented during the 2011 ASCO congress [20]. The study included 484 patients (the majority of patients (407) had primary ovarian cancer, while the remaining had primary peritoneal and fallopian tube cancers). The median follow-up was 24 months. More than 75% of patients experienced recurrence after 12 months.

One arm received treatment with gemcitabine and carboplatin (G – 1.000 mg/m2 on days one and eight, carboplatin AUC 4 on day one with placebo, the other arm received GC in combination with 15 mg/m2 of bevacizumab. The cycles were repeated every three weeks.

PFS analysis demonstrated a benefit for the bevacizumab arm: 12.4 month vs 8.4 month in the placebo arm, considered a statistically significant value \( (p < 0.0001) \). OS data also indicated a trend towards extending OS in the bevacizumab arm (35.5 vs 29.9 months) which was not further confirmed by data upon including deaths (48.6% of patients) and was as follows: 35.2 month for the placebo and 33.3 month for the bevacizumab arm. The final OS analysis is not yet available.

Dominant adverse effects were hypertension and proteinuria (24.9% in the placebo and 34.8% in the bevacizumab group).

Currently, another phase III trial is underway Avastin Use in Resistant Epithelial Cancer (AURELIA), the first study in platinum-resistant patients with ovarian cancer [21]. It is a two-arm, open-label, and randomized study: one arm received (depending on researcher’s decision) paclitaxel 80 mg/m2 on days one, eight, 15, and 22 or topotecan 4 mg/m2 on days one, eight, and 15 every four weeks or 1.25 mg/m2 on days one to five every three
weeks or pegylated liposomal doxorubicin (PLD) 40 mg/m² on day one. The schema was repeated every four weeks, the other arm received chemotherapy combined with bevacizumab 15 mg/kg repeated every three weeks. A total of 361 patients were randomized.

Initial analysis carried out in November 2011 and presented at the 2012 ASCO Congress indicates a PFS benefit (4.0 vs 5.7 months with bevacizumab). Final analysis will be available in 2013.

Initial results of the OCTAVIA trial were also presented during the 2012 ASCO Congress [22, 23]. A total of 189 patients with advanced FIGO Stage I-IV ovarian cancer were included as was the case in ICON7.

The aim of the study was to assess the safety of bevacizumab treatment in combination with NOVEL chemotherapy (paclitaxel 80 mg/m² on days one, eight, 15 (six to eight cycles), carboplatin AUC 6 every three weeks, and bevacizumab 7.5 mg/m² up to one year.

Initial analysis was carried out in March 2012. More than or equal to six courses of chemotherapy were administered to 90% of patients. Initial assessment included that the schema was well-tolerated, hypertension and proteinuria were less common than in the third arm of ICON with bevacizumab, and main symptoms were hematologic manifestations (anemia, neutropenia, and thrombocytopenia). Analysis of PFS (26.3 months of observation) for all patients with bevacizumab was 23.7 months and for high-risk group patients corresponding to ICON-7 (FIGO IV and III with residual disease above one cm after surgery) was 18.1 months. The OS data will be available in 2013.

Another study, ROSiA (Research in Ovarian Cancer: Safety with Avastin) is currently in the phase III of clinical development for treatment of primary untreated ovarian cancer [24]. This study includes patients with FIGO Stages I to IV, treated with paclitaxel in combination with carboplatin and bevacizumab up to 36 months as maintenance therapy. This study also aims to evaluate the safety of bevacizumab. Results will be processed next year.

Introduction of antiangiogenic therapies is certainly an achievement that improves PFS as well as OS. However, molecular analysis of VEGF isoforms, mutual relationships between serums, and presence of VEGFb isoforms might be an important mechanism in angiogenesis regulation and affects bevacizumab treatment results [3, 25].

At the 2012 ASCO Conference, Prof. M. Sained noted that ovarian cancers are an incredibly heterogeneous group, i.e. serous cancers have numerous somatic mutations and an unstable genome. Molecular trials of DNA in a greater number of patients could allow to establish a homogenic group, that would most likely benefit from targeted therapy with bevacizumab.

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Clinicopathological characteristics and outcome of patients with small cell neuroendocrine carcinoma of the uterine cervix: case series and literature review

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Summary
Objective: To analyze the clinicopathological data of 13 cases of small cell neuroendocrine carcinoma (SCNEC) of the uterine cervix who received treatment at this medical institution over the past five years with patient survival as the primary endpoint. Materials and Methods: The clinicopathologic data of 13 cases were reviewed. Immunohistochemistry was performed using antibodies against synaptophysin and chromogranin A and Ki-67. Survival was analyzed using the Kaplan-Meier method and log-rank tests. Results: The median age of these patients was 37 years (range 21-62). Immunohistochemistry showed that the positive rate of synaptophysin and chromogranin A was 100% (13/13) and 69.23% (9/13), respectively. The median survival of patients with early-Stage I-II SCNEC of the uterine cervix (17.5 months) was significantly higher than that of patients with advanced stage SCNEC of the uterine cervix (four months) (p < 0.05). There was no local recurrence in all 13 patients. Five patients died of distant metastasis in less than six months. Conclusion: SCNEC of the uterine cervix is a highly-malignant disease and early-stage patients showed significantly longer survival compared to late-stage patients. Early diagnosis and prompt combination treatment may improve the outcome of patients with SCNEC of the uterine cervix.

Key words: Small cell neuroendocrine carcinoma; Uterine cervix; Immunohistochemistry; Clinical characteristics; Survival.

Introduction
Neuroendocrine carcinoma (NEC), which arises from peptidergic neurons and neuroendocrine cells, is a type of heterogeneous malignant carcinoma with an incidence about five times higher than that 30 years ago [1]. It occurs in various organs and tissues, such as the digestive tract, lungs, nasopharynx, throat, mediastinum, thymus, breast, and uterus. NECs of the digestive tract account for about 55%-70% of all NECs, followed by NECs in the lungs. Small cell NEC (SCNEC) of the uterine cervix is a rare tumor with a mean annual incidence of 0.06 per 100,000 women [2], accounting for one to six percent of all cervical cancers [3, 4], the most common malignant disease of the female genital tract. SCNEC of the uterine cervix occurs frequently in women of relatively young age. With improvement in clinical diagnosis in recent years, the number of SCNEC of the uterine cervix cases has actually increased. Despite such improvement, the rate of early diagnosis is still very low.

The tumors are characterized by a high incidence of early nodal and distant metastases and are associated with a more dismal prognosis than other subtypes of cervical cancers [5-7]. However, due to its rarity, there have been insufficient reports on SCNEC of the uterine cervix and consequently there is a paucity of knowledge about this disease. Furthermore there are no consensus diagnoses, treatment guidelines, and optimal treatment strategies for this aggressive tumor. Here, the authors retrospectively analyzed the clinicopathologic data of 13 cases of SCNEC of the uterine cervix who received treatment at the present medical institutions over the past five years and the primary endpoint of this analysis was patient survival.

Materials and Methods
Subjects and tumor specimen acquisition
The authors retrospectively reviewed the clinicopathological data of 13 consecutive cases of SCNEC of the uterine cervix who were treated at the Sichuan Cancer Hospital, Sichuan, China, between January 2006 and December 2010. The study protocol and acquisition of tissue specimens were approved by the local Institutional Review Board. Frozen primary tumor samples were obtained from the Tissue Banks at Sichuan Cancer Hospital and Huaxi Hospital. Human tissue acquisition and use in this study complied with the National Regulations on the Use of Clinical Samples in China. Tissue specimens were obtained from archived tissue samples of these SCNEC patients. SCNEC of the uterine cervix was confirmed pathologically in these patients by two independent and experienced pathologists (W.G.S. and Y.W.). Histopathologic diagnosis was based on morphologic criteria and on immunohistochemical staining for neuron-specific enolase (NSE), synaptophysin, and chromogranin A as previously described [8, 9]. All tumors were staged according to the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system for cervical cancer, based on physical examination, chest X-ray, intravenous pyelography, cystoscopy, sigmoidoscopy, and abdomino-pelvic computed tomography (CT) scan or magnetic resonance imaging (MRI).

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nonspecific binding sites were blocked with 0.3% normal goat peroxide/methanol to deplete endogenous peroxidase. Then, the sections were immersed for ten min in 0.3% hydrogen peroxide and 3-amino-9-ethylcarbazole (AEC) chromogen. The reaction product was sequentially incubated with a streptavidin peroxidase reagent for ten min at room temperature. Finally, the reaction product was ten min at room temperature. Finally, the reaction product was

Treatment

The chemotherapeutic regimen was comprised mainly of taxol or irinotecan plus platinum (cisplatin or carboplatin) with one to eight cycles. Radical hysterectomy was performed with pelvic lymph node dissection, resection of bilateral fallopian tubes, and bilateral ovarian transposition or resection. Pelvic external radiation with brachytherapy was also carried out where appropriate.

Immunohistochemistry

For formalin-fixed and paraffin-embedded tissue specimens, consecutive four-µm thick sections were cut and used for immunohistochemistry. The sections were immunohistochemically stained by the labeled streptavidin-biotin peroxidase method according to the manufacturer’s recommendation. The following primary antibodies were used: anti-synaptophysin and chromogranin A and anti-NSE and Ki-67 monoclonal antibodies. The sections were immersed for ten min in 0.3% hydrogen peroxide/methanol to deplete endogenous peroxidase. Then, nonspecific binding sites were blocked with 0.3% normal goat serum for ten min. The primary antibodies were then incubated with the sections overnight at 4°C. After washing with phosphate buffered saline (PBS) (0.01 M, pH 7.4), biotinylated goat anti-mouse IgG was incubated with the tissue sections for ten min at room temperature. After washing with PBS, the sections were sequentially incubated with a streptavidin peroxidase reagent for ten min at room temperature. Finally, the reaction product was visualized by incubating the slides in a solution of 0.3% hydrogen peroxide and 3-amino-9-ethylcarbazole (AEC) chromogen. The sections were counterstained with hematoxylin and eosin (H&E). Negative controls included parallel sections treated without the primary antibodies and adjacent sections from the same block but without the primary antibody, which was replaced by PBS. The density of positive staining was scored using a scale from – to +++ (– for no immunostaining, + for light brown color, ++ for medium brown color, and +++ for dark brown color). In all areas, only malignant cells were scored. The immunoreactions were read by two pathologists (W.G.S. and Y.W.) who were blind to patient data (Figure 1).

Follow-up

The patients were followed up by telephone calls, letters, and clinic visits every six months. All patients were advised regarding adjuvant chemotherapy and radiotherapy. The primary endpoint of this retrospective analysis was any cancer-related death. All endpoints were calculated from the date of radical hysterectomy to death, or censored at the last follow-up. Survival was defined as the period from the time of diagnosis to the time of death or the final follow-up.

Statistical analysis

Survival was evaluated using the Kaplan-Meier method and log-rank tests. The significance level for all analyses was set at less than 0.05. All analyses were carried out using the SPSS 13.0 software. All endpoints were updated in October 2011.

Results

Patient demographic and disease characteristics

Characteristics of the patient population are summarized in Table 1. There were 13 female patients and their median age was 37 years (range 21-62). Four patients were diagnosed with Stage IB, three with Stage IIA, one with Stage IIB, one with Stage IIIA, three with Stage IIIB, and one with Stage IV SCNEC of the uterine cervix. Nine patients received radical hysterectomy with pelvic lymph node dissection, resection of bilateral fallopian tubes, and bilateral ovarian transposition or resection. Twelve cases received chemotherapy including two patients who received interventional chemotherapy. Ten cases underwent pelvic external radiation with brachytherapy. One case of Stage IB SCNEC of the uterine cervix refused adjuvant chemotherapy and radiotherapy.

Immunohistochemical characteristics of study patients

Immunohistochemical examination of tissue specimens showed that 100% (13/13) of the patients were positive for synaptophysin and 69.23% (9/13) were positive for chromogranin A. Seven (100%, 7/7) patients were positive for NSE; immunohistochemical staining with NSE was not performed in the remaining six cases. Among seven patients whose Ki-67 results were available, five (71.4%) patients had Ki-67 index > 60%. Synaptophysin and chromogranin A were both positive in 69.23% (9/13) of patients. Among four cases with negative chromogranin A, three had Ki-67 index > 60%, and one was positive for NSE (Table 1).

### Table 1. — Clinicopathological data of 13 patients with small cell neuroendocrine carcinoma (SCNEC) of the uterine cervix.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>FIGO Stage</th>
<th>CgA</th>
<th>Syn</th>
<th>Ki-67</th>
<th>NSE</th>
<th>Therapeutic modality</th>
<th>Survival (month)</th>
<th>Survival status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>IIIB</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>radiation + chemotherapy × 3</td>
<td>10</td>
<td>dead</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>IIA</td>
<td>+++</td>
<td>+++</td>
<td>N/A</td>
<td>++</td>
<td>surgery + radiation + chemotherapy × 5</td>
<td>46</td>
<td>dead</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>IIA</td>
<td>--</td>
<td>N/A</td>
<td>+</td>
<td>N/A</td>
<td>radiation + interventional chemotherapy × 6</td>
<td>53</td>
<td>alive</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>IIA</td>
<td>+</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
<td>surgery + chemotherapy × 1</td>
<td>49</td>
<td>alive</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>IB</td>
<td>--</td>
<td>+</td>
<td>60%</td>
<td>N/A</td>
<td>surgery + chemotherapy × 1</td>
<td>43</td>
<td>alive</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>IV</td>
<td>++</td>
<td>+</td>
<td>N/A</td>
<td>+++</td>
<td>(surgery + chemotherapy × 2) + chemotherapy × 1</td>
<td>3</td>
<td>dead</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>IIIB</td>
<td>+++</td>
<td>+++</td>
<td>80%</td>
<td>++</td>
<td>radiation + chemotherapy × 3</td>
<td>4</td>
<td>dead</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>IIIB</td>
<td>++</td>
<td>++</td>
<td>N/A</td>
<td>+++</td>
<td>radiation + interventional chemotherapy × 1</td>
<td>3</td>
<td>dead</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>IIIA</td>
<td>+</td>
<td>+</td>
<td>30%</td>
<td>N/A</td>
<td>surgery + radiation + chemotherapy × 2</td>
<td>11</td>
<td>alive</td>
</tr>
<tr>
<td>10</td>
<td>39</td>
<td>IB</td>
<td>--</td>
<td>+</td>
<td>&gt; 90%</td>
<td>N/A</td>
<td>surgery + radiation + chemotherapy × 3</td>
<td>19</td>
<td>alive</td>
</tr>
<tr>
<td>11</td>
<td>41</td>
<td>IB</td>
<td>++</td>
<td>+</td>
<td>80%</td>
<td>N/A</td>
<td>surgery + chemotherapy × 6</td>
<td>15</td>
<td>alive</td>
</tr>
<tr>
<td>12</td>
<td>35</td>
<td>IB</td>
<td>--</td>
<td>+</td>
<td>80%</td>
<td>N/A</td>
<td>surgery + radiation + chemotherapy × 1</td>
<td>16</td>
<td>alive</td>
</tr>
</tbody>
</table>

CgA: chromogranin A; N/A: not available; FIGO: International Federation of Gynecology and Obstetrics; NSE: neuron-specific enolase; Syn: synaptophysin.
Patient survival

The patients were followed up for a mean duration of 15 months (range four to 53). The median survival was 17.5 months (Figure 2). Among the 13 patients, eight (61.54%) had early stage (Stage I-II) diseases with a median survival of 17.5 months, while five (38.46%) had late stage (Stage III-IV) SCNEC of the uterine cervix with a median survival of four months. There was a significant difference in survival time between patients with early SCNEC and those with late SCNEC (p = 0.017). Five patients died within six months after diagnosis of distant metastasis.

Discussion

Middle-aged and young females were the main population of this study, accounting for 0.395% of cervical carcinoma patients admitted in these hospitals. Common initial symptoms included irregular vaginal bleeding and discharge, which are similar to those seen in cervical cancer patients, while symptoms suggestive of carcinoid syndrome-like spasmodic abdominal pain, diarrhea, and flushing were not found in these patients.

Due to the non-specificity of the symptoms of SCNEC of the uterine cervix, the diagnosis mainly depends on the morphological features of the carcinoma cells under light microscopy and immunohistochemical findings. SCNEC of the uterine cervix is poorly-differentiated and highly-malignant and consists mainly of small or medium-sized cells with significant nuclear atypia, multifocal necrosis, and high mitotic figures. Similar to NEC, it sometimes has an organ structure and expresses neuroendocrine differentiation markers such as synaptophysin and chromogranin A.

SCNEC of the uterine cervix can be classified into 3 grades depending on the proliferation activity and histology. If neurocrine cells account for fewer than 50% of the whole tumor tissue, and are dispersed but appear as a part of the tumor tissue, they are called carcinoma with neuroendocrine differentiation. Patients in this study were confirmed to have SCNEC of the uterine cervix by
histopathology and immunohistochemical staining. All 13 cases were not staged due to the limitation of the pathological diagnosis standard at the time they were treated, however as can be seen in Table 1, the Ki-67 index was higher than 20% in all seven cases who were examined. They can be staged as G3 (G1, G2, and G3 represents low, middle, and high grades, respectively) according to the current standard. It has been acknowledged that immunohistochemical markers such as synaptophysin and chromogranin A and Ki-67 are the most reliable and feasible markers for diagnosing NEC [10, 11] while markers like NSE and others are no longer recommended [12].

The authors consider tumor stage the most important prognostic factor. A unified diagnostic criterion will be beneficial for early diagnosis of this disease. The distant metastasis rate in patients with early-stage disease is low, which is similar to the clinical characteristic of small cell lung cancer. In addition, how to effectively control distant metastasis is also very important. Five of the patients died within six months after diagnosis of distant metastasis. Chemotherapy is an important way to control and eradicate residual and micro-metastatic lesions. Korum et al. [13] suggested that survival in patients with early-stage small cell carcinoma of the cervix was better with surgery combined with chemotherapy. Huang et al. [14] showed that radical hysterectomy followed by adjuvant chemotherapy resulted in a higher two-year survival rate compared to radical hysterectomy followed by adjuvant radiotherapy (62.5% vs 16.7%). These findings indicated that the addition of adjuvant chemotherapy tends to be more effective than single treatment in increasing the survival rate [15-17]. Cohen et al. [18] showed that the five-year disease-specific survival rate in Stages I-IIA, IIIB-IIVA, and IVB of the disease was 36.8%, 9.8%, and 0.0%, respectively. They further showed that for Stage II-III patients, adequate chemotherapy is positively correlated with control of metastasis.

No local recurrence occurred in this study after surgery or radiotherapy regardless of the stage of the disease. The authors deduced that these two regional regimens are both effective. In addition, chemotherapy can prevent distant metastasis. These three therapeutic modalities constitute traditional comprehensive therapy; however this model has encountered a bottleneck. The neuroendocrine characteristic of the tumor should be regarded as a target to improve the efficacy of treatment and prognosis. The use of drugs that inhibit the neuroendocrine function of the tumor (such as somatostatin analogues), was supported by the PROMID study [19], which demonstrated that octreotide significantly lengthened the time to tumor progression compared with the placebo in patients with functionally active and inactive metastatic midgut neuroendocrine tumors.

In conclusion, early diagnosis and prompt treatment of SCNEC of the uterine cervix and traditional comprehensive therapy in combination with targeted therapy would bring a new prospect to the treatment of endocrine carcinoma (including carcinoma with neuroendocrine differentiation).

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Epidemiology of HPV-related female cancers in the Umbria region of Italy: pre-vaccination period

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Summary

The authors describe the incidence and mortality rates of human papillomavirus (HPV)-related female cancers in Umbria (Italy) in the pre-vaccination period from 1978-2008. Joinpoint regression was applied on age-adjusted incidence and mortality rates to evaluate temporal trends. Mouth and pharynx cancers incidence and mortality trends decreased about three percent per year. For anorectal cancer, incidence and mortality trends presented a non-significant decrease. For malignant neoplasm of oral cavity, the annual percentage change decreased from 2001 (-1.8%). Mortality trend showed a non-significant decrease. Incidence and mortality rates from vaginal cancer were non-significantly decreased. For malignant neoplasm of cervix uteri, circumcision of opportunistic and programmed screening led to a much-reduced disease burden. It is expected that the implementation of vaccination in the future will lead to a further decrease of HPV-related cancer incidence and mortality.

Key words: Incidence; Mortality; HPV-related cancers; Vaccination.

Introduction

Human papillomaviruses (HPVs) are responsible for about 500,000 cases of cervical cancer annually on a global level [1] and ten million further cases of high-grade cervical intraepithelial neoplasia (CIN) [2], pre-invasive lesions are reported. It is estimated that 30 million women and men acquire anogenital warts (condyloma acuminata) or low-grade CIN annually [2] and these data are probably underestimated given the inadequacy of reporting in many countries and the evidence of a rising incidence over time.

HPV infection can be detected from virtually all cervical cancers and CIN II/III [3, 4]. HPV types are also associated with development of squamous cell cancer in sites other than the cervix. HPV is estimated to be responsible for five percent of the global cancer burden [5].

About 40% and 80% of vulvar and vaginal cancers, respectively, are reported to be positive to HPV, supporting the notion of mixed etiology of these cancers [6].

The causal role of the HPV infection in oropharyngeal cancer is currently debated [7-9]. Recent research has highlighted the risk conferred by HPV infection in head and neck cancers [10, 11]. The incidence of head and neck cancers has increased in recent years, particularly among younger age groups, which may be at least partially attributed to HPV infection [12, 13]. Increase of both HPV-positive tonsil and base of tongue cancers has been reported in several recent studies [12, 14-16].

Most HPV-related cancers arise as a consequence of infection with a small subset of HPV types (i.e., HPV 16 and HPV 18) that, as a consequence, earned the definition of high-risk types (HR-HPV). HPV types detected in cervical cancers and in other pre-invasive lesions vary, depending on the geographical region and study sample type (general population vs high-risk population).

HPV 16, the most common HR-HPV, has been reported to be present in 49%-81% of pre-invasive lesions in the cervix. HPV types 16 and 18 have been detected in 52%-64% and 11%-22% of cervical, 27%-58% and 2%-10% of vulvar, and 46%-77% and 3%-27% of vaginal cancers, respectively [3, 4, 6, 17-19]. HPV type 16 has been the most usual type detected from oro-pharyngeal, and penile cancers [20-22].

Cervical cancer is responsible for the main health burden among HPV-associated cancers. Early diagnosis and treatment of cervical disease has proved to be a successful population strategy to decrease morbidity and mortality associated with cervical cancer [23]. Screening introduction in a previously unscreened population leads to a dramatic decrease in the incidence of infiltrating cervical cancer and mortality in the screened cohort [24].

Opportunistic cervical cancer screening has been diffused in Umbria since 1972 when pap testing was offered free of charge. An organized cervical cancer screening program, targeted to all women aged 25-64 years, was begun in 1999. In 2008 the organized screening coverage reached 80% of the target population in all four regional Local Health Units [25]. Screening, however, does not interfere with the circulation of HR-HPV infection.
Prophylactic vaccines against HR-HPV are now available. The quadrivalent HPV vaccine, for instance, has the potential to prevent about 70% of cervical cancers and over 90% of condylomas, by targeting HPV types 16 and 18 and types 6 and 11, respectively, according to available evidence [26-28]. Efficacy against vulvar and vaginal intraepithelial neoplasia grade 1, 2 was 100% (72% to 100%) [29]. High-efficacy against condyloma was also demonstrated (92% to 100%) [30]. A bivalent vaccine is also available and is targeted at HR-HPV types 16 and 18 only. Duration of protection so far has been shown to be at least nine years with the prototype HPV 16 vaccine, and immune memory has also been documented. Some cross-protections have been shown against closely-related HPV types (31 and 45) with bivalent and quadrivalent vaccines [31-33].

A vaccination strategy based on active invitation of all 12-year-old girls and using the bivalent anti-HPV vaccine was adopted at a national level and introduced in Umbria in 2008. Moreover, vaccination was offered for free to 13-year-old girls and at a reduced price to older women.

The aim of this paper is to describe the current epidemiological trends of HPV-related female cancers in the Umbria region in the pre-vaccination period. This study may be used as a baseline for future comparisons and to evaluate the effectiveness of vaccination.

Materials and Methods

Incident data were collected from the Umbrian Population Cancer Registry (RTUP), established in the early 1990s, from 1994 to 2008 [34]. Furthermore, for the 1978-1982 period, an ad hoc survey was carried out in the region to determine the incidence of cancer [35]. Mortality data were supplied by the regional Nominative Causes of Death Registry (ReNCaM), based on the Registry population Offices of Umbrian municipalities that are linked with death certificates collected by Local Health Districts and later used for national survey by the National Institute of Statistics (ISTAT). Incidence and mortality data are classified according to the International Classification of Diseases (ICD X): cancers of the mouth and oropharynx (C00-C06, C09-C10, and C13-C14), anus and anal canal cancer (C21), cancer of the vulva (C51), vaginal cancer (C52), and cervix uteri cancer (C53) [36]. All cases were collected, coded, stored, and analyzed in accordance with standard methods recommended for cancer registries [37], using the ICD X classification [36].

Age-adjusted incidence and mortality rates (using Umbrian, Italian, and world population standards) were calculated for each site. Site-specific trends for standardized rates were analyzed by “joinpoint regression” [38], using the SEER software [39]. The aim of the approach is to identify possible “joinpoints” where a significant change in the log-linear trend occurs. For each linear segment the average annual percentage change (APC), its significance, and corresponding 95% confidence intervals were calculated [39]. The Umbrian population in the 2001 census was used as the standard in the “joinpoint analysis” to reduce bias due to differences in age structure.

Results

The annual number of incident cases for the different sites and incidence rates per 100,000 inhabitants throughout the period 1978-2008 are presented in Table 1. Mortality data are shown in Table 2. Mortality rates for C21 and C52 are not present for the 1978-1982 period, because of classification problems (i.e., tumors of anus and anal canal were classified within the “rectum” three digit category according to the IX version of the ICD in use. Similarly, vaginal cancers were included among malignant neoplasm of vulvar cancer category. These cancer sites were identified by the fourth digit of the ICD IX classification and this resulted in lower accuracy). The curves by age for incidence and mortality, in the four periods taken into account, are shown in Figure 1.

Incidence of mouth and oropharynx cancers begins increasing in the 55-59 age group. The increase is less pronounced in the most recent study period, thus the incidence in the elderly is lower in the 2004-08 period than in previous periods. Mortality is shifted toward older ages with respect to incidence; age-specific mortality rates are increasing for the age-classes 60-64 years and older.

The anus and anal canal cancer incidence rates by age showed a rapid increase in the 69-74 age group; this increase was more marked in the 1994-1998 period. A decrease in the anus and anal canal cancer incidence was observed in the oldest age group, except for the 1999-2003 interval. The anus and anal canal cancer mortality rates showed an increase with age. The age-specific incidence and mortality curves for vulval cancer increased with age and remained constant over the study period. Vaginal cancer incidence in the 75-85 age group was higher in the 1999-2003 time period than in the other study periods. Mortality from vaginal cancer was low and showed some variability; however, it increased among women over 80 years of age. The cervix uteri cancer incidence rates by age resulted different by period. The age-specific incidence curve for cervical cancer showed a steady increase among women 35-39 years of age and then remained stable or increased slowly. The age distribution was quite different in the 1978-82 period, when the curve steadily increasing among the age groups over 35-39 years until it reached a peak at 60-64 years. Moreover, a slow but progressively decreasing incidence was observed by period among middle-aged women. Results of the joinpoint analysis by cancer site, applied to incidence and mortality rates, are reported in Figure 2.

Both incidence (annual percentage of change (APC) -3.0, 95% confidence interval (CI) from -6.1 to +0.3) and mortality (APC - 3.3, 95% CI from -7.3 to +0.9) for mouth and oropharyngeal cancer non-significantly decreased over the study period. Again, for anus and anal canal cancer, incidence and mortality trends presented a non-significant decrease over the study periods. For malignant neoplasm of vulva, a significantly decreasing trend was found for incidence rates (APC -1.8% 95% CI: from -3.4 to -0.3). The mortality trend had a similar but non-significant APC (- 1.8% 95% CI: from -5.2 to 1.6). Incidence and mortality rates from vaginal cancer decreased non-significantly. For malignant neoplasm of cervix uteri, incidence rates showed a significant decrease by 2.1% per year (95% CI: - 4.1 to 0.1), and mortality rates presented a non-significant decrement by 4.6% per year.
Discussion

Invasive cervical cancer is an infrequent disease in Western countries. It represents a long-term consequence of a subset of lasting HPV infections that are otherwise transient and common. To control cervical cancer, screening is effective [24]. However, there are drawbacks to this strategy. The main limitation of screening is that it does not interfere with circulation of HR-HPV infection and, thus, there is the need to indefinitely maintain the intervention and high-level of adherence to avoid progression of premalignant lesions. Moreover, cervical cancer screening contributes minimally to overall control of all other HPV-related diseases.

The availability of a prophylactic vaccine, a primary prevention tool, therefore opens alternatives to prevention of cervical and other HPV-related cancers by eliminating their widespread cause, i.e., infection with HR-HPV strains. Pro-
Figure 1. — Incidence and mortality rates for the selected sites, by age and period.
Epidemiology of HPV-related female cancers in the Umbria region of Italy: pre-vaccination period

Providing vaccination both to males and females is justified by the goal to prevent HPV related cancers, including cervical cancer. Theoretically, vaccinating both girls and boys against HPV would be a radical and powerful approach, which would lead to a rapid decrease in HPV infections [40].

Justifying the cost of vaccination of both sexes has proven to be difficult, and, thus, an anti-HPV vaccination strategy targeted mainly at 12-year-old girls was begun in 2008 in Umbria. The bivalent vaccine, protecting against HPV 16 and 18 was used in the Umbria vaccination program as in the rest of Italy [41]. This strategy does not aim to eliminate relevant HR-HPV types nor is it aimed to protect from HPV-related diseases occurring in males.

Vaccination coverage for the birth cohort of 1997 was 79% for the first dose, 77.5% for the second dose and 73.3% for the third dose to 30 June 2010 [42]. However, it will take decades before the benefits of this preventive intervention will become apparent. An early indirect evaluation of vaccination results could be obtained through the surveillance of HPV-related cellular abnormalities in young women participating in the screening. In general, cervical cancer screening will allow some evaluation of the vaccination effectiveness and will ensure cervical cancer prevention for non-vaccinated women. How to combine in the future primary and secondary prevention of cervical cancer effectively remains to be determined [43].

While HPV is a proximal cause of cancers, sexual behavior determines exposure to HPV. Sexual behavior is associated with cancer risk of head and neck subsites previously associated with HPV infection [44]. The epidemiologic pattern of HPV infection in the population is a reflection of sexual behavior in given socio-cultural circumstances, and is both socially conditioned as well as depending on personal choices.

The analysis of incidence and mortality trends is an important tool for monitoring cancer control and assessing primary or secondary prevention interventions. In Western countries, the incidence of HPV-related cancers is generally low. Recently, an increase of HPV-related oro-pharyn-

Figure 2. — Observed standardized rates/100,000 inhabitants and “best” joinpoint model estimates for the selected sites.
Cervical cancers has been documented in many countries [45-47].

In Italy, data from cancer registries show a regular incidence and mortality decrease of HPV-related cancers over the last two decades [48]. Similarly, in Umbria, incidence of HPV-related cancers consistently decreased and a shift towards older age of incidence was also evident in the data. This pattern may be a consequence of the adoption of safer sexual behavior (e.g., use of protection devices, avoiding multiple sexual partners) perhaps following anti-AIDS awareness campaigns.

Certainly, HPV infection is not responsible for all HPV-related cancers. The etiologic fraction is highest for cervical cancer and lowest and perhaps variable for cancer of the mouth and pharynx, which recognize alcohol consumption and tobacco smoking as the main risk factors [5].

Thus the observed incidence trends may not be interpreted directly and unequivocally as a result of the changing exposure to HPV infection. Cervical cancer epidemiologic data showed some peculiarities, largely due to the ongoing screening.

Studies from other European countries showed that the incidence and mortality rates of HPV-related cervical cancer varied greatly throughout Europe [49]. All recent trends analyses confirm the dramatic contrast in the burden of cervical cancer between the 15 original and most of the ten new EU member states and between Western and Eastern Europe in general [50, 24].

With regards to age, incidence of cervical cancers was about two times higher in women 50 to 55 years of age with respect to 45-49-year-olds, and peaked at 64-69 years. This incidence pattern is similar to the one reported for many European countries, characterized by a lower incidence of the disease in pre-menopausal women [51].

Several European countries have nationally adopted organized cervical screening programs but others continue with opportunistic screening. There is limited but consistent evidence that organized screening is an improvement over opportunistic screening [52].

Generally, organized screening has greater potential ability to reduce cancer mortality and in some instances cancer incidence due to higher achievable levels of population coverage, follow-up, and quality control of the screening and treatment process. In the absence of organized call and recall systems, opportunistic screening tends to be less efficient, contributing to health inequalities and achieving lower coverage [53].

In Umbria, opportunistic screening has been present since 1972 and a regional organized cervical cancer screening program was introduced in 1999 for women 25-64 years of age. Presently screening participation in Umbria is among the highest in Italy (85%). However, opportunistic screening is not yet diffused among women and accounts for only 28% of screening tests according to a recent national health survey [54].

Cervical cancer screening has undergone some variations over the study period. In addition to liquid-based cytology and computer-assisted image analysis that were implemented to various extents by the four regional screening services, molecular testing was introduced. In Umbria, in accordance with the GISCI (Gruppo Italiano Screening del Cervicocarcinoma, that is the cervical cancer screening Italian study group) recommendations, a pilot program to evaluate HPV-DNA testing in primary screening of women in the 35-64 age group, and to test the diagnostic utility of p16INK4 as marker of progression to cervical dysplasias and carcinomas was started in 2010.

Effective integration of HPV vaccination, molecular testing, and cervical cytology will be a critical and evolving challenge. The cancer registry database has been linked to screening services and expanded to include pre-malignant cervical lesions in order to provide a more refined tool for HPV-related disease surveillance and evaluation of the effectiveness of cervical cancer screening, and the anti-HPV vaccination campaign in the near future.

Conclusion

The authors observed a consistent decrease of HPV-related cancer incidence and mortality in women. A mix of opportunistic and organized screening has certainly contributed to improving incidence and mortality trends for cervical cancer. Safer sexual behavior is likely involved in the reduced health burden from all HPV related cancers. The implementation of vaccination will lead to a further reduction of cases of cervical and other HPV-related cancers.

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Epidemiology of HPV-related female cancers in the Umbria region of Italy: pre-vaccination period


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Diagnostic approach and therapeutic management in early-stage endometrial cancer

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Summary

Objective: The effectiveness of pelvic and para-aortic lymphadenectomy in the morbidity of patients affected by early-stage endometrial carcinoma (EC) is the subject of this study. Study design: Ninety-two cases with endometrial cancer that underwent para-aortic and pelvic lymphadenectomy, from June 1995 to June 2006, were studied and compared with 30 cases of patients with endometrial cancer without lymphadenectomy. Results: According to the results, systematic pelvic and para-aortic lymphadenectomies improved disease-free and overall survival rates among the patients with endometrial cancer. The mean number of removed para-aortic lymph nodes was 19.01 ± 5.88, whereas the mean number of removed iliac lymph nodes was 32.94 ± 6.69. Forty-two and 31 metastatic iliac and para-aortic nodes were found, respectively. No surgery-related deaths and major intraoperative injuries occurred. The frequency and the type of postoperative complications were not affected by the performance of lymphadenectomy. The morbidity rate was 6.2%, similar to the group without lymphadenectomy (5.79%). No recurrence occurred in the group with lymphadenectomy, while in the other group the recurrence rate was 23.3%. Conclusions: Lymph nodes metastases can be observed in early stages of EC. Pelvic and para-aortic lymphadenectomies seems to provide profound information about the Stage of the disease and the patient’s survival, identifying which patients are suitable for supplementary treatment, without significant clinical increase of morbidity

Key words: Endometrial cancer; Paraortal iliac lymphadenectomy; Morbidity; Early stages.

Introduction

Endometrial cancer (EC) is the most common gynecological cancer [1]. Approximately 90% of EC cases are sporadic, whereas the remaining ten percent of cases are hereditary [2]. A dualistic model of endometrial tumorigenesis is currently recognized, broadly termed type 1 and type 2, based on a classification system hypothesized by Bokhman in 1983. Type 1 represents the majority of sporadic cases of EC, accounting for 70%-80% of new cases and type 2 is less common, accounting for ten to 20% of ECs [3]. Type 1 EC more often represents low-grade tumors and is associated with unopposed estrogen exposure, while type 2 EC has no relation to estrogen exposure and is associated with early spread and poor prognosis.

Abnormal uterine bleeding occurs in 80%-85% of patients with EC. In 75% of the cases diagnosed in early stages, the damage is confined to the corpus uteri [4]. All women with the clinical appearance of abnormal bleeding should immediately undergo a clinical examination, cervical smear test, and transvaginal ultrasound (TVUS) examination. Tissue sampling is required to confirm the presence of carcinoma [5]. It was confirmed that about ten percent of cases include occult positive pelvic lymph nodes and in six percent of cases, lymph node metastases occur in para-aortic area [6]. The purpose of this study was to analyze the efficacy of preoperative diagnostic and pelvic para-aortic lymphadenectomy in early stages of EC.

Materials and Methods

One hundred twenty-two patients with histologically proven EC were evaluated retrospectively, from June 1995 to June 2006, in the Department of Obstetrics-Gynecology of Aschaffenburg-Hospital Clinicum, Teaching Hospital of the University Würzburg in Germany. Patients were identified from the tumor registry, charts were retrospectively reviewed, and current status was determined for all women. The clinical presentation, the pathological characteristics, the tumoral stage according to the FIGO histological classification of uterine cancers, the diagnostic procedures, and finally the treatment of the patients recruited for this study, were evaluated. Preoperatively, blood sampling (full blood count, electrolytes), were assessed, as also TVUS and computer tomography (CT) were performed. In all patients, the diagnosis was feasible by hysteroscopy and curettage of the uterine cavity. The entire cohort of patients included in the study, underwent a surgical staging procedure with intraoperative frozen sections of hysterectomy specimens and the depth of gross myometrial invasion was measured intraoperatively.

The participants were enrolled and divided in two groups according to whether they underwent or not a radical lymphadenectomy (iliacal and para-aortic). Patients with severe cardiopulmonary disease and without severe comorbidities were included in group 1 (30 patients) and underwent total hysterectomy with bilateral adenectomy. Group 2 (92 patients) included patients that underwent total hysterectomy and bilateral adenectomy in combination with a radical iliacal and para-aortic lymphadenectomy. Participants of group 1 were treated postoperatively with radiation according to final histology, while no radiation occurred in patients of group 2.

The authors retrospectively investigated the complications of patients with EC, with pelvic and para-aortic lymphadenectomies (group 2), in comparison with the patients with EC who

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were treated without lymphadenectomy (group 1), in order to evaluate the benefit and risk of this procedure.

**Results**

The mean age of the women in groups 1 and 2 was 51.7 ± 8.5 and 60.6 ± 6.2 years, respectively. There was no statistical difference in body weight between the two groups: 85.4 ± 12.5 (range 67-128 kg) in group 1 and 74.2 ± 5.4 (range 55-105 kg) in group 2. Preoperatively all patients underwent TVUS on the same day of surgery and one or two measurements of endometrial thickness were taken. The thinnest endometrium was zero mm, while the thickest one was 25 mm. A hysteroscopically satisfactory visualization of the endometrium was obtained in all 122 examined cases.

Women in group 2 had longer surgical time (165 ± 35 min vs. 86 ± 12 min in group 1, \( p < 0.05 \)), greater blood loss (550 ± 180 ml vs 189 ± 57 ml in group 1, \( p < 0.05 \)) with more transfusions (12 vs four in group 1, \( p < 0.05 \)) and a median of two days longer length of stay (eight vs five days in group 1, \( p < 0.05 \)). No difference in postoperative complication rates was detected (5.79% vs 6.20%) (Table 1). Postoperative complications in group 1 included three cases of excess blood loss above 1,000 ml, one case of small-bowel obstruction, and one case of deep venous thrombosis. In group 2 the following postoperative complications were registered: five cases of excess blood loss above 1,000 ml, three cases of small bowel obstruction, three cases of deep venous thrombosis, and six cases of lymphoceles requiring drainage. The lymphoceles were diagnosed ultrasonographically between the eighth and ninth postoperative days. Catheter drainage allowed complete clinical and sonographic remission in both cases. Three cases, despite the anticoagulant prophylaxis and early mobilization, developed deep venous thrombosis. There was no case of postoperative bowel problems requiring laparotomy. No surgery-related deaths occurred and there was no intraoperative complication that led to lymphadenectomy procedure withdrawal. Furthermore node dissection was feasible in cases with grossly metastatic nodes and extracapsular spread to surrounding structures. No intraoperative complications occurred in group 1. Endometrioid adenocarcinoma were 99 out of 122 in total. Nineteen out of 30 (63.3%) adenocarcinoma in group 1, and 80 out of 92 (86.95%) in group 2 (Table 2). Other histological types included were clear cell adenocarcinomas and serous papillary. Women with FIGO IA tumors were present in group 1, 26.6%, while in group 2 the percentage was very low (2.17%) (Table 2). The remaining cases were classified as FIGO IB (73.3% and 97.8% in group 1 and 2, respectively). Grade 1, 2, and 3 classifications in group 1 were as follows: G1: 3.33%, G2: 70.0%, G3: 26.6%. Grade 1, 2, and 3 classifications in group 2 were as follows: G1: 0%, G2: 13.04%, G3: 86.95% (Table 2). In this study 32.95 ± 6.69 iliac nodes and 19.01 ± 5.88 para-aortic nodes were removed, while 42 and 31 metastatic iliac and para-aortic nodes were histologically confirmed, respectively (Table 2).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>51.7 ± 8.5</td>
<td>60.6 ± 6.2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(range 39 - 61)</td>
<td>(range 41 - 72)</td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>85.4 ± 12.5</td>
<td>74.2 ± 5.4</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>(range 67 - 148)</td>
<td>(range 55 - 115)</td>
<td></td>
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<tr>
<td>Operative time (min)**</td>
<td>86 ± 12</td>
<td>165 ± 35</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>mean</td>
<td>(range 40 - 100)</td>
<td>(range 80 - 200)</td>
<td></td>
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<tr>
<td>Blood loss (ml)*</td>
<td>280 ± 107</td>
<td>499 ± 280</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>mean</td>
<td>(range 60 - 600)</td>
<td>(range 150 - 700)</td>
<td></td>
</tr>
<tr>
<td>Transfusion (%)***</td>
<td>5</td>
<td>9</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Hospital stay (days)**</td>
<td>5</td>
<td>8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>median</td>
<td>(range 3 - 11)</td>
<td>(range 6 - 9)</td>
<td></td>
</tr>
<tr>
<td>Postoperative complications (%)***</td>
<td>5.79</td>
<td>6.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

No recurrence occurred in group 2 (zero out of 92 women), while the recurrence rate in group 1 was 23.30% (seven out of 30 women) (\( p < 0.001 \)). The two treatment groups differed significantly statistically, according to survival years (5.01 in group 1 vs 5.54 in group 2, \( p < 0.01 \)).

**Discussion**

Until today, no standardized methodology exists in the evaluation of women with abnormal vaginal bleeding except for endometrial biopsy or curettage [7]. The gold standard for diagnosing abnormalities in the endometrial tissue of patients with postmenopausal bleeding is endometrial sampling [8]. However since the sensitivity of preoperative endometrial sampling has been estimated to range from 85% to 95%, there has been a growing trend towards the uses of non-invasive procedures, such as high-resolution TVUS, for endometrial thickness measuring, and case classification as low or high-risk [9-12]. In this retrospective study, in group 1, the patients were treated only by total hysterectomy with bilateral adnecotomy due to comorbidities, while in group 2, the patients underwent pelvic and para-aortic lymphadenectomies. The patients were staged depending on the revised guidelines of FIGO Committee in 2009 [13]. It was reported that most patients in early-stage EC had a less than two percent risk of nodal metastases, that was also confirmed in this study [14]. According to many studies, it is possible that some patients have positive lymph nodes without pelvic nodal involvement. Metastasis of the para-aortic lymph nodes has been reported to vary from zero to six percent of cases, and para-aortic nodal recurrence has been referred to be relatively low [15, 16]. According to the results in the present study, the incidence and severity of intra- and postoperative complications in radical lymph node dissection was low (6.2%), and the average hospital stay was similar to that without lymphadenectomy. After complete lymphadenectomy with negative lymph nodes, many patients could avoid the potential risks of postoperative external radiotherapy. These findings were in accordance with other
stages of EC must be proven in future major prospective studies [17, 18]. It is significant that both longer surgical time and hospital stay and the increased blood loss observed in the patients of group 2 were not associated with an increased incidence of febrile morbidity, blood transfusion, postoperative complications or mortality. The literature, reports that the overall frequency of complications in cases of surgical staging without radiation therapy is 5.9% - 24%, while serious complications occur in 5.9% - 18.1%. The most common complications associated with surgical staging procedures are small bowel obstruction or prolonged ileus (2.6%), deep venous thrombus (2.6%), lymphocysts requiring drainage (2.4%), and small-bowel obstruction requiring requiring exploration (1.8%) [19]. Several authors have reported comparable survival rates in patients treated with lymphadenectomy alone, while other studies failed to prove the value of adjuvant radiation on survival [20-22]. According to these results, the authors confirm that patients with radical lymphadenectomy had a statistically significant higher survival year in comparison with those without lymphadenectomy.

The therapeutic effect of lymphadenectomy in early stages of EC must be proven in future major prospective randomized multicentric studies.

References


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Role of omentectomy and appendectomy in surgical staging of endometrioid endometrial cancer


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Summary

Purpose: The purpose of this study was to determine whether it was necessary to add omentectomy and appendectomy to the surgical staging of endometrioid endometrial cancer. Materials and Methods: Records were reviewed from June 2005 to June 2009 for endometrioid endometrial cancer patients who underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, infracolic omentectomy and appendectomy. Results: In total, 186 patients were included in the analysis. Disease was limited to uterus in 93% of patients and 87% of patients had Stage I disease. There was only one omental metastasis in all stages. Conclusion: Routine omentectomy and appendectomy are unnecessary in surgical staging of endometrioid endometrial cancer unless there is suspicion of gross metastases during intraoperative examination.

Key words:

Uterine cervical neoplasms; MRI; Morphology; Growth pattern; Intra uterine fluid.

Introduction

Every year endometrial cancer affects more than 140,000 women over 40 years of age worldwide and approximately 42,000 women die from this cancer [1]. The main treatment for endometrial cancer is surgery [1]. It has been demonstrated that extraterine involvement is a poor prognostic factor in endometrial cancer [2-5]. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) recommended a surgical staging process which requires a total abdominal hysterectomy, bilateral salpingo-oophorectomy (TAH+BSO), including pelvic and para-aortic lymphadenectomy (FIGO Stages 2009). Omentectomy and appendectomy are not routinely performed at the time of surgery and are not recommended by FIGO at present [6].

There are several reports regarding the significance of omentectomy and appendectomy for the treatment of endometrial cancer in addition to TAH+BSO and pelvic-para-aortic lymphadenectomy [7-10]. This is supported by the presence of metastases to the omentum, peritoneal surfaces, and the appendix in patients with endometrial cancer grossly limited to the uterus [11]. Some authors have suggested that omentectomy and appendectomy should be performed during surgical staging [7-10, 12]. However, some investigators proposed that omentectomy and appendectomy should not be performed in the staging process [13, 14] and FIGO staging does not include omentectomy and appendectomy in the procedure. The importance of omentectomy and appendectomy in addition to TAH+BSO is not well-defined. Therefore, the objective of this study was to determine if omentectomy and appendectomy were necessary in surgical staging of endometrioid endometrial cancer.

Materials and Methods

In total, 299 women who had undergone surgery for endometrial cancer at the Dr. Zekai Tahir Burak Women’s Health Training and Research Hospital between June 2005 and June 2009 were identified. Of these, 110 patients with non-endometrioid tumor types and with endometrioid endometrial cancer in which omentectomy and appendectomy were not performed, were found ineligible. The remaining 189 (63.2%) patients participated in the present study. All patients had TAH+BSO, pelvic and para-aortic lymphadenectomy (up to renal vessels bilaterally), infracolic omentectomy, appendectomy. Age, grade, myometrial invasion, cervical and adnexial involvement, positive peritoneal cytology, lymph node, omentum, and appendix involvement were recorded. Surgical staging was carried out by 2009 FIGO staging. Standard methods are used for examining the pathologic specimens, including omentum and appendix for microscopic disease detection during pathologic examination. The study was approved by the Institutional ethical committee.

Results

One hundred eighty-nine patients with endometrioid endometrial cancer were included in the study. The mean age of the patients was 50 ± 9 years. Of all patients, 93% had a disease limited to the uterus, 7.4% had extraterine disease (Table 1), and 87% of the patients had Stage I disease (Table 2). Grade, myometrial invasion, and positive peritoneal cytology data are shown in (Table 3). Only one patient had omental involvement whereas no patients had metastasis to the appendix. The patient with omental metastases had grade 2 tumor and Stage 4B disease (metastases at three pelvic lymph nodes, < 50% myometrial invasion).

Discussion

The peritoneal spread of disease is an important prognostic factor in endometrial cancer. Although performing an omentectomy and appendectomy are suggested in the
Role of omentectomy and appendectomy in surgical staging of endometrioid endometrial cancer

surgical staging of uterine serous and clear cell cancers, their role is not clear in the staging of endometrioid cancers [13]. Of 186 patients studied, the authors only found one omental metastasis and no appendix metastasis in all stages.

In a prospective study of 84 patients, Chen et al. found omental metastases in seven (8.3%) of 84 patients with Stage I endometrial cancer [12]. A majority of the metastases (five) consisted of microscopic disease. They concluded that silent metastases to the omentum frequently are clinically neglected in patients with Stage I endometrial carcinoma during primary surgery and that a routine omental biopsy should be part of the procedure. They also recommended a complete omentectomy for patients with high-risk variables [12]. In another study; Nieto et al. demonstrated that there is a six percent omental metastasis risk in early clinical Stage endometrial cancer [8]. Omentectomy influenced the management of around 15% of their high-risk patients with no obvious detriment to the low-risk women who had also undergone an omental biopsy [8]. Recently, Dilek et al. showed microscopic omental involvement in three cases (6%) and metastasis to the appendix in two cases (3.9%) in a study of 51 women with clinical Stage I endometrial cancer [9]. The authors proposed that the major advantage of extended surgical staging procedure was to be able to instantly initiate definitive adjuvant therapy in systemic relapse in cases that were diagnosed as Stage I disease. They also concluded that omentectomy gives additional information regarding extrauterine spread of the tumor without increasing operative morbidity, regardless of tumor grade. It was also suggested that omentectomy could be performed as a component of surgical staging in the presence of deep myometrial invasion even if the omentum grossly appeared normal [9]. Saygili et al. diagnosed six (6%) omental metastases out of 97 patients which were microscopic in four of them. They also found a statistically significant correlation between omental metastasis and tumor grade. In their series there was only one (two percent) metastasis to the appendix out of 55 appendectomy specimens. Furthermore, the authors concluded that in patients with deep invasion (> 50%) of myometrium or in grade 3 endometrial cancer, omentectomy may be included in the surgical staging procedure due to the likelihood of omental involvement in clinical Stage I disease during surgery. However omentectomy and appendectomy and biopsies from peritoneal sites should be performed in the presence of grossly suspicious disease [7].

In a recent study conducted by Metindir et al. published a rate of 6.2% metastasis to the omentum at the time of presentation with apparent early clinical Stage endometrial cancer. Seven patients (10.8%) had positive peritoneal cytology and there was a significant correlation of omental metastasis with peritoneal cytology. They have stated that despite the presence of normal appearing omentum, omentectomy should be performed as a component of surgical staging in the presence of positive peritoneal cytology. Authors also recommended omentectomy in all patients, as a part of routine laparotomy, if peritoneal cytology could not be diagnosed during operation [10].

All of the authors cited above established omental metastases in approximately six percent and proposed that omentectomy may be helpful in certain conditions.

On the other hand, a prospective study performed by Fujiwara et al. demonstrated omental metastasis in four patients (3.0%) out of 134 in which significant correlation with peritoneal cytology and adnexal metastases was observed. Incidence of omental metastases was lower than that of lymph node metastases and positive peritoneal cytology in clinical Stage I endometrioid adenocarcinoma. The authors concluded that performing an omentectomy in all patients as a part of routine laparotomy cannot be recommended at present. However close inspection and palpation during surgery may be necessary since omental metastasis is a poor prognostic factor when adhesion or thickening is noted and the omentum should be excised and histologically examined [14].

Gehrig et al. investigated the significance of omentectomy in the cases of endometrial serous adenocarcinoma.

<table>
<thead>
<tr>
<th>Table 1. — Pathological features of the cases.</th>
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<tbody>
<tr>
<td>Metastasis (n = 189) (%)</td>
</tr>
<tr>
<td>Limited to uterine corpus (not involving the uterine serosa)</td>
</tr>
<tr>
<td>Cervix (11/17 involving cervical stroma only)</td>
</tr>
<tr>
<td>Adnexae</td>
</tr>
<tr>
<td>Parametrium</td>
</tr>
<tr>
<td>Lymph node</td>
</tr>
<tr>
<td>Omentum</td>
</tr>
<tr>
<td>Appendix</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2.— Surgical Stages in 189 patients of endometrioid endometrial cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage (n = 189) (%)</td>
</tr>
<tr>
<td>1A</td>
</tr>
<tr>
<td>1B</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3A</td>
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<tr>
<td>3B</td>
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<tr>
<td>3C1</td>
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<tr>
<td>3C2</td>
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<td>4A</td>
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<td>4B</td>
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<table>
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<tr>
<th>Table 3. — Grade, myometrial invasion, and positive peritoneal cytology.</th>
</tr>
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<tbody>
<tr>
<td>Grade (n = 189) (%)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
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</table>

| Myometrial invasion (%)                     |
| None                                         | 24 (12.70)  |
| < 50%                                        | 102 (53.97) |
| > 50%                                        | 63 (33.33)  |
| Positive peritoneal cytology (%)             | 3 (1.59)    |
and reported that most cases of omental metastases could be detected by inspection because the sensitivity was 0.89 and the specificity was 1.00 for the intraoperative diagnosis via surgical inspection [15].

In the present study, the authors found one omental metastasis and no appendix metastases in 189 patients who had appendectomy and omentectomy. The omental metastases were in the form of multiple macroscopic metastases and the former did not affect the Stage of the disease since there was also pelvic lymph node metastasis in the patient. Therefore, the omental and appendix metastases rates were only 0.53% and 0%, respectively, which were much lower than the other recent mentioned studies. Although all Stages were included in the study, the authors expected a higher percentage of metastasis.

To the authors’ knowledge, this is one of the major series which investigates the role of omentectomy and appendectomy in endometrioid endometrial cancer [7-10, 12]. Additionally, the current study is improved by the investigation of all Stages of disease, which was not done before. However, the current study was mainly limited by its retrospective design.

In conclusion, omentectomy and appendectomy are unnecessary unless there is suspicion of gross metastases during intraoperative examination. Since there are conflicting results from various centers, multicenter, prospective, and randomized large numbers of studies are needed to clarify the exact role of omentectomy and appendectomy.

References

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Effect of tamoxifen on postmenopausal endometrium

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Summary

Purpose: The objective of this study was to evaluate the effect of tamoxifen on the endometrium of 45 postmenopausal women with breast cancer, as evidenced by hysteroscopic, ultrasound, histological methods, and by immunohistochemical investigation of the expression of Bcl-2 and Ki67. Materials and Methods: Forty-five postmenopausal women with breast cancer (ER and/or PgR positive) undergoing tamoxifen therapy for six to 48 months, were selected from the files of the 2nd Department of Obstetrics and Gynecology, University of Athens Aretaieion Hospital, among a total of 120 patients treated from 2004-2009. Results: The ultrasound findings during the follow-up period revealed 18 cases of thickened endometrium, 14 cases of suspected polyps, one case with accumulation of endometrial fluid, and 12 cases of heterogeneous endometrial echo texture. The patients had undergone hysteroscopy because of thickened endometrium (18/45 patients), postmenopausal bleeding (14/45 patients), and polyps (13/45 patients). The endometrial tissue samples were examined in the Pathology Department of Aretaieion Hospital and showed in 23 cases with adenomatous endometrial polyps, 15 cases with endometrial cystic atrophy, two cases with adenomatous hyperplasia, and five cases with mucosal endometrial adhesions. Immunohistochemical investigation of Bcl-2 and Ki67 expression was undertaken on paraffin blocks and showed elevated expression in the cases with endometrial polyps and hyperplasia, in contrast to atrophic endometria. Conclusion: Long-term tamoxifen therapy of postmenopausal women with breast cancer is associated with uterine pathology. Ultrasonography alone is useful in asymptomatic patients selecting cases with increased endometrial thickness for further investigation. Hysteroscopy is an accurate method for diagnosing endometrial disease because it provides a direct view of the uterine cavity, reveals focal lesions, and enables targeted biopsies to be performed at the same time. Pathological findings show elevated expression of Ki67 and Bcl-2 in hyperplastic endometria and adenomatous polyps, consistent with an elevated glandular cell proliferation due to tamoxifen effect.

Key words: Tamoxifen; Ultrasonography; Hysteroscopy; Endometrium; Polyps; Hyperplasia; Bcl-2; Ki67.

Introduction

The non-steroidal anti-estrogen tamoxifen is probably the most widely-used agent for breast cancer that exhibits estrogen receptors [1]. The decline of breast cancer mortality in developed countries may be attributed to the use of tamoxifen but long term use has been associated with endometrial thickening and endometrial pathology. Patients who take tamoxifen as hormonal therapy for breast cancer have a two to three times higher relative risk to develop endometrial cancer, the risk depending on the duration of the treatment and the dose itself [2]. It is recommended that all patients who receive tamoxifen for a long term must be enrolled in an ultrasonography screening, and in cases with specific ultrasonographic characteristics, must undergo further endometrial evaluation by an office biopsy, sonohysterography, dilatation, hysteroscopy and curettage [3].

In the 2nd Department of Obstetrics and Gynecology, University of Athens, Aretaion Hospital, a systematic evaluation of women with breast cancer receiving tamoxifen was undertaken in 2004 and all findings were evaluated ultrasonographic, hysteroscopic, histologic, and specific immunohistochemical findings about the endometrial hormonal receptor status and apoptosis-related agents. Bcl-2 is a proto-oncogene that prolongs the survival of cells by inhibiting apoptosis and it is strongly expressed in endometrial simple and complex hyperplasia and adenomatous polyps [4]. Ki-67 is a nuclear and nucleolar protein associated with cell proliferation normally observed during the proliferative phase of the cycle [5].

The aim of this study was to correlate the ultrasonographic with the hysteroscopic and histological findings of the endometria of postmenopausal patients who received tamoxifen for breast cancer and investigate the expression of Bcl-2 and Ki67, as well in the endometrial specimen.

Materials and Methods

Forty-five postmenopausal patients were selected among 120 patients with breast cancer (ER-positive) who received tamoxifen for at least six months and were examined at the 2nd Department of Obstetrics and Gynecology, University of Athens Aretaion Hospital, from 2004-2009. Patients that had already received chemotherapy, as well as cases with negative breast cancer hormonal receptors were excluded from the study [6]. Twenty-six patients were asymptomatic and 19 presented abnormal vaginal bleeding. All patients were enrolled in a surveillance program which included ultrasound examination, hysteroscopy, and endometrial biopsy [7-9].

Ultrasonography was performed with a vaginal probe at 65 MHz. The widest endometrial thickness was measured on the midline sagittal scan, including the double layer of the endometrium. If endometrial fluid was present, the anterior and posterior layers were measured separately and added together. The patients underwent diagnostic hysteroscopy with a 3.5
mm sheath. The authors classified hysteroscopical findings as normal and abnormal.

Normal findings included functional endometrium and atrophic endometrium with or without cystic changes. Abnormal findings included unevenly thickened mucosa with or without irregular spaced gland openings, vascular atypias, single or multiple polyps, and malignant endometrial growth. Diagnostic hysteroscopy was performed using saline infusion as a distension medium.

Endometrial tissue (sampling) was obtained from all patients and a routine pathological examination with Hematoxylin-Eosin (H&E) stained histological sections was performed at the Pathology Laboratory of Aretaieion Hospital. Additional sections of neutral formalin-fixed and paraffin-embedded tissue blocks were processed by an immunohistochemical method using an appropriate system. For the investigation of the expression of Ki67, an ab-neomarker clone SP6 was used and for the Bcl-2, an ab-Cellmarque clone 124. As positive and negative controls, sections from tonsils were used [10]. The intensity of Bcl-2 staining was semi-quantitatively evaluated as negative (-) and as positive (+) when strong and distinct [11]. Ki-67 immunostain-positive nuclei were counted per 100 cells and the expression was graded as negative (-) or positive (+, < 25% cells), and ++ (when > 25% cells). Only the glandular endometrial cells were evaluated for Bcl-2 and Ki67 expression [12].

Statistical analysis was performed with MedCalc software version 11.4.4.0 sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the probability of entering competence with respect to the various parameters was calculated.

Results

The demographic and clinical characteristics from the patient's files are as follows: the patients age was 63 ± 8.9 years and the menarche age was 12.3 ± 1.8 years, the age of the menopausal 26.8 ± 4.9, and parity reported was 2.1 ± 2.9. Sixteen of the 45 patients (34, 8%) reported one or two pregnancies, nine patients (21%) reported three or more pregnancies, and 11/45 (25%) reported one or more abortions [13]. Breast feeding was reported in 32 cases (61.1%). The body mass index (BMI) was between 26.8 ± 4.9% of the cases. Thirteen of the 45 (28%) patients were asymptomatic, 19/45 (42%) were symptomatic reporting vaginal bleeding, five of the 45 patients (11.1%) had type II diabetes and five of the 45 patients (11.1%) had hypertension. All women had been previously treated for infiltrating breast cancer (Er+) by surgery (radical or partial mastectomy or tumorectomy with axillary node dissection) and tamoxifen (dose 20 - 40 mg/day). The duration of the tamoxifen use was six to 48 months.

All the women had undergone hysteroscopy and all the endometrial samples were histologically examined. Hysteroscopy was indicated because of the thickened endometrium in 40% (18 patients), postmenopausal bleeding in 31.1% (14 patients), and suspected polyps in 28% (13 patients) [14]. The ultrasonographic and hysteroscopic findings are presented in Tables 1 and 2.

Histological examination revealed in 23 cases (48.8%) fragments of endometrial adenomatous polyps, in 15 cases (33.3%) with atrophic changes, of simple and cystic type, and in two cases (4.4%) simple and focally complex hyperplasia without atypia. In five cases (11.1%) the specimens were inadequate for histological examination. The immunohistochemical investigation showed a focal positive Bcl-2 cytoplasmic immunostain reaction in 19/22 cases of adenomatous polyps [15]. In all cases (3/3) there was adenomatous hyperplasia and in five cases there was cystic atrophy. A positive (+) Ki-67 nuclear immunoreaction was observed in five to 15 percent of the glandular cells of endometrial polyps and hyperplastic endometrium, but not in atrophic endometrial tissue (Tables 3 and 4).

Table 5 shows sensitivity, specificity, and PPV and NPV of each test when polyps were diagnosed. The diagnostic test was histological examination. The estimate of sensitivity and specificity for hysteroscopy was 65.22 and 100.0, respectively, and the estimate of PPV and NPV was 76.72 and 67.22, respectively. The estimate of sensitivity and specificity for ultrasound was 60.87 and 100.0, respec-
tively and the estimate of PPV and NPV was 100.0 and 74.55, respectively. Both hysteroscopy and ultrasound had a high significance level < 0.0001. The estimated sensitivity and specificity for immunhistochemistry was 100.0 and 31.82, respectively, and the estimated PPV and NPV was 56.14 and 100.0, respectively, with a significance level of 0.0017 (Figure 1).

Table 6 shows sensitivity, specificity, PPV and NPV of each test when hyperplasia was diagnosed. The diagnostic test was histological examination. The estimate of sensitivity and specificity for ultrasound and hysteroscopy was both 100.0 and 62.79, respectively, and the estimated PPV and NPV was 56.14 and 100.0, respectively, with a significance level of 0.0017 (Figure 1).

Table 6. — *Hyperplasia histological diagnosed vs test.*

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Sign. level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial thickness</td>
<td>100.0</td>
<td>62.79</td>
<td>15.96</td>
<td>100.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>ultrasound</td>
<td>(15.8-100.0)</td>
<td>(46.7-77.0)</td>
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<tr>
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<td>100.0</td>
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<td>100.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>hysteroscopic</td>
<td>(15.8-100.0)</td>
<td>(46.7-77.0)</td>
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</tbody>
</table>

Discussion

Tamoxifen is widely used to treat menopausal women suffering from estrogen-receptor positive breast cancer [16, 17]. An improvement in breast cancer behavior follows tamoxifen administration, both as adjuvant treatment and in relapsed or advanced disease. In post-menopausal women tamoxifen is associated with increased proliferative activity of glandular endometrial cells and increased incidence of endometrial cancer. This is probably due to an imbalance between cellular proliferation and cellular death, as expressed by the apoptotic index as reported in recent studies [18].

The endometrial lesions that may arise during hormonal adjuvant treatment can be diagnosed through hysteroscopy and transvaginal ultrasound. Ultrasonography is useful in asymptomatic patients because it permits selection of patients with increased endometrial thickness who should undergo hysteroscopy and dilation and curettage [19]. A limitation of ultrasound is that an abnormal finding may not be diagnostic: ultrasound may not be able to distinguish between hyperplasia and malignancy and the next step in clinical treatment requires tissue sampling; therefore, hysteroscopic examination seems to be the “gold standard” in diagnostic procedures.

Hysteroscopy is a valuable method for diagnosing endometrial disease because it provides a direct view of the uterine cavity, reveals focal lesions, and enables targeted biopsies to be performed at the same time [20-22]. This is an accurate method in detecting polyps, and hyperplastic and neoplastic changes of the endometrium. Therefore, an evaluation plan using transvaginal sonography as the initial screening evaluation, followed by endometrial biopsy or, more likely, hysteroscopy, tends to become the standard of care globally [21, 23]. It remains unproven whether certain patients at higher risk for carcinoma should proceed directly to invasive evaluation.

The most common pathologic change detected in this present study is the presence of endometrial adenomatous polyps after tamoxifen use. This is in accordance with other researchers [20, 24-27], while others suggest other pathologic conditions as more common in women undergoing tamoxifen use (hyperplastic lesions, endometrial hypertrophy, etc.) [28-31].
The observed elevated levels of Bcl-2 expression in polyps and hyperplastic endometrium found in the present study, are in accordance with recent reports. Bcl-2 exerts its biological anti-apoptotic action, which, in turn, favors the accumulation of hyperplastic glandular cells being responsible for the formation of endometrial polyps [21].

Women on tamoxifen with persistent recurrent bleeding, women with significant risk factors for carcinoma, and women with life-threatening hemorrhage comprise this group.

Further studies are still necessary to evaluate high-risk patients and determine whether ultrasound or biopsy is really the most cost-effective initial test.

In conclusion, the authors demonstrated that tamoxifen acts on the postmenopausal uterus as an estrogenic substance, inducing a significant increase in the endometrial thickness. They believe that these preliminary data confirm the potential value of the transvaginal sonography for the detection of the uterine pathology.

For further evaluation, especially for symptomatic patients, hysteroscopy and histological examination of endometrial samples is mandatory. Transvaginal sonography, hysteroscopy, and histological examination can identify women at risk who need further invasive diagnostic treatment.

References


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The effect of vitamin E on plasmatic malondialdehyde levels during surgical removal of ovarian and endometrial carcinomas

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Summary
This study deals with the monitoring of plasmatic levels of malondialdehyde, as the main indicator of oxidative damage to biomembranes. Malondialdehyde is determined by high-performance liquid chromatography (HPLC) after derivatization employing 2,4-dinitrophenylhydrazine. A clinical study involving 20 female patients suffering from ovarian and endometrial carcinomas has demonstrated elevated levels of malondialdehyde (10.1 ± 1.1 µM), compared with the control group (7.5 ± 2.7 µM). It has been further verified that surgical removal of the tumor leads to an additional increase in the plasmatic malondialdehyde content. This unfavourable situation can be effectively eliminated by administration of a single dose of vitamin E prior to surgery.

Key words: Cancer; Lipid peroxidation; Malondialdehyde; Vitamin E; Gynaecology.

Introduction
The oxidative stress, defined as a non-equilibrium between the oxidative and antioxidative processes at the cellular level, is a principal cause of many degenerative illnesses connected with ageing, such as cancer, cardiovascular diseases, brain dysfunctions, and cataract [1]. One of the most common biomarkers of oxidative damage to biomembranes is malondialdehyde (MDA) [2, 3]. MDA is formed by the lipoperoxidation process, in which hydroperoxides are first formed by the effects of reactive oxygen and nitrogen species on the chains of polyunsaturated fatty acids, followed by degradation of the carbon skeleton of phospholipids to simple organic compounds, of which MDA is most important for diagnostics. Liberated MDA is a dangerous reactive substance which is covalently bound to DNA and proteins under physiological conditions [4, 5]. MDA adducts with DNA bases and the DNA-protein adducts formed by the MDA effects are genotoxic, because they induce the formation of mutations and finally may lead to tumor growth [6]. It has further been demonstrated that the MDA interaction with collagen and plasmatic proteins leads to development of atherosclerosis and other cardiovascular diseases [7].

Although MDA is considered to be a non-specific indicator of the overall oxidative damage to biomembranes, several clinical studies have clearly demonstrated a distinct connection between the MDA plasmatic level and the appearance of some concrete diseases. Elevated levels of plasmatic MDA have been observed in smokers and explained by the presence of free radicals in cigarette smoke [8]. Analogously, the formation of free radicals by the autooxidation of glucose increases the MDA levels during hyperglycemia in diabetics [9]. Elevated MDA levels have also been demonstrated with neurodegenerative diseases, such as Alzheimer and Parkinson [10] or preeclampsia [11]. MDA is intensely monitored in connection with the development of carcinogenesis. An elevated extent of lipoperoxidation, measured by means of the monitoring of plasmatic MDA, has been demonstrated for patients suffering from breast and lung carcinoma [12]; another study has demonstrated increased MDA levels in patients suffering from uterine cervical carcinoma [13]. The reason for increased lipoperoxidation is the breaking of the antioxidative defence of the organism, due to the rapidly growing tumor. The initial conditions leading to the formation of uterine cervical carcinoma are considered to be connected with insufficient supply of antioxidants in patients with a low social status [14].

One of the main antioxidant active in membranes is vitamin E. This name denotes the group of eight lipophilic substances, of which α-tocopherol exhibits the highest biological activity [15]. Although the original assumptions concerning wide use of vitamin E in curing and preventing various diseases have been substantially reduced, this vitamin retains its usefulness in present-day medicine [16]. Vitamin E is employed during pregnancy to support good embryonic development [17] and to prevent preeclampsia [18]; vitamin E also prevents the development of cardiovascular diseases [19] and is commonly administered to patients suffering from cystic fibrosis [20]. Among the attempts to use vitamin E for prevention of cancer, the only positive results have so far been obtained with prostate cancer [21].

The present study is directed to the monitoring of plasmatic MDA levels in female patients suffering from malignant tumors and treated in this gynaecological department. The changes in the MDA levels are monitored prior to tumor removal and after, in connection with administration of vitamin E.
Materials and Methods

This study deals with 20 patients with tumors indicated, treated at the Department of Gynaecology and Obstetrics, Faculty Hospital Královské Vinohrady in Prague (nine patients suffering from ovarian tumors and 11 patients with endometrial tumors). Three samples of venous blood were gradually collected from the patients; the first one taken 24 hours prior to the operation, the second one at one hour postoperatively, and the third at 24 hours postoperatively. The effect of vitamin E was monitored as follows: a single pellet containing 1,200 mg of vitamin E was administered to a group of ten randomly-selected patients at 18 hours prior to tumor removal. The other group of ten patients did not have vitamin E administered. The results were compared with those obtained in a control group of 14 healthy women of the same age. Both the patients and the control group were non-smokers, for whom diabetes mellitus and liver diseases were not indicated. The whole clinical study was approved by the Ethics Committee of the Third Faculty of Medicine, Charles University in Prague and Faculty Hospital Královské Vinohrady in Prague.

Samples of non-precipitating blood (a vacuette sampling vessel with the ethylenediaminetetraacetic acid (EDTA) anticoagulant) were centrifuged immediately after the collection; the plasma separated was frozen and stored at a temperature of -20°C. To determine plasmatic MDA, a high-performance liquid chromatography (HPLC) procedure with UV photometric detection was used, after prior derivatization of MDA with 2,4-dinitrophenylhydrazine, which is previously described in detail [22]. To summarize the procedure: a volume of 100 µl of the melted plasma was used and it was hydrolyzed in 1M NaOH at 60°C for 60 min. The overall content of plasmatic MDA, i.e., the free substance and that bound to plasmatic proteins, was determined [2, 23]. The HPLC separation took approximately seven min., with a LOD value of 0.3 µM for MDA. MDA was used as the internal standard. The calibration dependences were linear within the test concentration range, 1 – 20 µM. The Origin 8.0 program was used for evaluation and statistical treatment of the experimental data.

Results and Discussion

Rising of plasmatic MDA in patients with tumors

In the first stage of the study, plasmatic MDA levels in patients suffering from cancer were compared to those in healthy women (data corresponding to the blood collection 24 hours prior to the tumor removal were used). The ages in the two groups are similar and thus the age effect on the MDA levels is eliminated. The plasmatic MDA levels are 7.5 and 10.1 µM for the healthy controls and the patients, respectively (Table 1) and this difference thus amounts to 35%, which is statistically significant (ANOVA test at a significance level of 0.05). This finding is in agreement with the results of the previous studies, in which increased levels of plasmatic MDA have been found for patients suffering from carcinomas of prostate, breast, lungs, uterine cervix, stomach, and from chronic lymphocytic leukemia [12, 13, 24-26]. MDA is not liberated directly in the tumor, i.e. in cells which are less-differentiated and in which the lipoperoxidation is decreased, but in the surrounding differentiated tissue. In this differentiated tissue, the antioxidant protection is decreased because antioxidants are consumed by the tumor [27]. In this way the carcinoma increases the MDA level which itself is genotoxic and its adducts with DNA may cause the development of carcinogenesis.

Protective effect of vitamin E administration

The second stage of the study monitored the time variations of the plasmatic MDA levels in carcinoma patients during the surgical removal of the tumors. One group of the patients obtained a single dose of vitamin E prior to the operation, the other group did not (Figure 1 and Table 2). In the control group without vitamin E, the MDA level amounted to 13.8 µM one hour postoperatively, which is 37% more compared with the first blood collection. An increased MDA level lasts even 24 hours postoperatively (13.1 µM), which is 31% more than the state prior to surgery. The invasive action: surgical removal of the tumor, causes degradation of the tissue and this has a negative result, increasing lipoperoxidation of biomembranes.

With the group of patients with tumors, to whom a single dose of vitamin E was administered 18 hours before sur-
surgery, the MDA level equalled 11.2 µM one hour after surgery, which is only 11% more than the value before surgery, and the value 24 hours after surgery was 10.2 µM; this is fully comparable with the MDA level before surgery. Even if the two groups (those with and without vitamin E) had comparable levels of plasmonic MDA preoperatively, the differences in the levels of plasmatic MDA one hour and 24 hours postoperatively were statistically significant. Therefore, a single administration of vitamin E several hours before surgery very efficiently compensates the negative effect of surgery on biomembrane degradation. This fact is in agreement with the results of a previous study, in which the protective effect of vitamin E has been demonstrated on the decrease of MDA levels in erythrocytes in children with type 1 diabetes [28].

Conclusion
The present study has discovered increased lipoperoxidation in patients suffering from ovarian and endometrial tumors, on the basis of determination of plasmonic MDA levels. This provides an indirect proof of oxidative damage to the system. It has further been demonstrated that surgical removal of tumors causes a further increase in the lipoperoxidation. The unfavourable effect of surgery can be effectively decreased by administering single-dose vitamin E prior to surgery; this contributes to more rapid reconvalescence of the patients. Vitamin E could be considered a suitable supplement in surgical procedures.

Acknowledgement
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Embryonal rhabdomyosarcoma of the uterus in a 35-year-old woman: case report and review of the literature

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Summary

Embryonal rhabdomyosarcoma (RMS) is a rare sarcoma that characteristically occurs in children. The current treatment protocols are based on trials performed in patients under 21 years of age. Embryonal RMS in women over 20 years of age is rare, and studies on treatments and outcomes are limited. The authors here in report a case of a 35-year-old woman with ectocervical RMS who was treated with radical hysterectomy followed by chemotherapy. She is currently disease-free. Based on a literature review, the authors recommend a surgical approach in combination with chemotherapy for treatment of embryonal RMS in adult patients.

Key words: Rhabdomyosarcoma; Adult; Ectocervical.

Case Report

A 35-year-old woman presented to the present department because of irregular vaginal bleeding and increasing leukorrhea in April 2010. Her medical history was negative for relevant pathologies. Her gynaecological and obstetrics anamneses were normal, with menarche at the age of 12 years and regular, subsequent cycles with respect to rhythm, quantity, and length. Two pregnancies had resulted in successful spontaneous deliveries.

Physical examination of her pelvis revealed the presence of ectocervical swelling and ectocervical polypoid masses of two-cm in diameter. Cervical and endometrial smears were negative intraepithelial lesion malignancy (NILM), and she was diagnosed with cervicitis. Magnetic resonance imaging (MRI) showed cervical swelling and hypertrophy of the vaginal wall. The authors were initially unable to achieve a definitive diagnosis, but carefully followed up the patient because of the possibility of a malignant tumor.

They performed another pathological examination on May 21. Histologically, the tumor comprised of a sheet-like growth pattern of undifferentiated cells with scant cytoplasm; some foci showed cells with granular eosinophilic cytoplasm consistent with rhabdomyoblasts. Beneath the epithelium, a zone of increased cellularity composed of undifferentiated rhabdomyoblasts (cambium layer) was present. Deep to the surface, many rhabdomyoblasts in varying degrees of differentiation were present, dispersed in an edematous and myxomatous stroma. Immunohistochemical analysis revealed the rhabdomyoblasts to stain with desmin, muscle-specific actin, and focally, myoglobin, and vimentin. These findings are consistent with an embryonal RMS (Figures 1 A-D).

Computed tomography (CT) showed no evidence of lymphadenopathy or metastatic disease. On June 2, the patient was admitted to the present hospital for surgery.

Another physical examination was performed. The authors found that the anterior cervical lip was occupied by a “grape-like” tumor that barely bulged out of the vaginal introitus. Sonographically, it was hypoechogetic and dishomogeneous with an irregular border. They judged that this new polypoid mass was a skip lesion from the ectocervical sarcoma botryoides and that the progression was rapid.

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According to the protocol of the Japanese Pediatric RMS Study Group (JRSG), the patient initially received adjuvant chemotherapy comprising of vincristine at 1.5 mg/m², actinomycin-D at 0.045 mg/kg, and cyclophosphamide at 2.2 mg/m² (VAC) every three weeks. Laboratory test results showed that her neuron-specific enolase level was not increased.

On June 21, VAC chemotherapy was begun. After one course, the “grape-like” ectocervical tumor was reduced to a two-cm polyp-like mass. The skip lesion was also reduced. After two courses, the tumor was further reduced in size. The patient underwent three courses of chemotherapy.

On September 3, the patient underwent radical surgery. First, the authors removed the “grape-like” mass by a transvaginal approach. Rapid pathological examination led to a diagnosis of malingnant sarcoma botryoides, so they performed a total hysterectomy with bilateral salphtingoophrectomy, pelvic lymphadenectomy, and vaginal wall segmentectomy.

Pathologic results showed a residual tumor confined to the cervix and metastatic lesions of the lymph nodes. The tumor Stage was IRS-V 2B; therefore, the patient underwent chemotherapy according to the JRSG treatment protocol. VAC therapy was administered for one year. She remains in good health with no evidence of disease 24 months from diagnosis.

Discussion

RMS accounts for < 5% of all adult soft tissue sarcomas [8]. Although uncommon in adults, RMS tends to be more aggressive and more resistant to chemotherapy than its
childhood counterpart. In children, primary uterine cervical RMS accounts for 15% of cases. It is the third most common gynecologic site after the vagina (54%) and uterine corpus (17%) [9, 10].

In adult patients, RMS might be considered in the clinical and histological differential diagnoses along with other uterine primary neoplasms, such as carcinosarcoma, leiomyosarcoma, endometrial stromal sarcoma, and adenosarcoma. Sarcoma botryoides, a subtype of embryonal RMS, arises beneath the mucous membrane and produces a classical polypoid appearance. The botryoid type is generally found in the vagina during early childhood, in the cervix during adolescence and the reproductive period, and in the corpus uteri during the postmenopausal years [11].

As in a previous report, the present patient presented for evaluation of polypoid masses, and a definitive diagnosis was achieved by histological examination (immunostaining). In many reported cases including this one, the tumor initially appeared as a benign intracervical or endometrial polyp protruding from the vaginal introitus. Thus, a long period of time was required to obtain the final diagnosis.

Histologically, RMS is divided into favorable and unfavorable histologic groups [12]. The botryoid, well-differentiated or spindle cell and embryonal subtypes are considered favorable histologic types, while the pleomorphic and alveolar subtype are included in the unfavorable histologic group.

The embryonal pattern is the most common histologic type in all sites [13]. Approximately half of all cases of embryonal RMS occur in the head and neck region, 20% occur in the extremities, and the remainder are visceral and trunk lesions.

In contrast to the anatomic distribution of this tumor in the pediatric population, the tumor tends to favor the proximal extremities or the genitourinary sites in adults as seen in the present case. In female patients, the vagina and vulva are the most frequent sites of occurrence [14].

Arndt et al. [15] studied the data from the IRSG trials I-IV and found that children and adolescents with alveolar subtype histology had a five-year survival rate of 66% compared with an 83% five-year survival with the embryonal variant, both found within the female genital tract. Among the pediatric and adolescent data, uterine RMS carries a worse prognosis (36% mortality) than RMS arising from the vagina (4% mortality) or other genitourinary sites [16].

The most effective treatments for children and adolescents with RMS have been extensively studied by the IRSG. Treatment recommendations from this study include a multimodality approach comprising of surgery, radiotherapy, and chemotherapy [17]. IRSG-IV revealed that VAC chemotherapy (vincristine, actinomycin-D, and cyclophosphamide) with or without radiotherapy, remains the gold standard of treatment in the child/adolescent population [17]. Of note, because of its infrequent occurrence, no standard treatment for adult patients has been established in the literature.

However, a recent analysis of 171 adult patients with RMS [18] reported that treatments similar to those recommended in the pediatric literature (surgery, chemotherapy, and radiotherapy) produced similar outcomes in the adult population and that both adults and children should receive the same treatments.

Ferguson [10] reported encouraging results from retrospective studies with multi-agent chemotherapy based on pediatric guidelines, with improved survival and response rates of > 80%. The Intergroup RMS Studies defined the treatment protocols for RMS in children that led to dramatically improved survival rates of > 70% for all patients and > 85% for those with non-metastatic diseases.

The five-year survival rate of the patients from the first group of the IRS-III, who were treated with vincristine and actinomycin-D (VA) for one year, was about 93%. According to the IRS, chemotherapy increased the survival rate while radiotherapy was ineffective for Stage I patients.

The authors performed radical surgery and chemotherapy according to IRSG protocols. The main strategy comprises surgery, chemotherapy, and radiotherapy, but the present protocol excluded radiotherapy. Zeisler reported that radical surgery with adjuvant chemotherapy seems to be the most appropriate treatment for women with no fertility-preservation concerns [19].

In 2007, Stankovic presented a case of minimally invasive surgery in combination with adjuvant chemotherapy that resulted in an excellent survival with complete preservation of the bladder and rectum [20].

However, if a local relapse is identified, radiotherapy may be the most appropriate second treatment for achieving local control.

In summary, the authors reported a case of uterine RMS in a 35-year-old woman. She underwent radical surgery and adjuvant chemotherapy. After treatment according to protocols, without radiotherapy, she has been disease-free for 24 months. If she develops local recurrence, radiotherapy may be indicated. Continued studies are needed due to the rarity of these tumors, limited recommendations for specific treatments, and lack of information on prognosis.

References

Embryonal rhabdomyosarcoma of the uterus in a 35-year-old woman: case report and review of the literature


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Mesonephric carcinosarcoma of the uterine cervix: a case report

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Summary

Cervical carcinosarcomas are rare neoplasms that aggressively progress and belong to the histological group of mixed tumors with both epithelial and mesenchymal components (malignant mixed Müllerian tumors). At diagnosis, most patients present with vaginal bleeding and a palpable cervical mass. Given the rarity of this neoplasm, there is no consensus regarding the management of these patients and should be approached on a case-by-case basis, taking into consideration the clinical and pathological features of the tumor. The authors describe a woman with mesonephric cervical carcinosarcoma and review the literature regarding these rare tumors to better understand the natural history of these neoplasms.

Key words: Malignant mixed Müllerian tumor Cervix; Mesonephric carcinosarcoma; Vaginal bleeding; Palpable cervical mass.

Introduction

Among malignant cervical neoplasms, squamous cell carcinomas account for approximately 80% to 90% of all cases, while 10% to 20% are adenocarcinomas [1]. Other less frequent histological groups have been identified, including carcinosarcomas, also termed malignant mixed Müllerian tumors (MMMT). Carcinosarcomas represent fewer than five percent of all malignant tumors localized in the body of the uterus [2]. These neoplasms are even more rare in the uterine cervix, where they probably account for less than three percent of all uterine MMMT cases [3]. Cervical carcinosarcoma is characterized by malignancy of both epithelial and mesenchymal components. Most such tumors contain a homologous mesenchymal component, and cases with a heterologous component are extremely rare. The information available to date regarding their natural history is based on case reports or small series of cases. Because of the lack of information regarding these neoplasms, there is as yet no consensus regarding their prognosis and treatment.

The authors describe a woman with mesonephric carcinosarcoma of the cervix and review the literature in order to better understand its natural history, differential diagnosis, clinical, and therapeutic management.

Case Report

An 80-year-old woman was referred to this department because of postmenopausal metrorrhagia. Antecedents of interest were medical treatment for hypertension, type 2 diabetes mellitus treated with oral antidiabetics and dyslipemia. Her gynecological antecedents were two uncomplicated vaginal deliveries and menopause at 42 years of age.

Gynecological examination disclosed posterior cervicovaginal synechiae and cervical bleeding. Cytological analysis identified atypical cells compatible with adenocarcinoma. Hysteroscopy was indicated to explore the uterine cavity and obtain a biopsy under visual guidance. This examination disclosed a grossly normal uterine cavity and endocervical canal with evidence of neoplasia, from which a biopsy was obtained. The pathology report indicated poorly-differentiated squamous cell carcinoma of the cervix. Rectal examination of the patient ruled out the presence of parametrial involvement. Because of the physical examination and patient’s age, an abdominal total hysterectomy and bilateral adnexectomy were performed and her postoperative course was uneventful.

The specimen received for pathological examination consisted of uterus with bilateral adnexa with a total weight of 60.5 g. Two different lesions were identified on gross examination. One of them consisted of an irregular area in the cervical canal that measured three cm in diameter by four mm in thickness. This lesion was in intimate contact caudally with an area of nodular, whitish, elastic tumor tissue measuring three cm in diameter, which extended to the external cervical orifice, surrounding the entire circumference of the cervix, and infiltrating the wall of the cervix on macroscopic inspection.

Histological analysis of the irregular lesion revealed an endocervical tumor comprising of two components; one of them was a compound of keratinized and poorly-differentiated infiltrating squamous cell carcinoma, associated with a high-grade squamous intraepithelial component (H-SIL). The second component was a characteristic-appearing endocervical adenocarcinoma associated with adenocarcinoma in situ. Immunohistochemical studies demonstrated positivity for monoclonal carcinoembryonic antigen (CEA) and negativity for vimentin and estrogen receptors.

The histological examination of the nodular lesion revealed a biphasic epithelial and mesenchymal malignant tumor (carcinosarcoma). In this tumor, the epithelial component consisted of an adenocarcinoma with tubular glands lined by atypical epithelial cells containing eosinophilic secretion (Figure 1). The immunohistochemical profile of these cells indicated mesonephric carcinoma, were positive for epithelial membrane antigen (EMA), CD10 and vimentin, and negative for hormone

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receptors. The malignant mesenchymal component (Figure 2) was homologous and high-grade tumor that was positive for CD10 and negative for actin and desmin (Figure 3). The final diagnosis was cervical MMMT associated with adenocarcinoma and squamous cell carcinoma of the cervix.

Treatment was continued with external radiotherapy and adjuvant endocavitary brachytherapy to prevent local recurrence because of the deep invasion of the cervix stroma and the size of the tumor. On follow-up examination 31 months later, the patient was free of disease.

Discussion

Cervical carcinosarcoma is an extremely rare tumor, with only 128 documented cases in the literature [4]. This neoplasm is included in the histological group of mixed epithelial and mesenchymal tumors according to the WHO 2005 classification. Cervical carcinosarcoma mainly occurs in postmenopausal women, with a mean age at diagnosis of 64 years and a range of 25 to 93 years [4]. The present patient was 80-years-old. Patients usually present with vaginal bleeding as the initial symptom, which leads to a diagnosis of a cervical mass [1]. This patient initially presented with only vaginal bleeding at the time of diagnosis. Most cervical carcinosarcomas are detected in Stage IB, and at the time of diagnosis the disease is confined to the cervix in most women, including this patient [3-5]. Cases of extracervical neoplastic disease are associated with a worse prognosis [5]. Cervical carcinosarcoma usually presents at an earlier stage than carcinosarcomas of the body of the uterus and is therefore associated with an earlier diagnosis and better prognosis [1, 3, 6].

The histological features of carcinosarcoma are mixed, comprising of an epithelial (squamous cell carcinoma or adenocarcinoma) and a mesenchymal component (sarcoma). Depending on the degree of differentiation observed in the mesenchymal component, this neoplasma can be subclassified as homologous or heterologous. In the present patient, the histological features indicated that the mesenchymal component was homologous, whereas the epithelial component consisted of mesonephric adenocarcinoma. This latter type is manifested as a tubular growth pattern with intraluminal secretion accompanied by areas of more solid and retiform growth. To date, only one case of uterine carcinosarcoma of mesonephric origin has been described [7].

The differential diagnosis of cervical carcinosarcoma includes cervical spread of the carcinosarcoma from the body of the uterus. Accurate diagnosis depends mainly on the predominant localization of the neoplasm based on pelvic examination, imaging studies, and histological studies of the hysterectomy specimen [3].

Human papilloma virus (HPV) infection can be an important cofactor in the carcinogenesis of cervical carcinosarcoma [1, 3, 8, 9]. Grayson et al. reported that HPV
DNA was detected in all eight cases of the cervical carcinosarcomas they reviewed. Because this neoplasm is so rare and complex, evidence-based recommendations for treatment guidelines are unavailable [1]. In their review of five cases, Sharma et al. reported that radical surgery was effective both with and without adjuvant radiotherapy. Although it is difficult to determine the best treatment for these women, tumors in the initial stages with low metastatic potential (IB1 and IB2) have a favorable prognosis after treatment with radical surgical treatment associated with adjuvant radiotherapy [1]. In the present patient, the tumor was diagnosed in an initial stage and was treated with surgery and local adjuvant radiotherapy, and on clinical follow-up one year later, she was free from disease and her prognosis was good. Information on the use of chemotherapy is currently insufficient, although this treatment modality is of particular importance given its increasingly frequent use for cervical cancer and many types of sarcoma (such as rhabdomyosarcoma) as adjuvant or neoadjuvant therapy [4]. The chemotherapeutic agents used most often are cisplatin, doxorubicin, ifosfamide, and cyclophosphamide [10].

In conclusion, surgery is the mainstay of treatment for cervical carcinosarcoma. Although radiotherapy with or without adjuvant chemotherapy has also been used, the role of these modalities in the management of these tumors remains unclear [10]. Further studies are needed to better characterize the natural history of mesonephric carcinosarcoma of the uterine cervix and develop optimum treatments for these patients.

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References
Uterine angiomyolipoma with metastasis in a woman with tuberous sclerosis: a case report

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Summary
Extrarenal angiomyolipomas (AMls) have been reported at various anatomical sites such as the liver, spleen, abdominal wall, retroperitoneum, oral cavity, penis, spermatic cord, skin, and lung but are infrequently described in gynecological regions. However, only a few cases of extrarenal AML in the uterus have been reported. The authors describe a case of uterine AML in a 41-year-old woman with evidence of tuberous sclerosis. Initial diagnosis concluded with myoma based on the interpretation of imaging and other pathological parameters. However, after successful laparoscopic surgical staging, AML was diagnosed. To date, the feasibility of laparoscopic surgical diagnosis and the risks associated with this technique have not been reported. The authors briefly review the implementation of laparoscopic surgical staging to diagnose uterine AML.

Key words: Angiomyolipoma; Lymph node; Metastasis; Uterine neoplasms.

Introduction
Angiomyolipoma (AML) is a benign mesenchymal neoplasm composed of blood vessels, smooth muscle cells, and adipocytes. Renal AML has been frequently reported; however, uterine AMLs are rare, with only a few documented cases [1-3]. The first report of uterine AML was described as “hamartoma of the uterus” by McKeithen et al. [4] in 1964. On the other hand, tuberous sclerosis (TS) is a rare, multisystem genetic disorder with symptoms that include, seizure, mental retardation, and facial angiofibroma [2].

Whereas renal AML is commonly associated with TS, most uterine AMLs are not associated with this condition [2]. Most AMLs are benign; therefore, metastases to the lymph nodes are scarcely reported [3, 5].

In this report, the authors describe the case of a woman with TS who was found with uterine AML with metastasis to the pelvic lymph nodes.

Case Report
A 41-year-old nulliparous woman, with regular menstrual cycles, presented with an eight-month history of dysmenorrhea and a palpable mass. Her medical history also included hypertension and diabetes mellitus, and was also a carrier of hepatitis B. Her blood pressure was 120/80 mmHg, with a pulse of 78 beats/min. Pelvic examination revealed a large, palpable mass on the lower abdomen. Ultrasonography showed the presence of multiple myomas and a high echoic and homogeneous mass on the left ovary, measuring 15 cm (greatest dimension). The right ovary appeared normal. The laboratory results were non-specific, except for the presence of elevated serum CA125 levels of 190.2 U/ml. Magnetic resonances imaging (MRI) of the mass revealed low signal intensity on T1-weighted images (Figure 1a) and high T2 intensity signals (Figure 1b). A total hysterectomy was performed, and the final pathologic diagnosis was AML (Figure 2). No further treatment was administered, but short-term examination was recommended.

At the 11-month follow-up visit, the serum levels of CA125 had increased to 262 U/ml. Computed tomography (CT) of the pelvis revealed an enlargement of the left external iliac lymph node (Figure 3). Laparoscopic lymphadenectomy was performed and confirmed an angiomyomatous lesion present on the lymph node. The lymph node was also positive for smooth muscle actin, vimentin, and HMB-45 (Figure 4). In addition, MRI of the brain detected subependymal nodules (Figure 5). The patient recovered without event and has been alive without recurrence for over six years.

Discussion
AML is a benign tumor composed of smooth muscle cells, adipocytes, and blood vessels [3]. The incidence of AML of the uterus is extremely low, occurring in women aged 22 to 77 years (mean age, 48). Unfortunately, uterine AML is not officially registered by the World Health Organization (WHO) as a category of uterine tumor. As a result, cases of uterine tumors with diverse nomenclature have been reported, including lipoleiomyoma, benign lipomatous lesion, angiolipoleiomyoma, and lipoleiomyomatous tumor [1].

It has been reported that AML occurs frequently with TS [3], with renal AML often associated with this condition. However, most extrarenal AMLs develop without evidence of TS [6]. TS can also involve the brain, kidney, retina, skin, heart, lung, and bone [7], and the patient displayed subependymal nodules on the brain MRI, which represents a typical sign of TS. The present patient did not present with mental retardation and had no history of seizures.

In most cases, AML is found together with leiomyoma [8]. The clinical presentation of AML can include bleeding, abdominal discomfort, pelvic mass, urinary frequency, and...
being asymptomatic, which is identical to that of myoma. This makes it difficult to diagnose AML preoperatively [3], as demonstrated in the present case, where the palpable mass was also preoperatively diagnosed as myoma.

Diverse hypotheses have been suggested on the pathogenesis of uterine AML. McKeithen et al. [4] regarded that lesion as hamartoma, whereas Demopoulos et al. [9] suggested that AML arose from mesenchymal stem cells that differentiated into smooth muscle cells, adipocytes, and blood vessels. Salm et al. [10] hypothesized that uterine AML is closely associated with fatty metaplasia from leiomyoma. However, the pathogenesis of AML has not yet been clearly demonstrated.

CT and MRI imaging with fat suppression mode are reported to be useful in explaining the presence of adipose tissue [11]. The sonographic feature of AML is a hyper-
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...echoic lesion with sharp margination and with a very similar fat component to that of an ovarian dermoid cyst [12, 13]. However, generally, it is very difficult to diagnose AML using sonography, CT, and MRI preoperatively [9]. In the present case, sonography showed a hyperechogenic region in the center of the myoma and the MRI results revealed that the uterus was composed of multiple myomas with variable signal intensity that could be differentiated from uterine sarcoma. The necrotic findings from MRI were also used as a basis for diagnosing leiomyosarcomas. On MRI, necrosis shows high signal intensity on T1-weighted images and heterogeneous features on T2-weighted images [14]. The location of myoma was intramural, which represents the most commonly reported site.

In a review of the literature, the authors found only one report of uterine AML with metastasis to the lymph node. In this case, an 18-year-old nulliparous woman presented with a 7.5-cm uterine mass and four-cm mass on the right iliac fossa simultaneously. She had no history of tuberous sclerosis. It is interesting that in the present case, lymph node metastasis was detected 11 months after total hysterectomy for AML.

Recently, immunohistochemistry was used for the molecular understanding of AML. HMB-45 is a monoclonal antibody that reacts specifically with melanocytic tumors...
and AML [15]. Immunohistochemical patterns of HMB-45 closely associate with epithelioid cells in the kidney [16]. Therefore, renal AML is positive for HMB-45; however, extrarenal AML is negative for this marker [1]. It is also interesting that HMB-45 was positively detected in the present case of uterine AML. Most HMB-positive cells in renal AML are epithelioid-type smooth muscle cells; however, most uterine AMLs consist of spindle-shaped cells. Therefore, the expression of HMB-45 can be related with the shape of the cells [1]. Microscopic analysis of the present AML case showed spindle-shaped cells; moreover, it showed positivity for smooth muscle actin, vimentin, and trichrome staining.

To the best of the authors’ knowledge, this is the first case of uterine AML with metastasis to the lymph nodes reported in a woman with TS. This report also highlights the significance of preoperative ultrasound findings of AML. AML should be considered in the differential diagnosis in all women with diagnosis of uterine myoma. In conclusion, uterine AMLs are very rare tumors with metastatic potential, and the authors recommend long-term follow-up of patients with AML for the early detection of metastasis to the lymph nodes.

References


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Carcinosarcoma of the uterus in advanced stage: a case report

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Summary
This is the case of an advanced stage carcinosarcoma uteri, in a patient with limited therapy options. Carcinosarcomas (malignant mixed Müllerian tumors) are histologically composed of malignant epithelial and mesenchymal components. Sarcomatous component of this mixed tumor in the present patient was of heterologous-type chondrosarcoma. The primary treatment option for uterine carcinosarcomas is surgery, but adjuvant therapy is always necessary. The optimal treatment is still uncertain, as the histogenesis of this tumor remains controversial.

Key words: Carcinosarcoma uteri; Heterologous type of carcinosarcoma uteri; Advanced stage of disease; Therapy options.

Introduction
Carcinosarcomas of the uterus (MMMT-malignant mixed Müllerian tumors) are uncommon and highly aggressive tumors, composed of epithelial and mesenchymal elements. They commonly arise in the uterus, but may also arise in the ovaries, fallopian tubes, vagina, and peritoneum, and very rarely in other sites such as in the lungs [1].

Carcinosarcomas are composed of two histological subtypes, based on their sarcomatous component: homologous and heterologous. Heterologous type has a sarcomatous component constituted of non-native tissue to the uterus, like cartilage, skeletal muscle, or bone, and has been defined as rhabdomyosarcoma, chondrosarcoma, osteosarcoma or liposarcoma. Homologous type tends to be fibrosarcoma, endometrial stromal sarcoma, or leiomyosarcoma. In both cases, the carcinomatous component may be composed of endometrioid, serous, or clear cell type [2]. It is currently believed that carcinosarcomas have a monoclonal origin from a common multidirectional progenitor stem cell, but there remains a percentage of carcinosarcomas with a biclonal origin [3].

Uterine carcinosarcoma represents 1.5% of all malignant uterine tumors [1]. Despite advances in imaging and adjuvant therapies, survival rate is not significantly improved.

Case Report
A 63-year-old woman referred to the present Clinic with excessive vaginal bleeding and abdominal pain. She had had two normal pregnancies, three artificial abortions, and her menopause occurred nine years ago. The patient was overweight, hypertensive, with diabetes mellitus type II for almost six years, and with cerebrovascular insult two years prior. Vaginal bleeding commenced eight months prior, and was not severe for a few months. Simultaneously she suffered from some non-identifiable abdominal pains. At the moment of hospitalization, she presented with anemia, severe bleeding, and the passage of necrotic tissue per vagina. By physical examination the authors found an enlarged and softened uterus and a few suspected nodules in the vagina. Serum Ca-125 levels were an elevated. Detailed transvaginal and abdominal ultrasonographic scanning were performed. The uterus was enlarged, 11.6 x 9.5 x 11.6 cm, with a volume of 668 ml, non-homogenous, with evident invasion of tumor tissue to the myometrial wall. Approximate size of the tumor tissue in the uterine cavity was 5.6 x 4.9 x 6.8 cm, and with a volume of 99 ml, with extremely high vascularisation and with resistance indices (RI) ranging from 0.25 - 0.4 (Figure 1). Metastatic area 3.8 x 2.8 x 3.2 cm, with volume of 19 ml, was found just below the posterior wall of the urethra, with high vascularisation, and RI of 0.63. Para-aortic lymph nodes were enlarged (4.7 x 2 cm and 2.9 x 2.9 cm), as well as para-iliac nodes (up to 2.5 cm) (Figure 2). Liver and kidneys had normal morphology, without evident metastatic areas.

Pathohistological finding after exploration of the uterine cavity and cervix was carcinosarcoma endometrii of heterologous type. Sarcomatous component was predominantly 70%, composed of poorly-differentiated endometrial stromal sarcoma elements and elements of chondrosarcoma; carcinomatous component was serous papillary adenocarcinoma and presented at 30%. Metastatic fields in vagina were consisted of only undifferentiated carcinoma (Figure 3). This case of carcinosarcoma uteri was in Stage IIIC2 according to the new FIGO staging for endometrial carcinoma [4]. As the patient was in advanced stage of diseases and also in bad condition, taking account her pre-existing illnesses, she was not subjected to surgery. She underwent external beam radiotherapy (EBT), plus vaginal brachytherapy (to control vaginal metastatic nodules). As the epithelial component was the predominant histology in the primary extrauterine metastasis, as well as in the distant failure sites, she was prescribed to be subjected to chemotherapy as well, but her condition deteriorated, and she could not tolerate the chemotherapy, so palliative therapy was conducted only. She died seven months after carcinosarcoma uteri was diagnosed.

Discussion
The absolute risk for uterine carcinosarcoma is low in any population (two per 100,000 women annually) [1]. This tumor is predominantly identified in postmenopausal women, with median age of 65 years, as it was in the present patient, but it can also found in young women and
Figure 1. — MMMT and blood flow in the uterus and tumor; a) Enlarged uterus by transvaginal scan; b) Approximate tumor area with myometrial infiltration; c) Low left uterine artery vascular resistance and increased flow; d) Increased vascular blood flow in the MMMT and low RI.

Figure 2. — Metastatic areas of MMMT. a) Para-urethral metastatic nodes; b) Vascularization in para-urethral metastatic tissue; c) Para-aortic metastatic lymph nodes; d) Para-iliac metastatic nodes.
Figure 3. — Carcinosarcoma endometrii with chondrosarcoma elements (a, b, c) and metastatic undifferentiated carcinoma of the vagina (d).
children [5]. Uterine carcinosarcomas and endometrial carcinomas share a similar risk factor profile, and this patient has almost all risk factors for developing of uterine malignances. The symptoms were typical for pelvic neoplasms, with vaginal bleeding, necrotic tissue per vaginum, and abdominal pain. The mass of the tumor was large and soft, and it filled and distended the uterus, as it is described by Kuyumcuoglu et al. [6]. Elevated levels of serum Ca-125 are also reported with carcinosarcomas uteri and are correlated with extraterrestrial spread of disease and increased myometrial invasion [7]. Ultrasound investigations showed that uterine carcinosarcomas typically appear as a mass within the uterine cavity, with accompanying dilation of the cavity and myometrial invasion, most often involving the fundus [8]. Carcinosarcomas often present in an advanced stage, commonly FIGO Stages III or IV, as occur in approximately 60% of patients [9].

Histologic patterns unusual to conventional adenocarcinoma are more commonly seen in the epithelial component of carcinosarcoma (such as serous growth pattern). Metastatic lesions almost always contain elements of carcinoma, as in the present patient, with or without coexisting sarcoma. Solitary sarcomatous metastasis are uncommon [10]. Uterine carcinosarcomas behave like endometrial carcinomas and spread through the lymphatics, usually to pelvic or para-aortic lymph nodes, lung, peritoneum, etc. Neoplastic nests in lymphovascular spaces and metastases, more often mimic the epithelial component. Sarcomatous metastases are more frequently seen in anatomic sites with hollow spaces, that allow polypoid growth, such as the peritoneal cavity and vagina [11].

The primary treatment option for uterine carcinosarcomas is surgical staging, with total abdominal hysterectomy, bilateral salpingo-oophorectomy, lymph node dissection, and resection of all gross disease. High rates of postoperative relapse and metastases require adjuvant therapies [11]. Adjuvant therapy requires radiation for locoregional control, and chemotherapy depending on Stage. Benefits of lymphadenectomy remain undetermined [12].

Radiotherapy contributes to decreased pelvic recurrences, but controversies also remain regarding the techniques of radiation: localized pelvic radiation by vaginal brachytherapy, versus whole abdominal radiation by external beam [12]. As the carcinomatous element is the driving force, adjuvant chemotherapy should be given for a high-stage, high-grade endometrioid adenocarcinoma, or for an aggressive histologic subtype of endometrial adenocarcinoma, such as serous or clear cell adenocarcinoma.

Combination chemotherapy gives better results in comparison to monotherapy, but it is more toxic. Several combinations of chemotherapeutic agents are recommended for the treatment of uterine carcinosarcoma, since 2005: cisplatin and ifosfamide, cisplatin, ifosfamide and mesna, ifosfamide and paclitaxel, paclitaxel and carboplatin, etc. [10].

Chemotherapy response rate in patients with predominant carcinomatous element seems to be better (overall response rate 87.5%), than in patients with dominant sarcomatous elements.

Prognosis of uterine carcinosarcoma is generally worse than for high-grade carcinoma of the corresponding site. The most important prognostic factor is the extent of the tumor at initial presentation [13]. Patients with advanced, unresectable carcinosarcoma, as it was in the present case, have a poor prognosis with median survival of less than one year. [14]. One of the reasons for the poor survival outcome, is the fact that over one-third of carcinosarcomas have already spread beyond the uterus at the time of diagnosis. A full understanding of the pathobiogenesis of this tumor is necessary to predict the “gold standard treatment”. To date, no national consensus guidelines have been established for the management of uterine carcinosarcomas.

References


Successful treatment of isolated fibular bone metastasis in a uterine endometrial cancer of clear cell carcinoma

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Summary

Clear cell carcinoma of the endometrium is an uncommon histological subtype and isolated metastasis to bone is rare. The authors present a case of a 61-year-old woman who underwent laparoscopic staging surgery for clear cell carcinoma of uterine endometrium (FIGO Stage IB) and early recurrence with isolated fibular bone metastasis three months later. With salvage radiotherapy (RT), she remains disease-free after 46 months. Curative-intended treatment with RT is possible as in this case.

Key words: Endometrial carcinoma; Clear cell carcinoma; Solitary bone metastasis; Treatment.

Introduction

Endometrial cancer with the histological subtype of clear cell carcinoma is uncommon and compared to endometriod adenocarcinoma is often associated with worse prognosis [1]. Distant metastasis to bone is rare in endometrial carcinoma. Appropriate detection and diagnosis with a treatment design is important. The authors report a rare case of isolated fibular bone metastasis with endometrial clear cell carcinoma that has been treated successfully with radiotherapy (RT) and has long disease-free survival.

Case Report

A 61-year-old woman had past history of colon adenocarcinoma (Figure 1A) with DUKES' C2 and received extended right hemicolectomy and chemotherapy five years prior to this episode. She began to have post-menopausal bleeding. She was diagnosed with clear cell carcinoma of the endometrium after endometrial curettage. She underwent laparoscopic staging surgery including washing cytology, laparoscopic-assisted vaginal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymph node dissection. She was surgically staged as endometrial carcinoma FIGO Stage IB (T1bN0M0) (FIGO staging 1998 version) with 45% myometrium invasion (Figure 1B). After this surgery, she received curative RT, which was delivered to the true pelvis by four-field box technique at 5,040 cGy in 28 fractions and boosted to 7,000 cGy in 35 fractions by image-guided radiotherapy. After this treatment, the metastatic tumor regressed (Figure 2C) and achieved complete remission. She had been regularly followed without evidence of disease, and the bone lesion remains stationary for more than four years (54 months).

Discussion

Endometrial cancer is the most common gynecologic malignancy and accounts for six percent of all new cancer cases and for three percent of deaths among women [2]. The most common histological subtype is endometrioiid adenocarcinoma, and clear cell carcinoma is uncommon (five percent) and has a more unfavorable prognosis [1]. Endometrial carcinoma usually spreads through local invasion or lymphatic dissemination. Distant metastasis is uncommon and the majority distant metastasis usually involves the lung or liver. Bone metastasis is rare, and once the diagnosis is made, prognosis is poor [3]. The reported sites of bone metastasis include vertebrae, skull, mandible, nasal sinuses, humerus, hallux, ischiium, femur, tibia, fibular, calcaneous, and tarsus. The rate of bone metastasis ranges from two to 14 percent, and isolated extremity bone metastasis is rarer [4, 5].

S.M. Kehoe et al. [3] summarize the clinicopathologic features of bone metastasis and outcome in patients with primary endometrial cancer. The retrospective study resulted in that the majority of histology with bone metastasis (76%) is endometrioid adenocarcinoma, rather than the
more aggressive histological subtype, such as clear cell carcinoma or papillary serous carcinomas. The median time to death after diagnosis of bone metastasis is ten months, similar to previous case reports and literature reviews. According to this study, cases with early bone recurrence (defined as < eight months) and multiple bone metastases or involving other metastatic sites have poor prognosis. Compared to later recurrence, the median disease-specific survival for those with early recurrence was 13 months vs 34 months [3]. In two case reports and this study, clear cell carcinoma with bone metastasis had poorer prognosis than endometriod adenocarcinoma and the time to death after bone recurrence was from one month to 13 months [6, 7].

In the present case, the patient had early recurrence in isolated bone (< four months) and the histology was clear cell carcinoma, but she had long-term disease-free survival which is more than 46 months. Patients with endometrial cancer who have unexplained bone pain should be aware of bone metastasis. Early and proper diagnosis is important, especially the treatment of isolated bone metastasis, often associated with better outcome. The image techniques include of conventional X-ray, CT scanning, nuclear magnetic resonance (MRI), and bone scan. Position emission tomography (PET)/CT scan can be considered a tool for detection metastasis [3-7]. After detecting a bone mass, tissue proof is necessary if patients can tolerate it. In this patient, she had right knee tenderness and X-ray, MRI and bone scan detected a metastatic bone tumor. Tissue from CT-guided puncture confirmed a metastatic carcinoma. Tracing back the history, the authors differentiated the origin from colon cancer or endometrial cancer, thus immunohistochemical stain was used. Because of the result of negative for CDX2 and CX20 (K20.8), and positive with CX7, metastatic tumor with endometrial origin was favored [8].

Clear cell carcinoma in endometrial cancer represents a poor prognosis and high recurrence rate. Staging surgery with RT is considered beneficial for overall survival [9]. Moreover, palliative radiation for bone metastasis has the role of symptom relief and local therapy. Pain relief could improve the quality of life, and some literature suggests that RT is effective for single bone metastasis [3, 10]. In this case, the authors arranged post-operative pelvic radiotherapy and once bone metastasis was diagnosed, they delivered local radiation to the metastatic site. She had responded well to these treatments with obvious regression of the bone tumor.

In conclusion, metastasis of endometrial clear cell carcinoma to the isolated bone in the extremity is rare, but this condition should be considered when a patient with primary
endometrial cancer has a symptom of unexplained bone tenderness and swelling. Proper diagnosis and aggressive treatment may prolong survival.

References


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Endometrial cancer metastasize to the skin of lower leg and vagina: case report and literature review


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Summary
Endometrial cancer is the most frequent malignancy of the female reproductive system, while cutaneous metastasis is extremely rare in endometrial cancer. The authors herein report a case of endometrial adenocarcinoma (FIGO Stage IIIC2, Grade 2) with metastasis to the skin of right lower leg and vaginal orifice. The patient was treated with local excision and combination chemotherapy, but she did not respond to therapy and died within 11 months. The authors reviewed the clinico-pathologic features, treatment, and prognosis of such case with cutaneous metastasis.

Key words: Endometrial cancer; Metastasis; Skin; Vaginal orifice; Prognosis.

Introduction
Endometrial cancer is the most common malignancy of the female reproductive system. The majority (about 70%) of cases with endometrial cancer belong to Stage I, and only eight percent presenting distant metastases in lung, liver, bone, and other organs [1]. Cutaneous metastasis is extremely rare in endometrial carcinoma and there are only a few cases reported. The authors herein report one case of endometrial adenocarcinoma, for the first time in China, with metastasis to the skin of right lower extremity and vaginal orifice, and they review the literature to provide a thorough overview of clinico-pathologic features, multidisciplinary therapy, and prognosis of the disease.

Case Report
A 60-year-old woman who had experienced menopause for 15 years, was admitted to the present hospital with a one-month history of vaginal bleeding. The magnetic resonance imaging (MRI) examination of the pelvis revealed an intrauterine expandable mass lesion with myometrial invasion and serum CA125 was 204 U/ml. A dilatation and curettage had been performed, and endometrial histopathology revealed endometrioid adenocarcinoma. Total abdominal hysterectomy with bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy with peritoneal washing were performed. Pathological examination revealed moderately differentiated endometrial adenocarcinoma with two-thirds of myometrial, endocervical stromal, Douglas pouch, presacral, and para-aortic nodes invasion. Peritoneal cytology was negative and vascular invasion presented. According to International Federation of Gynecology and Obstetrics (FIGO) staging system in 2009, Stage of the neo-adenocarcinoma was IIIC2. After surgery, the patient was treated with TP chemotherapy for three cycles and serum CA125 decreased to 6.7 U/ml, but she could not receive any more chemotherapy or radiotherapy due to her poor general status. Seven months after the surgery, the patient developed a firm, erythematous non-tender skin nodule on the right lower leg, two cm in diameter, and gradually expanded (Figure 1). Three months later, she was admitted to the hospital again with vaginal bleeding. One firm, hemorrhagic, 1.5 cm nodule was observed in her vaginal orifice. Pathological examination of the excisional biopsy specimen taken from the skin nodule and vaginal lesion both revealed moderately to poorly differentiated adenocarcinoma, consistent with metastasis from the primary endometrial adenocarcinoma (Figure 2). The computed tomographic (CT) scan of chest and whole abdomen to evaluate the extent of metastasis showed no other lesions. The patient was treated with combination chemotherapy using docetaxel and cisplatin for six courses. There was partial resolution of the vaginal lesion, but recurrent pelvic mass was detected by CT scan and the CA125 remained elevated. By the time of this report, the patient died due to widespread disease and cachexia 11 months after cutaneous metastasis.

Discussion
Cutaneous metastases are uncommon and occur in 0.7%-9% of all malignant diseases [1]. The most common primary cancers presenting cutaneous metastasis in women include breast cancer (69%), colorectal carcinoma (9%), melanoma (5%), and ovarian cancer (4%). It is rare to detect cutaneous metastases from endometrial cancers and only 16 cases have been reported [2-15]. To the authors’ knowledge, this is the first report of such disease in China. The clinico-pathological features, treatments, and outcomes of the 16 cases endometrial cancer presenting cutaneous metastasis are summarized as follows (Table 1). The mean age at diagnosis was 63.7 years (54-77 years). In total 68.8% (11/16) cases were endometrial adenocarcinoma, the other histologic types included clear cell, papillary serous adenocarcinoma, and mixed mesodermal tumors. There were more cases (68.8%, 11/16) in early Stage (I or II) than in late Stage (31.2%). It seems that patients of endometrial adenocarcinoma with an early stage may have recurrence of cutaneous metastasis. While all cases except one were moderately to poorly differen-
tiated (Grade 2 or 3), which indicated that the aggressive subtypes of endometrial cancer were more likely to metastasize to the skin. The mean time interval between primary diagnosis of endometrial cancer to cutaneous metastasis was 21.6 months (one to months). The possible mechanisms of metastasis include lymphatic, hematogenous, transcoelomic spread, and implantation in surgical scars. La Fianza [7] suggested that retrograde lymphatic flow may cause cutaneous metastasis and lymphatic vascular space invasion (LVSI) was detected in the present case. The frequent sites of cutaneous metastasis include the head and neck (28%), trunk (40%), extremities (18%) and multiple sites (14%). Daniilidis [15] recently reported a case of endometrial adenocarcinoma presenting umbilical and vaginal metastasis. Most cases appeared as multiple dermal nodules located on the abdominal wall, lower extremity, scalp, pubic area, vulva, and initial surgery site, etc. Cutaneous metastasis usually indicated widespread disease and 12 of 16 cases accompanied with other distant metastasis such as lung, liver, vaginal, lymph nodes and bone metastasis. There is no standard treatment for cutaneous metastasis in patients with endometrial cancer. Given the combined treatment including surgery, chemotherapy, radiotherapy, and hormone treatment, the mean overall survival after skin metastases was 6.6 months (three to 15 months).

The present case represents a rare occurrence of lower extremity cutaneous metastasis arising from endometrial adenocarcinoma. The patient presented vaginal orifice metastasis at the same time and was treated with local excision, combination chemotherapy, and 5-FU local injection. Cutaneous metastasis typifies widespread disease and poor prognosis despite comprehensive treatments. There was no dramatic changes in survival and the patient presented in this case report died 11 months after detection of cutaneous metastasis.

Table 1. — Clinico-pathological features of endometrial cancer with cutaneous metastasis.

<table>
<thead>
<tr>
<th>Author and year of publication</th>
<th>Age</th>
<th>FIGO Stage/Grade</th>
<th>Interval* (months)</th>
<th>Site of cutaneous metastasis</th>
<th>Other metastases</th>
<th>Post-metastases survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damewood et al.</td>
<td>57</td>
<td>II/3</td>
<td>1</td>
<td>left posterior calf</td>
<td>pulmonary metastases</td>
<td>3.5</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>IB/3</td>
<td>1</td>
<td>scalp</td>
<td>sacrum, left clavicle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>69</td>
<td>IIIB</td>
<td>5</td>
<td>abdominal wall</td>
<td>right vaginal wall, lung</td>
<td></td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>IVB</td>
<td>2</td>
<td>scalp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patel et al.</td>
<td>68</td>
<td>IB/3</td>
<td>84</td>
<td>axilla</td>
<td>lung</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>73</td>
<td>IA</td>
<td>36</td>
<td>umbilical</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Esponos et al.</td>
<td>77</td>
<td>IB/3</td>
<td>4</td>
<td>laparotomy scar</td>
<td>peri-aortic lymph nodes</td>
<td>3</td>
</tr>
<tr>
<td>Spencer et al.</td>
<td>73</td>
<td>I/3</td>
<td>84</td>
<td>lower half abdomen;</td>
<td>vaginal introital mass</td>
<td></td>
</tr>
<tr>
<td>Kushner et al.</td>
<td>56</td>
<td>IC/1</td>
<td>15</td>
<td>scalp</td>
<td>right pleural effusion</td>
<td>3</td>
</tr>
<tr>
<td>Alfredo et al.</td>
<td>67</td>
<td>IA/2</td>
<td>8</td>
<td>periumbilical region</td>
<td>inguinal lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Mandrekas et al.</td>
<td>58</td>
<td>IIIC/2</td>
<td>48</td>
<td>right bid toe</td>
<td>lung</td>
<td>6</td>
</tr>
<tr>
<td>Elit et al.</td>
<td>65</td>
<td>III</td>
<td>8</td>
<td>abdominian wall</td>
<td>para-aortic adenopathy</td>
<td>9</td>
</tr>
<tr>
<td>Ozsaran et al.</td>
<td>60</td>
<td>IB/2</td>
<td>24</td>
<td>abdominal wall</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Stonard et al.</td>
<td>73</td>
<td>IC</td>
<td>3.5</td>
<td>left lower leg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kim et al.</td>
<td>54</td>
<td>IIIB/3</td>
<td>7</td>
<td>pubic wall and vulva</td>
<td>bone and hepatic</td>
<td>5</td>
</tr>
<tr>
<td>Baydar et al.</td>
<td>58</td>
<td>IB/2</td>
<td>15</td>
<td>initial surgery site</td>
<td>vaginal orifice</td>
<td>6</td>
</tr>
</tbody>
</table>

*Interval: interval between primary diagnosis to skin metastasis.
References


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Primary signet-ring cell adenocarcinoma of the uterine cervix: case report and review of the literature

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Summary

Signet-ring cell adenocarcinoma is a rare subtype of the uterine cervix; thus there are no guidelines and the prognosis is unknown. There seems to be a significant role for reporting the treatment and outcome of this rare disease in order to establish guidelines and to assist in decision-making. However, treatment should be tailored to each patient according to clinical status and disease stage. Excluding extra-genital origin is mandatory, as it will change treatment management considerably.

Key words: Cervical cancer; Radiotherapy; Signet-ring cell; Adenocarcinoma.

Introduction

Adenocarcinoma of the uterine cervix is a rare disease, constituting less than 5%-20% of all uterine cervix cancers [1]. The most common form is the endocervical cell type. Other rare subtypes of adenocarcinoma include intestinal type, signet-ring cell, adenoma malignum, villoglandular papillary, endometroid, and papillary serous adenocarcinoma [1]. Signet-ring cell adenocarcinoma is a rare subtype of the uterine cervix; thus, there are no guidelines and the prognosis is unknown. In this report, the authors describe a case of primary adenocarcinoma of the uterine cervix, signet-cell type.

Case Report

A 37-year-old patient, para 4, gravida 4, presented to our department a year after giving birth to her fourth child, with complaints of post-coital bleeding. Vaginal examination indicated a bulky uterine cervix (more than four cm) with left parametrial involvement (FIGO Stage 2B2). Biopsy from the uterine cervix showed signet-ring cell adenocarcinoma. The absence of immunoreactivity to chromogranin A and synaptophysin excluded neuro-endocrine differentiation. Serum carcinoembryonic antigen (CEA) level was 63 ng/ml. Systemic workup included gastroscopy, colonoscopy, transvaginal ultrasound (TVUS), mammography, and breast ultrasound, with no evidence of other primary disease. Fluorodeoxyglucose-positron emission computed tomography (FDG-PET/CT) revealed uptakes in the uterine cervix and left internal iliac lymph nodes (Figure 1). The patient was prescribed concomitant chemo-radiotherapy, consisting of 50.4 Gy (1.8 Gy per fraction) of pelvic-external radiation (EBRT) and 40 mg/m² of weekly cisplatin, followed by intracavitary high-dose rate brachytherapy to a total dose of 27.5 Gy (5.5 Gy per fraction, once a week). The patient was still breastfeeding at that time, and was instructed to stop prior to starting treatment. After 48.6 Gy (of the 50.4 Gy planned), the patient was evaluated under anesthesia for insertion of a cervical stent for brachytherapy. The examination indicated a bulky mass in the uterus cervix and the procedure was aborted. A multidisciplinary consultation reviewed the possibility of interstitial brachytherapy; due to the possibility of a large residual tumor which did not shrink by EBRT and cisplatin, the patient was referred to surgery. FDG-PET/CT performed prior to the procedure was negative for uptake.

The patient underwent radical hysterectomy, bilateral salpingooophorectomy, selective pelvic lymphadenectomy, and omentectomy. Histology of the uterine cervix, indicated two foci of carcinoma in situ, but the uterus was negative for carcinoma. Left obturator lymph nodes were positive for carcinoma; these lymph nodes were not seen on the initial FDG-PET/CT.

Discussion

Primary adenocarcinoma signet-cell type of the uterine cervix is rare and there are only a few reports in the literature [2-16]. It is imperative to exclude other possible sources of adenocarcinoma in these patients, as it almost impossible to differentiate primary tumor from metastatic disease according to cytology, and most signet-ring cell carcinomas in the female genital tract are of extra-genital origin [2, 11]. Evaluation should include complete endoscopy, chest, abdominal and pelvic evaluations, and complete breast evaluation (ultrasound and mammography). Some reports indicated the use of magnetic resonance (MRI) for evaluating the pelvis [2, 11], as MRI has been found to be superior to FIGO staging and CT for determining soft tissue involvement and parametrical involvement in advanced stages [17]. In the presented case, parametrical involvement was obvious from the vaginal exam and the tumor was estimated to be more than four cm, thus primary surgery was excluded. Currently, treatment recommendations for uterine cervix adenocarcinoma are to treat according to FIGO stage. The majority of reports have shown that adenocarcinoma carries a worse prognosis, with 10%-20% lower five-year survival rates compared to squamous cell carcinoma [1]. It is difficult to draw conclusions regarding the prognosis of the signet-cell subtype due to the paucity of case reports and different disease stage at presentation. However, in most cases, survival was less than two years [2-9].

Immunohistochemical and molecular studies of this entity, which can aid to differentiate it from extra-genital metastatic neoplasms is discussed in a recent report by...
Giordano et al. [11]. The features of primary cervical tumor are summarized in Table 1.

In the current case, the patient did not have a good “clinical response” to EBRT and weekly cisplatin. Although there was no uptake in FDG-PET/CT after EBRT treatment, it was decided to proceed with surgery. The patient had two cervical foci of carcinoma and positive left obturator lymph nodes not detected on FDG-PET/CT. This may due to the low sensitivity of FDG-PET/CT in signet-ring cell cancer [18], or that the lesions after EBRT were too small to be detected by this modality [17]. As indicated by the literature, this disease has a poor prognosis due to systemic failures [2-16]. In the current case, it was determined by a multidisciplinary team not to give further adjuvant treatment. It was decided to use FDG-PET/CT for follow-up, keeping in mind that uptake of FDG by the tumor may be low and the CT should be evaluated meticulously for suspected lesions not showing metabolic activity on FDG-PET. Currently, the patient is four months after surgery with no evidence of recurrent disease.

There seems to be a significant role for reporting the treatment and outcome of this rare disease in order to establish guidelines and to assist in decision-making. However, treatment should be tailored to each patient according to clinical status and disease stage. Excluding extra-genital origin is mandatory, as it will change treatment and outcome of this rare disease in order to establish guidelines and to assist in decision-making. Excluding extra-genital origin is mandatory, as it will change treatment and outcome of this rare disease in order to establish guidelines and to assist in decision-making.

Table 1. — Features of primary signet-cell carcinoma of the uterine cervix.

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Histology and molecular features</th>
</tr>
</thead>
<tbody>
<tr>
<td>• History of cervical HPV infections</td>
<td>• HPV type 18 in tumor tissue</td>
</tr>
<tr>
<td>• Complete history and work-up (complete endoscopy, breast, abdominal and pelvic evaluation), to exclude the possibility of metastatic disease</td>
<td>• Positive stain for CEA, sialomucins, keratin 7, CA-125, and p16</td>
</tr>
<tr>
<td>• Negative immunoreactivity to chromogranin A and synaptophysin</td>
<td>• Presence of other subtypes of endometrioid carcinomas</td>
</tr>
<tr>
<td>• Estrogen and progestrone receptors may be negative</td>
<td></td>
</tr>
</tbody>
</table>

References

Primary squamous cell carcinoma of endometrium: clinicopathologic analysis of two cases with review of the literature

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Summary

Two cases of primary squamous cell carcinomas of the endometrium (PSCCE) are reported, and both were postmenopausal and presented with vaginal bleeding. Histologically, the endometrial curetting revealed extensive squamous metaplastic papillae with vacuolated cytoplasm. Numerous keratin debris were present in the superficial epithelium with neutrophil infiltration. Atypia existed in the basal and parabasal-layer cells. It can be regarded as precancerous lesion when postmenopausal woman’s endometrial curetting show extensive squamous papillae.

Key words: Endometrium; Primary squamous cell carcinoma; Pathology; Frozen section.

Introduction

Primary squamous cell carcinoma of the endometrium (PSCCE) is very rare, and Fluhman proposed the following three criteria required for its diagnosis [2]: 1) no coexisting adenocarcinoma appearing in the endometrium; in the surface and the papillae were lined by non-ciliated cuboidal cells. The enlarged cells in the intermediate and superficial layers had vacuolated cytoplasm of varying sizes (Figure 2). Nuclei were relatively uniform and located in the center of the cells. Mitotic figures were rare and nuclei atypia were conspicuous in the several layers of parabasal squamous cells. The tumor invaded the myometrium. The grey-white friable lesion in the myometrium was invasive squamous epithelium carcinoma. Pathology diagnosis was PSCCE.

Case 2: a 79-year-old woman, 16-year menopause, presented with vaginal bleeding for three months. Her TCT was negative. Fractional curettage was performed and revealed massive squamous papillae, with mild atypia, static endometrium at the periphery, which was highly suspicious of malignancy. HC2 was positive. Subsequent radical TAH+BSO+pelvic lymph node dissection were done. Macroscopically the enlarged uterine cavity filled with pink cotton-like mass and pyometria. On section, the mass was grey-coloured with invasion to the superficial myometrium. Microscopically, extensive squamous metaplasia papillae were in the surface of the uterine cavity associated with parakeratosis and keratinized cells (Figure 3). The superficial layer of the squamous metaplasia cells were composed of non-ciliated cuboidal cells. There were many neutrophils within round lacunae, the latter of which were of varying size. Parabasal cells were atypical, and disorganized with low mitotic activity. The tumor invaded the myometrium. Pathology diagnosis was PSCCE.

Immunohistochemistry features

Both cases of PSCCE proved to be positive for CK5/6, P63. Cells in the two-thirds upper layer revealed strong stain for CK7. Cells in the upper third layer showed positivity for CEA. The several basal-layer cells were positive for vimentin in case two and negative in case one. P53, P16, PR, and ER were negative in both cases.

Discussion

The definition and histopathogenesis of PSCCE

PSCCE is very rare and Fluhman proposed the following three criteria required for its diagnosis [2]: 1) no coexisting adenocarcinoma appearing in the endometrium;
2) no relationship with the cervical squamous epithelium; 3) no coexisting primary squamous cell carcinoma appearing in the cervix. The fourth histological criterion was added in 1975 by World Health Organization (WHO): 4) clear evidence of squamous differentiation such as intercellular bridges and/or keratin. The incidence is difficult to assess because the majority of the literature dealing with PSCCE is documented in the form of case reports. The present authors found two cases of PSCCE during one year. Both cases had “negative” Pap smear interpretation. Both endometrial curettings of case one revealed well-differentiated squamous epithelium, especially in the intermediate and superficial layers. The descriptive diagnosis was then made and resulted in highly-suspicious PSCCE. So the real incidence of PSCCE may be much greater than the previously documented one because of under-recognition of this neoplasm.

The histogenesis of PSCCE has long been disputed and its mechanism is still uncertain due to its rarity. Horn and Bilek [3] suggested that it may originate from the multipotential endometrial precursor cells with bi-phasic differentiation. One case of PSCCE described by Yamamoto et al. [4] showed squamous epithelium and mucosa glands arising in the endometrium, PAS-positive squamous cells in all but the basal layers, and both favoring an ectopic cervical origin. Observing extensive metaplasia, dysplasia, and carcinoma in situ in one case of PSCCE, an investigator proposed that PSCCE originated from the mode of metaplasia-dysplasia-invasive carcinoma [5]. Sheng Y.M. [6] agreed with this point of view. However, Houissa-Vuong [7] did not approve of it due to the absence of metaplasia in the PSCCE documented by him. Giordano et al. [2] believed it may be associated with the mutation of such tumor-suppressor gene as P53, but the two PSCCEs in this present report were negative for P53, positive for CK5/6, P63, CK7, and CEA, which had both squamous and glandular features. They were negative for P16, which distinguishes PSCCE from cervical squamous cell carcinoma. The authors found that vimentin did not express in case one but did express in the parabasal cells in case two, whereas CEA was positive in both case, all favoring the cervical adenocarcinoma immunophenotype. The authors therefore postulate that at least part of PSCCEs, originate from the ectopic cervical squamous cells or cervical glands metaplasted by multi-potential cells in the endometrium. The etiology of PSCCE is controversial. Several studies have found HPV type 31 [2] in PSCCEs, but some others did not detect HPV in them. Both PSCCEs in this report were positive for HPV-DNA, indicating HPV infection may be a risk factor for PSCCE.
Clinical features of PSCCE

PSCCE commonly affects postmenopausal or perimenopausal women. The mean age at diagnosis is 67 years, seven years older than those with common type of corpus cancer. Clinical features of PSCCE were conducted by Goodman [8]. The typical presentation is postmenopausal vaginal bleeding (44/64, 68%), then vaginal discharge (18/64, 28%), and abdominal pain (11/64, 17%).

Both patients presented for vaginal bleeding and illustrated negative Pap smears. Houissa-Vuong [7] reported that positive Pap smear in 81 cases of PSCCE was less than six.

Histopathology and prognosis of PSCCE

PSCCE may be misinterpreted as squamous metaplasia with mild atypia by the well-differentiation appearance in the curettage specimen. The characteristic architecture of PSCCE is crucial for a definitive diagnosis and the immunohistochemical demonstration for CK5/6, P63, CEA, CK7 and vimentin help for a correct diagnosis.

Practically, PSCCE should be suspected if the following occur in the curettage specimen of elderly women: 1) extensive metaplastic papillae; 2) round lacunae of varying size present in the metaplastic epithelium; 3) abundant keratin debris in the superficial epithelium with neutrophils infiltration; 4) atypical squamous cells in the parabasal layers at the presence of atrophic endometrium.

PSCCE should be distinguished from condyloma acuminatum, from extensive squamous metaplasia of the glandular in the endometrium, and from the neoplasms of cervical origin. Endometrial condyloma acuminatum is commonly the extension from that in the cervix and endometrial condyloma acuminatum only, to the authors’ knowledge, has not been previously reported. Condyloma acuminatum in the cervix features characteristic koilocytes and binucleated cells in the intermediate and superficial layers and no round lacunae due to hyperplasia present in the epithelium. Extensive squamous metaplasia in the endometrium is without papillae and without the atypical cells in the several lower layers. Cervical mucinous glands are commonly present in the squamous metaplasia. Majority of PSCCEs are well-differentiated squamous cell carcinomas or verrucous carcinomas. Cervical cytology smears usually reveal NILM or atypical squamous cells, which do not sufficiently point to the squamous cell carcinoma.

Many patients have been diagnosed with PSCCE after multiple curettages had been performed. The patient of case three reported by Goodman [7], underwent multiple pap smears that revealed atypical cells and inflammation and four curettages that showed acute inflammation and mature squamous cells in a period of eight years. Only 50% of PSCCE patients had been diagnosed correctly before TAH even in microglandular hyperplasia (MGH). Treatment was thus delayed for 11.5 months on average. The patient of case one in this present report was found to be affected by PSCCE after two curettages. Based on the experience of case one, in case two, the authors made a descriptive diagnosis as highly suspicious of PSCCE, due to the curettage specimen findings.

The tumor stage is key factor for prognosis. Follow-up was available for 42 patients with PSCCE, with a mean time of 36 months. Stage I PSCCEs had a survival rate of 80% (21/26). In Stage III PSCCEs, the survival rate was 20% (2/10), and all patients with Stage IV PSCCEs died (0/6) [3]. The poor outcome may be associated with patients whose PSCCE was diagnosed in an advanced stage or who had vascular and lymph node involvement.

The authors think that postmenopausal women should undergo hysterectomy due to curettage specimen that show abundant squamous papillae which are at possible risk of malignancy. Early treatment may improve the unfavorable outcome of PSCCE.

References


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Transition of low-grade to high-grade endometrial stromal sarcoma: a case report

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Summary

Background: The transition of low-grade endometrial stromal sarcoma (ESS) to high-grade ESS remains a rare clinical event. Case: A patient presented with abdominal pain and abnormal genital bleeding. She underwent a supracervical hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and resection of peritoneal disseminated lesions. Pathological examination revealed low-grade ESS in the uterus and omentum. Immunohistochemical examination showed immunoreactivity for CD10 and Ki-67 (MIB1) in the uterus and omentum. However, estrogen receptor, progesterone receptor, α-SMA, desmin, h-caldesmon, and CAM5.2 were negative. P53 immunoreactivity was noted only in the omental lesion. Despite performing six courses of adjuvant chemotherapy, she recurred in the abdomen. She underwent ileostomy and resection of peritoneal disseminated lesions. Pathology showed high-grade ESS in the recurrent lesion of the ileum, which was characterized by severe cytologic atypia, high mitotic index, multifocal necrosis, increased Ki-67 index, and immunoreactivity for p53. Conclusion: Although rare, the transition of low-grade ESS to high-grade ESS may occur and suggests the worsening of the prognosis. Pathological examination and immunohistochemistry are useful for the diagnosis of the transition of low-grade ESS to high-grade ESS.

Key words: Endometrial stromal sarcoma; Immunohistochemistry; Transition.

Introduction

Endometrial stromal sarcoma (ESS) is classified into two distinct subtypes, low-grade ESS and high-grade ESS, according to the morphology, mitotic activity, and histological structure. Low-grade ESS is composed of a diffuse growth of small oval to fusiform cells with low cytologic atypia and low mitotic activity (< 5/10 high power fields HPFs) [1]. Tumor cells are identical to endometrial stromal cells found in proliferative or hyperplastic endometria [2]. Low-grade ESS usually has an indolent clinical course, but develops local recurrence eventually [3]. In contrast, high-grade ESS demonstrates marked cellular pleomorphism and brisk mitotic activity [2] and is characterized by an aggressive clinical behavior with a frequent and early recurrence [3]. However, the transition of low-grade ESS to high-grade ESS or coexistence of these two types remains uncommon [4-8].

The authors report a case of the transition of low-grade ESS to high-grade ESS that was assessed by a comparative pathological and immunohistochemical analysis.

Case Report

A 63-year-old woman presented with lower abdominal pain and abnormal genital bleeding of one months’ duration. Pelvic examination showed a newborn head-sized uterus. A biopsy taken from the endometrium suspected endometrial adenocarcinoma. At laparotomy, the enlarged uterus was found to be ruptured and the small intestine was adhered to the uterine serosa with widespread peritoneal dissemination. She underwent a supracervical hysterectomy due to severe adhesion with bilateral salpingo-oophorectomy, omentectomy, and resection of peritoneal disseminated lesions. Pathological examination revealed low-grade ESS in the uterus and omentum (Figure 1). The small uniform and spindle-shaped tumor cells with minimum nuclear pleomorphism and cytologic atypia proliferated and resembled endometrial stromal cells. The tumor cells showed an expansive growth into the uterine serosa. The vessel invasion was observed, but no lymphatic invasion was noted. The greater omentum and surgical stump were positive for invasion. The mitotic rate was 12/10 HPFs in the uterus and 23/10 HPFs in the metastatic lesion of the omentum (Table 1). The area of tumor necrosis was focally observed in both lesions (Table 1).

She received six courses of chemotherapy consisting of paclitaxel (180 mg/m²) and carboplatin (AUC = 5). After completing chemotherapy, a positron emission tomography (PET)/CT revealed strong fluorodeoxyglucose accumulation in the ileum. Based on a diagnosis of recurrence in the ileum, she underwent ileostomy and resection of peritoneal disseminated lesions. Microscopically, the large round-shaped pleomorphic tumor cells with enlarged nuclei invaded the mucosa of the ileum from the mesentery and extruded into the intestinal cavity (Figure 2). Tumor cells corresponded to high-grade ESS (Figure 2). Multifocal necrotic areas were noted, and the mitotic rate was 58/10 HPFs (Table 1).

Table 1 shows the differences in the histological findings among the primary site (uterus), the metastatic site (omentum), and the recurrent site (ileum). The lesion of the ileum showing high-grade ESS had more severe cytologic atypia and an increased mitotic index compared with the uterus and omentum showing low-grade ESS.

Table 1. — Histological features.

<table>
<thead>
<tr>
<th></th>
<th>Primary lesion (Uterus)</th>
<th>Metastatic lesion (Omentum)</th>
<th>Recurrent lesion (Ileum)</th>
</tr>
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<tr>
<td>Cytologic atypia</td>
<td>mild to moderate</td>
<td>moderate</td>
<td>severe</td>
</tr>
<tr>
<td>Mitotic index</td>
<td>12/10 HPFs</td>
<td>23/10 HPFs</td>
<td>58/10 HPFs</td>
</tr>
<tr>
<td>Tumor necrosis</td>
<td>focal</td>
<td>focal</td>
<td>multi-focal</td>
</tr>
<tr>
<td>Spinal artery</td>
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</tr>
</tbody>
</table>
No effect of chemotherapy was appreciated histologically in high-grade ESS components. One month later, she developed a recurrence in the abdomen and died of the disease nine months after initial surgery.

A panel of immunohistochemical analysis with estrogen receptor, progesterone receptor, CD10, α-smooth muscle actin (SMA), desmin, h-caldesmon, CAM5.2, Ki-67 (MIB1), and p53 was performed in representative tumor areas, using a streptavidin-biotin method (Table 2). Focal immunostaining for CD10 was noted in the lesions of low-grade ESS (uterus and omentum) and in the lesion of high-grade ESS (ileum) (Figure 1). High-grade ESS expressed the proliferation index, Ki-67 (MIB1) more frequently than low-grade ESS (Figure 2). Although in low-grade ESS the immunoreactive p53 was scarcely detected in the uterus and at 6.3% in the omentum, the positive rate of p53 in high-grade ESS was elevated to 17.5% (Figure 3). Both low-grade ESS and high-grade ESS showed no immunostaining for estrogen receptor, progesterone receptor, α-SMA, desmin, h-caldesmon, and CAM5.2.

### Discussion

The present case developed as low-grade ESS of the uterus initially, but recurred as high-grade ESS in the ileum with a rapid progression. The transition of low-grade ESS to high-grade ESS remains uncommon. However, this transition indicates the propensity for the more aggressive tumor biology, affecting the prognosis of the patients. To identify the transition, a meticulous observation for pathological and immunohistochemical findings between the primary and recurrent lesions is necessary.

The H&E stain could differentiate low-grade ESS from high-grade ESS morphologically, but the authors further attempted to clarify the differences in tumor phenotypes between low-grade ESS and high-grade ESS with immunohistochemistry. Pathologically, the high-grade ESS in the recurrent tumor was characterized by severe cytologic atypia and a higher mitotic index compared with the low-grade ESS in the primary site of the uterus and the metastatic lesion of the omentum.

Low-grade ESS has been shown to be estrogen receptor-positive and have progesterone receptor isoform expression similar to normal endometrial stroma [9]. However, in the present case, estrogen and progesterone receptors were negative both in low-grade and high-grade ESS. The relatively specific endometrial stromal marker, CD10, was shown to display diffuse, focal, or patchy immunostaining in ESS (Figure 3) [10-12]. In the present case, CD10 was identified focally in both low-grade ESS and high-grade ESS.
Low-grade ESS and high-grade ESS in this case included tumor cells that were negative for α-SMA, desmin, and h-caldesmon. However, it is reported that they may be expressed in areas showing smooth muscle differentiation in ESS [12].

The Ki-67 (MIB1) index was higher in high-grade ESS than in low-grade ESS in the present case, reinforcing the data of mitotic index (Figure 4). Amant et al. [5] reported two cases of transition of ESS into high-grade sarcoma. When compared with the previous recurrence, the authors...
found an increase in the cytologic atypia, a high mitotic index, and strong immunohistochemical positivity for the MIB1 proliferation marker on the microscopic examination of the third debulking procedure, suggesting the findings consistent with high-grade sarcoma.

In this case, the p53 labelling index was higher in high-grade ESS compared with low-grade ESS (Figure 5). Ohta et al. [4] found that low-grade ESS was p53 positive in a part of the tumor, whereas high-grade ESS showed stronger and more frequent immunostaining for p53, suggesting that low-grade ESS showing p53 protein overexpression can progress to high-grade ESS.

Recent reports investigated the immunoreactivity for epidermal growth factor receptor (EGFR), although the authors did not examine this [4]. Immunoreactive EGFR was reported to be positive in most tumor cells in low-grade [4, 13] and high-grade ESS [4]. Ohta et al. [4] suggested the application of new therapies using monoclonal antibodies or small molecular inhibitors of EGFR in ESS.

In conclusion, awareness of the capacity of low-grade ESS to transit into high-grade ESS is necessary to determine the appropriate therapeutic modality when high-grade ESS develops at recurrence. The immunohistochemical examination may be useful to identify the alternation of tumor phenotypes of ESS.

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Coexistent gestational choriocarcinoma and mixed adenocarcinoma of the uterus


**Materials and Methods**

**Patient history and presentation**

A 52-year-old gravida 4 para 4 Chinese woman, presented at a local hospital three years ago complaining of intermittent, painless vaginal bleeding of five years duration. Her last pregnancy occurred 26 years prior and resulted in a term delivery. An endometrial biopsy was performed and histopathologic examination showed no tumor. She had an uneventful surgical and gynecologic history without any history of hormonal replacement therapy. There was no other complaint. The clinical diagnosis was “Dysfunctional uterine bleeding”. She was initially treated with norethisterone at increasing doses for long-time administration, taking two to four pills three times a day. The amount of vaginal bleeding significantly increased four months later, and it could not be stopped by norethisterone. She returned to hospital ten days later and a second endometrial biopsy revealed well to moderately differentiated adenocarcinoma of the endometrium with tumor giant cells resembling syncytiotrophoblast.

General physical and pelvic examination revealed no abnormalities except a slightly enlarged uterus. The serum levels of hormones and tumor markers were as follows: β-subunit hCG (β-hCG) 47,244 IU/l (< 10 IU/l); luteinizing hormone (LH): 17.1 IU/l; follicle-stimulating hormone (FSH): 34.63 IU/l; estradiol (E2): 79.72 ng/ml; hemoglobin (HB): 5.8 g/l; carcinoembryonic antigen (CEA), cancer antigen (CA) 125, and alpha-fetoprotein (AFP) levels were within normal limits. Transvaginal sonogram and abdominal computed tomography (CT) scans revealed space-occupying lesions of the uterine cavity, and no apparent myometrial infiltration was observed. Chest radiography and a CT scan confirmed the presence of multiple pulmonary nodules, with the largest tumor in the lung measuring two cm in diameter. No other extraterine disease was identified. Cranial CT scans showed no abnormalities.

After the endometrial biopsy proved positive for carcinoma, the patient underwent an exploratory laparotomy. Intraoperative findings included a soft, eight- to ten-week size uterus. A total

**Introduction**

Endometrial carcinoma (EC) remains the most common malignancy of the female genital tract. Approximately 10% of ECs occurring in women older than 75 years show a mixed histology, that is, at least one other component comprising at least ten percent of the tumor that is present. True trophoblastic differentiation is rarely seen in ECs. Choriocarcinomas are generally considered germ cell or gestation-related tumors. Gestational trophoblastic tumors (GTT) are unique among tumors in that they arise from a conceptus. As such, they are allografts and genetically distinct from the patient. They are highly responsive to cytotoxic drugs. GTTs are morphologically characterized by the presence of cytotrophoblast and syncytiotrophoblast cells and biochemically by the production of human chori‐

**Summary**

**Objective:** To report the first case of a uterine gestational choriocarcinoma coexisting with an endometrial carcinoma (EC) and to discuss its possible pathogenesis. **Materials and Methods:** All tissues were examined histologically and monoclonal antibodies were used to evaluate the expression of HCG, HPL, P53, PTEN, and ER. Genotyping was performed on DNA extracted from the freshly dissected choriocarcinoma and the paraffin-embedded endometrial carcinoma along with parental blood DNA using multiplex STR-PCR at 16 loci. **Results:** Histology identified two distinct tumors: a uterine tumor containing cytotrophoblastic and syncytiotrophoblastic cells and a second distinct neoplasm composed of adenocarcinoma resembling endometrioid and mucinous adenocarcinoma. Genotyping of the choriocarcinoma revealed alleles from both the patient and her husband and was classified as biparental in origin. The endometrial adenocarcinoma contained only maternal alleles and was thus classified as maternal in origin. **Conclusions:** This is the first description of the simultaneous diagnosis of a uterine gestational choriocarcinoma and an EC within the same patient. DNA genotyping and immunohistochemistry are valuable tools in distinguishing the different origins of coexisting tumors.

**Key words:** Gestational choriocarcinoma; Endometrial carcinoma.

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abdominal hysterectomy and bilateral salpingo-oophorectomy were performed. Postoperatively, the serum β-hCG titer was 10,155 IU/L.

After the operation the patient began to receive multiagent systemic chemotherapy (EMA-CO) against the choriocarcinoma. After two courses of chemotherapy, serum β-hCG titer returned to normal (< 10 IU/L). However, a CT scan and chest radiograph showed residual pulmonary masses. All masses, however, were reduced in size relative to the evaluation made before the initiation of chemotherapy. After seven courses of chemotherapy, all residual masses were removed by cytoreductive surgical excision. Histologic studies showed necrotic fibrous tissue alone. One cycle of postoperative chemotherapy was given and the patient remains disease-free 48 months after surgery.

Results

Gross pathology

The uterus measured 10 x 7 x 4 cm$^3$ with two separate endometrial lesions; one arising from the left side of the uterine bottom which showed a partially necrotic and hemorrhagic polypoid mass of approximately 4 x 2.5 x 2 cm$^3$. No apparent myometrial infiltration was observed. The other lesion was on the anterior endometrium of the internal os of the uterus and appeared as a partial bulge

<table>
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approximately 0.5 x 0.5 x 0.3 cm$^3$. The ovaries and fallopian tubes appeared normal with each ovary measuring 3 x 2 x 1 cm$^3$.

**Histology**

Microscopic examination revealed two distinct tumor types. The bottom endometrial lesion showed sheets of cyto- and syncytiotrophoblasts, with a typical plexiform pattern admixed with blood and necrotic tissue. The tumor infiltrated into the superficial myometrium of the uterus and had blood vessel involvement. The anterior endometrial lesion of the internal os of the uterus showed a FIGO grade I-II adenocarcinoma resembling endometrioid and mucinous adenocarcinoma, with the latter dominating. No cytotrophoblastic or hemorrhagic areas suggestive of choriocarcinoma were seen. No apparent myometrial infiltration was observed. Focal complex endometrial hyperplasia was observed. There was a close transition from the complex endometrial hyperplasia to the adenocarcinoma areas on several slides.

Immunohistochemical staining of the choriocarcinoma cells showed: HCG++, HPL+, P53+, PTEN+, ER-, and PR-; the endometrioid and mucinous adenocarcinoma cells showed: ER++, R++, HCG±, HPL±, P53+, and PTEN+ (Figures 1-4).

**DNA extraction and genotyping**

Peripheral blood was obtained from the patient and her husband. DNA was extracted from total blood by standard methods. DNA from the choriocarcinoma was extracted from fresh tissues and endometrial adenocarcinoma was identified and microdissected from a five-µm unstained section of tissue with reference to a consecutive section stained with haematoxylin and eosin. DNA was then prepared from this tissue using a modification of the method described by Wright and Manos. Fifty ng DNA from the patient, her partner, the choriocarcinoma, and the endometrial adenocarcinoma were amplified with 15 STR markers and a gender-determination marker using a commercially available kit. One of each pair of primers was labeled with the fluorescent dye FAM (blue), or HEX (green). Following amplification, five-µl of each polymerase chain reaction (PCR) product underwent electrophoresis on a one-percent agarose gel to assess the yield of the product. PCR products were diluted as appropriate and subsequently resolved by capillary electrophoresis using an analyser. Analysis and sizing of the microsatellite polymorphisms was done using a specific software. DNA from the choriocarcinoma showed biparental alleles and was classified as biparental in origin, whereas DNA from the endometrial adenocarcinoma...
Coexistent gestational choriocarcinoma and mixed adenocarcinoma of the uterus

Table 1. DNA analysis of tumors.

The use of β-hCG as a tumor marker in gestational trophoblastic disease and germ cell tumors is common. There also are reports of hCG positivity in the serum of patients with nontrophoblastic, nongonadal gynecologic malignant neoplasms, and in patients with ductal adenocarcinoma of the pancreas, biliary cancer, and carcinoma of the bladder, cervix, lung, colon, and kidney. However, true histologic evidence of trophoblastic differentiation is unusual, and trophoblastic differentiation in gynecologic nontrophoblastic tumors is very rare. To date, there have been a total of 15 cases of nongestational gynecologic cancers demonstrating trophoblastic differentiation, including nine endometrial adenocarcinomas [2-10], five ovarian cystadenocarcinomas [11-14], and one ovarian malignant mixed mesodermal tumor [15]. The simultaneous diagnosis of a gestational choriocarcinoma and a nontrophoblastic gynecologic malignant neoplasm within the same patient is very rare; Nguyen [16] reported a case of coexistent choriocarcinoma and malignant mixed mesodermal tumor of the uterus. The simultaneous diagnosis of a uterine gestational choriocarcinoma and an endometrial carcinoma within the same patient has not been previously described.

At the pathological level it is very difficult to differentiate an adenocarcinoma of the endometrium with trophoblastic differentiation from coexistent gestational choriocarcinoma and mixed adenocarcinoma of the uterus in both biopsies and surgical specimen. Either syncytiotrophoblast or cytotrophoblast elements, or both may be present. Investigating the DNA of these two tumors determined that the choriocarcinoma arose from a pregnancy, due to the existence of paternal genes. The endometrial adenocarcinoma, on the other hand, showed only maternal alleles and was classified as maternal in origin. Immunohistochemical staining may also be a helpful tool for differentiating adenocarcinoma of the...
endometrium with trophoblastic differentiation from coexistent gestational choriocarcinoma and mixed adenocarcinoma of the uterus. In this case immunohistochemical staining of choriocarcinoma cells showed: HCG++, ER-, and PR-, whereas immunohistochemical staining of endometrioid and mucinous adenocarcinoma cells showed: ER++, PR++, and HCG±. Thus, these tests helped to prove that the present case represents two simultaneous uterine primaries: one a gestational choriocarcinoma and the other an endometrial carcinoma.

The pathogenesis of adenocarcinoma of the endometrium with trophoblastic differentiation is not clear. Several theories have been discussed including the proliferation of primitive cells, dedifferentiation, retrodifferentiation, and multipotential differentiation [17, 18]. The authors favor the hypothesis that the trophoblastic component originated from the epithelial carcinoma. Another possibility is that this case may represent the dedifferentiation of a highly aggressive gestational choriocarcinoma into an endometrial carcinoma. Fetal trophoblasts are multipotent and may have differentiated into epithelial elements to give the appearance of endometrial carcinoma. The gestational choriocarcinoma may promote endometrial cancer progression by secreting hCG, which can promote the differentiation of the endometrial carcinoma cells in vivo and LH/hCG can regulate EC cell invasiveness. This result provides a rationale for the use of inhibitors of LH secretion, such as GnRH analogues in the treatment of EC. It is possible that this patient is estrogen dependent and sensitive to elevated levels of LH/hCG [17, 18].

Choriocarcinomatous differentiation rarely occurs in carcinomas of different origins, such as the stomach, colon, liver, gallbladder, breast, urinary bladder, prostate, uterus, and ovary [19-21]. The prognosis of these tumors is unfavorable due to rapid tumor growth with metastatic disease and resistance to usual chemotherapeutic regimens. The present case found a choriocarcinoma coexisting with an endometrial carcinoma. The patient showed good response to chemotherapeutic regimens including EMA-CO and remains disease-free 48 months after her initial diagnosis. This may suggest that the case is completely different from the cases reported before.
Acknowledgment

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