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.
The 21st century role of Piver type II hysterectomy in FIGO Stage IA, IB cervical cancer: A personal perspective
M.S. Piver, J.Y. Lee - Buffalo, NY (USA)
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Virchow’s node as a first manifestation of ovarian serous carcinoma: case report
F.B. Cebesoy, O. Balat, A. Aydin - Gaziantep, TURKEY
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J.G. Shen, Y.X. Chen, D.Y. Xu, Y.F. Feng, Z.H. Tong - Hangzhou, P.R. CHINA
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BRIEF COMMUNICATION

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A case of woman with three different tumors which developed after tamoxifen treatment for breast cancer is described.
The 21st century role of Piver type II hysterectomy in FIGO Stage IA, IB cervical cancer: A personal perspective

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Summary

Class II modified radical hysterectomy reported in 1974 by Piver, Rutledge and Smith for cervical cancer is an extended hysterectomy that has less dissection of the ureter from the paracervical tissues, ligation of the uterine vessels just medial to the ureter to ensure preservation of the distal ureteral blood supply, and less radical parametrectomy preserving the lateral parametrium. The authors present a 21st century personal perspective on the use of a type II hysterectomy based on the 1994 FIGO changes in classification of Stage IA1, IA2, IB1 and IB2.

Introduction

Invasive cancer of the cervix is the second most common cancer and the major cause of death from gynecologic cancer worldwide, with almost half a million cases diagnosed annually (493,000 new cases and 273,000 deaths) [1]. Current treatment of invasive cervical cancer includes primary surgery or radiation therapy with or without platinum-based chemotherapy.

In 1900 Wertheim [2] of Vienna described radical hysterectomy (RH) for the treatment of invasive cervical cancer. Meigs began to perform pelvic lymphadenectomy with RH and reported his series of 100 cases without an operative mortality in 1946 [3]. With improved blood products and antibiotics during the latter half of the 20th century, RH became the primary treatment for patients with early-stage invasive cervical cancer. In 1974 Piver, Rutledge and Smith defined the extent of radical hysterectomy by establishing five classes of hysterectomy (classes I-V) [4]. The classification of hysterectomy points out the significance of tailoring the radicality of surgery that is appropriate to the individual patient’s cervical cancer with the goal of reduction in surgical related complications and improvement in long-term cure rates.

In 1974 type II extended hysterectomy was felt to be suitable for a) microinvasive cancer, as then defined, when there was some question as to the depth of invasion that remained after cervical conization, and b) for small post irradiation recurrences limited to the cervix.

However, since our 1974 report using the original 1971 FIGO classification of Stage IA, FIGO has reclassified 1A in 1985 and subsequently in 1994 adding nuances not present at the time of the original description of type II hysterectomy.

The role of less aggressive surgery in the management of cervical cancer continues to be discussed. For many decades, surgery for early stage cervical cancer patients has focused on aggressiveness and technique in order to maximize survival with less consideration for patients’ quality of life. With recent emphasis on quality of life issues in cancer survivors, the ability to tailor the aggressiveness of treatment represents an ultimate goal.

The purpose of this paper is to present a personal perspective on the 21st century role of type II hysterectomy and pelvic lymphadenectomy with special emphasis on the 1994 revised FIGO classification of Stage IA1, IA2, IB1, and IB2.

Methods

Isolation of studies through computerized searches was conducted using PUBMED (www.pubmed.gov). The medical subject headings and text words used were: cervical cancer, radical hysterectomy, type II hysterectomy. The literature over the past 57 years (1951 to present) was reviewed.
Techniques for hysterectomy

Piver, Rutledge and Smith reported five classes of hysterectomies and defined the extent of radicality of each procedure [4].

*Type I (Extrafascial hysterectomy)*

This is a simple hysterectomy and the goal of this procedure is to ensure removal of all cervical tissue. Reflection and retraction of the ureters laterally without actual dissection from the ureteral bed allows one to clamp the adjacent paracervical tissue without cutting into the side of the cervical tissue itself.

*Type II (Modified radical hysterectomy) (Figures 1 and 2)*

This is basically the hysterectomy described by Ernest Wertheim [2]. The purpose of a type II hysterectomy is to remove more paracervical tissues while preserving blood supply to the distal ureters and bladder [4]. The ureters are freed from the paracervical position but are not dissected out of the pubovesical ligament. The uterine artery is ligated where it crosses the ureter thus preserving blood supply to the ureter, and medial half of the cardinal ligaments and proximal uterosacral ligaments are resected. The upper one-third of the vagina is resected. The operation described by Wertheim involved selective removal of the large nodes, rather than systematic pelvic lymphadenectomy. However, currently a pelvic lymphadenectomy is usually performed with type II hysterectomy.

*Type III (Radical hysterectomy) (Figures 1 and 2)*

The most commonly performed operation for Stage IB cervical cancer is that originally described by Meigs in 1944. Type III hysterectomy removes the central lesion with wide excision of the parametrium and paravaginal tissue along the upper vaginal margin [4]. The uterine artery is ligated at its origin from its superior vesicle or internal iliac artery, allowing removal of the entire width of the cardinal ligaments. Preservation of superior vesical artery is performed to prevent ureteral and bladder fistula formation. Uterosacral ligaments are resected at the sacral attachments. The upper half of the vagina is resected.

*Type IV (Extended radical hysterectomy)*

The aim of the type IV radical hysterectomy is complete removal of all periureteral tissue, more extensive excision of the paravaginal tissue [4]. This differs from the type III operation in three aspects: a) the ureter is completely dissected from the vesicouterine ligaments, b) the superior vesicle artery is sacrificed, and c) three-fourths of the vagina is excised.

*Type V (Partial exenteration)*

The indication for the procedure is removal of the central recurrence involving a portion of the distal ureter or bladder [4].

1994 FIGO Stage IA1 cervical cancer

In 1971 FIGO classified Stage IA cervical cancer as those cases of preclinical carcinoma, however, with no designation of the depth of invasion. Subsequently, in 1985 FIGO reclassified microinvasive Stage IA into IA1 described as “minimal microscopically evident stromal invasion” but without defining the depth of invasion and Stage IA2 as microscopic invasion that measured less than 5 mm in depth and less than 7.0 mm in horizontal spread. This definition of allotting all patients with less than 5 mm invasion to Stage IA did not provide the clinicians with evidence-based medicine as to which patients could best be treated by type I hysterectomy with negligible instance of pelvic lymph node metastasis and those with significant risk of lymph node metastasis who would be candidates for extended type II hysterectomy and pelvic lymphadenectomy.

In 1988, one of us (MSP) reviewed ten series of microinvasive cervical cancer cases reported from 1969-1986 [5]. There were 464 patients reported who had less than 3.0 mm invasive cervical cancer and only one or 0.21% had pelvic lymph node metastasis, a percentage too small to be clinically relevant. However, of the 132 women reported with 3.0-5.0 mm of invasive cervical cancer, there were nine or 6.8% with pelvic lymph node metastasis, a percentage that would be clinically relevant.

Ostor and co-authors in 1994 were able to identify 333 women with cervical cancer invading less than 3 mm in depth who underwent lymphadenectomy, five of whom had lymph node metastasis [6]. This less than 1% lymph node metastasis was similar to our 1988 report of 0.21% [5].

Appropriately, in 1994 FIGO again reclassified microinvasive cancer now allocating patients with less than 3.0 mm invasion and less than 7.0 mm horizontal spread to IA1 and those with patients with 3.0-5.0 mm of invasion and less than 7.0 mm horizontal spread to IA2. The depth of invasion is measured from the base of the epithelium, either squamous or glandular, from which it originates to the deepest point of invasion.
Not included in the 1994 FIGO classification of Stage IA1 and IA2 cervical cancer was the presence of tumor cells in lymph or venous space. However, the presence of lymphovascular space invasion (LVSI) clearly presents an important variable to the individual clinician presented with patients with FIGO Stage IA1 or IA2 with LVSI.

In 1986 in an excellent review of the then literature, Benedet and Anderson reported on 49 patients with Stage IA who had invasive cervical cancer equal to or less than 3.0 mm but who had LVSI, four of whom (8.2%) had lymph node metastasis [7]. Moreover, of the 371 reviewed by these authors with equal to or less than 3.0 mm of invasion but without LVSI, only three patients or 0.8% had lymph node metastasis.

Based on the above data, it is not unreasonable to conclude that in the 21st century patients with Stage IA1 without LVSI that a type I hysterectomy without lymphadenectomy or cervical conization in women wanting to preserve fertility is appropriate therapy. Based on the incidence of pelvic lymph node metastasis reported for patients with Stage IA1 but with LVSI, type II hysterectomy with pelvic lymphadenectomy should be considered. A more conservative approach for women wanting to preserve fertility would be cervical conization and retropertitoneal pelvic lymphadenectomy.

**1994 FIGO Stage IA2 cervical cancer**

As previously stated, our 1988 review identified a 6.8% incidence of lymph node metastasis in women with 3-5 mm of invasive cervical cancer. Similarly, Ostor and co-authors in 1994 identified 221 patients with 3-5 mm invasion of the cervical stroma who underwent lymphadenectomy with a 6% incidence of lymph node metastasis, nearly identical to the 6.8% reported by one of us (MSP) [6].

In the review by Benedet and Anderson, the authors identified 53 patients with 3-5 mm invasion and LVSI, four of whom or 7.5% had lymph node metastasis. Of importance, this 7.5% incidence of lymph node metastasis was almost identical to the 8.3% of the 180 patients without LVSI [7].

Based on this data, in the 21st century, patients who do not desire to retain fertility, those with Stage IA2 with or without LVSI would be candidates for type II hysterectomy and pelvic lymphadenectomy.
Prior to the 1994 FIGO classification of cervical cancer, FIGO Stage IB consisted of macroscopic lesions limited to the cervix. In 1975, a year after the publication of the five classes of hysterectomies, one of us (MSP) published a paper titled “Prognostic significance of cervical lesion size and pelvic lymph node metastasis in cervical carcinoma” [8].

Of the 145 women who underwent type II and type III hysterectomy with pelvic lymphadenectomy, those patients with cervical tumors equal to or less than 3 cm in diameter had an overall incidence of lymph node metastasis of 21.2% (Table 2); patients with tumors measuring greater than 3 cm had an incidence of lymph node metastasis of 35.1%. More importantly, those patients with tumors 1 cm or less had a five-year survival of 84.1% and those with tumors measuring 2-3 cm had a five-year survival of 90.1%. However, the five-year survival decreases to 69.9% for tumors measuring 4-5 cm and 60.0% for tumors greater than or equal to 6 cm in maximum diameter.

In 1994, FIGO reclassified Stage IB into IB1 and IB2 in which IB1 are those cervical lesions 4 cm or less in diameter and IB2 are those greater than 4 cm. This new classification is consistent with our 1975 results in which the five-year survival is 90.1% for cervical tumors measuring 2-3 cm treated by type II or type III hysterectomy but fell to 65.4% for those lesions 4-5 cm and 60.0% for those lesions measuring 6 cm or greater in diameter [8].

In the only randomized prospective trial of type II versus type III hysterectomy, Londoni et al. reported on 243 patients with Stage IB1-IIA cervical cancer [9]. Although patients treated by type II or type III hysterectomy had similar recurrence free and overall survival, this conclusion is clouded by the fact that 54% of the type II and 55% of the type III hysterectomy patients received post-hysterectomy radiation therapy lessening our understanding of long-term results of surgery alone.

As was clear from our 1974 report, complications from class II hysterectomies were significantly less as compared to the women who underwent class III hysterectomy. In the randomized trial reported by Londoni and co-authors, patients undergoing class III hysterectomy also had increased morbidity as compared to those treated by class II hysterectomy [9]. However, although it is evident that class II hysterectomy is associated with less morbidity, there are no evidence-based reports that confirm the less extensive parametrial resection of class II as compared to class III hysterectomy results in equal long-term survival, the ultimate goal of the operation.

As clearly stated by Hoffman in 2004 “currently, there is no adequate method to preoperatively identify many of the low-risk (cervical) cancer patients whose risk/benefit ratio weighs against doing a complete parametrectomy” [10].

Based on the above data, there is no 21st century evidence that a class II hysterectomy would be the preferred treatment of choice for FIGO Stage IB1 but rather type III hysterectomy and pelvic lymphadenectomy remains the treatment of choice. Because the long-term outcome for women with FIGO Stage IB2 is significantly worse than for Stage IB1, it appears evident that type II and even a type III hysterectomy are not suitable for these patients, although clearly a type III hysterectomy is performed for Stage IB2 in many centers.

1994 FIGO Stage IB1 and IB2 cervical cancer

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Table 1. — FIGO Stage IA & IB. International Federation of Gynecology and Obstetrics.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Lesion Characteristics</th>
<th>Patient Count</th>
<th>Metastasis Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Stromal invasion no greater than 3.0 mm in depth and 7.0 mm or less in horizontal spread.</td>
<td>145</td>
<td>39</td>
<td>26.9</td>
</tr>
<tr>
<td>IA1</td>
<td>Lesion 4.0 mm or less in greatest diameter.</td>
<td>72</td>
<td>16</td>
<td>22.1</td>
</tr>
<tr>
<td>IA2</td>
<td>Lesion more than 4.0 cm in greatest diameter.</td>
<td>45</td>
<td>16</td>
<td>35.5</td>
</tr>
<tr>
<td>IB</td>
<td>Clinically visible lesions confined to the cervix or microscopic lesion greater than IA2.</td>
<td>19</td>
<td>6</td>
<td>32.0</td>
</tr>
<tr>
<td>IB1</td>
<td>Lesion 4.0 mm or less in greatest diameter.</td>
<td>6</td>
<td>3</td>
<td>50.0</td>
</tr>
<tr>
<td>IB2</td>
<td>Lesion more than 4.0 cm in greatest diameter.</td>
<td>39</td>
<td>26.9</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. — Cervical lesion size and lymph node metastasis in Stage IB cervical cancer.

<table>
<thead>
<tr>
<th>Size (cm)</th>
<th>Patients</th>
<th>Metastasis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>22</td>
<td>4</td>
<td>18.1</td>
</tr>
<tr>
<td>2-3</td>
<td>72</td>
<td>16</td>
<td>22.1</td>
</tr>
<tr>
<td>4-5</td>
<td>45</td>
<td>16</td>
<td>35.5</td>
</tr>
<tr>
<td>≥ 6</td>
<td>6</td>
<td>3</td>
<td>&gt; 35.2</td>
</tr>
<tr>
<td>Totals</td>
<td>145</td>
<td>39</td>
<td>26.9</td>
</tr>
</tbody>
</table>


Discussion

The purpose of this paper was for one of us (MSP) to take a personal 21st century perspective of the merit of a class II hysterectomy in early-stage cervical cancer since the original classification of five classes of hysterectomy by the late Felix Rutledge and the artist rendition by Susan M. Piver based on the 1994 FIGO reclassification of Stage IA1/2 and IB1/2 cervical cancer.

Purposefully, this paper does not discuss type II versus type III nerve sparing RH [11], fertility sparing type III radical abdominal trachelectomy [12] or robotic-assisted laparoscopic type III radical hysterectomy [13].

It is our opinion based on this review that FIGO Stage IA1 without LVSII is treated by type I hysterectomy without lymphadenectomy but that type II hysterectomy with pelvic lymphadenectomy would be a reasonable choice for Stage IA1 with LVSII. Also, that all Stage IA2 patients with or without LVSII are suitable candidates for type II hysterectomy and pelvic lymphadenectomy.

Finally, until improved imaging allows for possible detection of early parametrial invasion, the type III hysterectomy plus pelvic lymphadenectomy in medically suitable patients is the preferred treatment for IB1. Patients with Stage IB2 may be considered for type III hysterectomy with tailored postoperative radiation [14].

References


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Epidemiological, clinical and viral determinants of the increased prevalence of high-risk human papillomavirus (HPV) infections in elderly women


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Summary

Background: Population-based studies have reported a second peak of human papillomavirus (HPV) prevalence among women > 55 years, but reasons for this U-shaped HPV prevalence curve are poorly understood. Objectives: To analyse determinants of high-risk HPV (HR-HPV) infections among postmenopausal women. Study design and Methods: A cohort of 3,187 women was stratified into three age categories: i) youngest age group < 25 years (n = 1,103); ii) women between 26-55 years (n = 2,004), and iii) women > 55 years (n = 80), analysed for epidemiological, clinical and virological determinants of their HR-HPV infections. Real-time PCR was used for HPV genotyping, analysis of viral loads for HPV16, 18/45, 31, 33/52/58, 35 and 39, and load of integrated HPV16. Results: Age-standardised prevalence of HR-HPV infections showed a second peak among women > 55 years, with a perfect U-shaped curve (R² = 0.966). The factors explaining this increased HR-HPV prevalence among older women include: i) cohort effect, ii) higher viral loads for HR-HPV types with cubic model curve (R² = 0.714) for HPV16, iii) distinct shift (p = 0.0001) from multi-type infections to single HR-HPV types, iv) transition from episomal to integrated HPV16 (p = 0.009), v) higher load of integrated HPV16 (p = 0.009), and, vi) higher proportion of incident infections, higher rate of viral persistence, and lower rate of HR-HPV clearance. Conclusions: These data suggest that in women who fail to eradicate their HR-HPV infection until menopause, selection of integrated viral clone has taken place, driving the process towards progressing disease. Consequent to this, most of the HR-HPV infections in women > 55 years were associated with high-grade CIN or invasive carcinoma.

Key words: High-risk HPV; Postmenopause; Prevalence; Second peak; Predictors; Sexual behavior; Viral load; Integration; CIN, cervical cancer; Follow-up.

Introduction

Since the recognition of human papillomavirus (HPV) as the causal agent of cervical cancer (CC) and its precursor (CIN) lesions, epidemiological data from different countries confirmed that the peak prevalence of cervical HPV infections (detected by Pap smear or DNA hybridisation techniques) occurs between 22-24 years of age, with a constant decline with progressing age [1-6]. This was neatly explained by the early studies (based on Pap smear screening data) implicating a particularly high (8%) annual incidence of cervical HPV infections among 22-year-old women [7, 8]. More recent studies on the natural history of HPV infections [9] have further refined the dynamics of these viral events in different populations. Accordingly, incident HR-HPV infections are clearly age-dependent, the 3-year cumulative incidence exceeding 50% among women under 20 years of age, following the onset of their sexual activity [10-12]. On the other hand, clearance of the virus did not show such strict age-dependence [13], but continued at a constant rate among women over 30 years of age [4, 14]. Using these age-specific incidence and clearance rates to estimate the age-specific preva-
ence of HR-HPV infections models the true figures quite closely except for a small gap in each of the 5-year age groups (15-75 years) [15]. This gap between the true- and estimated age-specific prevalence rates is due to the fact that instead of clearance, some of the acquired infections remain persistent. These persistent HR-HPV infections are considered as a prerequisite for developing a progressive cervical disease and are currently the subject of intense study for their predisposing co-factors [16-18].

During the past few years, this dynamic model of HPV acquisition, clearance and persistence, explaining the linearly declining age-specific prevalence curve [1-6] has been challenged by the data from several population-based studies, reporting a second peak in HPV prevalence among women > 55 years of age [19-21]. In some studies a similar peak among older women has been reported for HPV incidence as well [22, 23]. Indeed, the recently published population-based studies report highly contradictory results from different geographic areas. There are populations, where the age-specific prevalence curve is clearly U-shaped, with a second peak among postmenopausal women [19-22, 24-28]. In other studies, no such U-shaped prevalence curve was established, but the shape was that of a declining linear curve [29-33]. The IARC HPV Prevalence Survey data failed to give one single explanation for these differences, and several key questions still remain unanswered [34, 35].

The present study sheds new light on most of these open issues related to the shape of the age-specific HPV prevalence curves, and in particular to the determinants of the second peak observed among women over 55 years of age.

Material and Methods

Patients and study design

The subjects and the study design of this European Commission (EC)-funded cross-sectional and cohort study have been published earlier [36, 37]. The study cohort comprises 3,187 consecutive women attending six different outpatient clinics in three New Independent States (NIS) of the former Soviet Union between 1998-2002. These women derive from three different groups: i) cervical STD clinics (= STD patients). The mean age of the women was 32.6 (± 10.7 SD) years (median 30.6, range 15-85 years).

The study design has been detailed in a series of previous reports [12, 13, 15, 18, 36, 37]. All eligible women had Pap smears taken and were tested for HR-HPV using Hybrid Capture II (HCII) and the first 1,500 also with PCR and confirmative hybridisation [38]. Patients with ASC-US or higher Pap had biopsy confirmation [36, 37].

Follow-up

All women who presented with biopsy-confirmed low-grade lesions were assigned for prospective follow-up, while women with high-grade lesions were treated [36, 37]. Altogether, follow-up (FU) data are available on 887 women (median FU 16.7 months), divided into four sub-cohorts according to their baseline HPV/PAP smear status [12, 13, 15, 18]. Four possible outcomes were recorded: a) always Pap (or HPV) negative, b) incident Pap abnormality (or new HPV), c) persistent Pap abnormality (or HPV), and d) cleared disease (or HPV infection). The criteria for defining these four outcomes have been described in detail elsewhere [12, 13, 15, 18].

Age-group analysis

The present analysis was focused on assessing the epidemiological, clinical and viral predictors for HR-HPV infections in different age categories. In simple terms, we wanted to clarify the reasons for the U-shaped HPV prevalence curve, previously observed in this cohort [36, 37]. The whole cohort of 3,187 women was stratified into three age groups according to their different HR-HPV prevalence profiles established by HCII assay and PCR [36, 38]. These three age categories are: i) two youngest age groups (women > 20 years and those between 21-25 years; n = 1,103) with the peak HPV prevalence; ii) women between 26-55 years (n = 2,004) with linearly declining HPV prevalence; and iii) women > 55 years (n = 80) with a sharply increasing HR-HPV prevalence [36, 37]. In all analyses of this study, these three age categories were compared to each other.

Methods

Epidemiological questionnaire

At the first visit, all women who gave their consent to participate filled in a detailed inquiry concerning the risk factors of HPV, CIN and CC. This structured questionnaire contained questions exploring reproductive history, sexual history, current sexual practices, sexual hygiene, medical history, smoking habits and contraception [37, 39].

Papanicolaou (Pap) smears

Altogether, 3,097 women were subjected to conventional Pap smear, interpreted using the jointly agreed terminology [36].

Directed punch biopsy

On histological grading of the lesions, CIN nomenclature was used. The presence of HPV infection was recorded using the accepted morphological criteria [36].

Detection of HPV DNA by Hybrid Capture II assay

From 3,087 women, the sample for the Hybrid Capture II test was taken from the cervix using the HClI sampling kit (Digene, Silver Springs, MD, USA). The test was performed according to the provider’s instructions using the probe Panel B which detects 13 high-risk HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). The RLU/CO value of 1 pg/ml was used as the cut-off for a positive test [36, 38].

Detection and quantification of HR-HPV by real-time PCR

The same samples were then processed for DNA extraction using the high salt method of Miller et al. [40]. HR-HPV detection, genotype analysis, and viral load quantification was performed with a real-time PCR-based assay described recently [41]. With this method, HR-HPV types 16, 31, 39 and members of the group 18/45 and group 33/52/58 were detected in two different reactions. The amplification conditions used were described recently [41]. A total of six non-template controls, where DNA was substituted by water were included in each run. The dynamic range of the assay is 102-107 copies of HR-HPV per assay [41]. HPV35 detection was performed only from the baseline samples.
**Integration assay**

All HPV16 positive samples at the baseline and all follow-up visits were further analysed for their physical status, using a real-time PCR method, recently developed in our laboratory [42]. The amplification conditions, primers and probes were as described earlier. Two standard curves were obtained by amplification of a dilution series of five million to 500 copies of a clone of HPV 16 in pBR322. There was a linear relationship between the threshold cycle values plotted against the log-copy number over the entire range of dilutions [42]. When no E2 PCR signal was detected, the HPV16 genome was interpreted as integrated. When the ratio of copies of E2:E6 was above 0.5, the physical status was interpreted as episomal. Otherwise the sample was interpreted to contain both episomal and integrated forms of HPV16 (mixed form) [42, 43].

**Statistical analyses**

Statistical analyses were performed using the SPSS® and STATA software packages (SPSS for Windows, Version 14.0.1., SPSS Inc., Chicago, IL, USA and STATA/SE 9.2., Stata Corp.,

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Women under 25 years&lt;sup&gt;1&lt;/sup&gt; (n = 1,103)</th>
<th>Women between 26 and 55 years&lt;sup&gt;2&lt;/sup&gt; (n = 2,004)</th>
<th>Women over 55 years&lt;sup&gt;2&lt;/sup&gt; (n = 80)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (95% CI)#</td>
<td>21.7 (21.6-21.8)</td>
<td>37.3 (37.0-37.7)</td>
<td>61.6 (60.4-62.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Patient category:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STD</td>
<td>34.7% (383/1103)</td>
<td>16.9% (338/2004)</td>
<td>2.5% (2/80)</td>
<td></td>
</tr>
<tr>
<td>GYN27.7% (305/1103)</td>
<td>22.5% (451/2004)</td>
<td>15.0% (12/80)</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>SCR</td>
<td>50.6% (548/1103)</td>
<td>50.6% (1215/2004)</td>
<td>82.5% (66/80)</td>
<td></td>
</tr>
<tr>
<td>HPV positive (HCII test)</td>
<td>48.8% (522/1069)</td>
<td>24.5% (474/1938)</td>
<td>21.3% (17/80)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HPV positive (TaqMan assay)</td>
<td>40.3% (420/1042)</td>
<td>26.6% (493/1856)</td>
<td>20.3% (16/79)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pap Smear:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCUS or worse</td>
<td>18.5% (200/1079)</td>
<td>15.3% (297/1938)</td>
<td>22.5% (18/80)</td>
<td>0.030</td>
</tr>
<tr>
<td>LSIL or worse</td>
<td>8.0% (86/1079)</td>
<td>7.9% (154/1938)</td>
<td>17.5% (14/80)</td>
<td>0.025</td>
</tr>
<tr>
<td>HSIL or worse</td>
<td>0.2% (2/1079)</td>
<td>2.1% (40/1856)</td>
<td>13.8% (11/80)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cervical Biopsy:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN1 or worse</td>
<td>38.8% (88/227)</td>
<td>17.5% (30/174)</td>
<td>13.8% (11/80)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CIN2 or worse</td>
<td>13.2% (30/227)</td>
<td>21.3% (35/165)</td>
<td>17.5% (11/80)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CIN3 or cancer</td>
<td>3.1% (7/227)</td>
<td>21.3% (54/254)</td>
<td>17.5% (11/80)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ever been pregnant</td>
<td>67.3% (664/986)</td>
<td>81.2% (1485/1828)</td>
<td>88.8% (71/80)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Number of deliveries (M±SD)#</td>
<td>0.65 (±0.80)</td>
<td>0.97 (±0.87)</td>
<td>1.14 (±0.88)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ever had miscarriages</td>
<td>12.3% (117/948)</td>
<td>17.3% (311/1798)</td>
<td>21.8% (37/179)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ever had abortions</td>
<td>10.3% (18/948)</td>
<td>13.2% (21/179)</td>
<td>21.8% (37/179)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Number of abortions (M±SD)#</td>
<td>1.88 (±1.35)</td>
<td>2.16 (±1.62)</td>
<td>2.58 (±1.88)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Age at first sexual intercourse#</td>
<td>18.47 (±2.76)</td>
<td>18.52 (±2.92)</td>
<td>20.99 (±4.00)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sexual habits regular ever since</td>
<td>46.0% (439/954)</td>
<td>53.6% (354/663)</td>
<td>67.5% (52/77)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Currently, one sexual partner</td>
<td>84.6% (823/973)</td>
<td>83.8% (1500/1791)</td>
<td>62.0% (49/79)</td>
<td>0.0001</td>
</tr>
<tr>
<td>No. of partners during past 2 yrs</td>
<td>2.12 (±3.42)</td>
<td>2.07 (±3.15)</td>
<td>2.58 (±1.88)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mode of contraception:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No contraception</td>
<td>46.4% (442/952)</td>
<td>49.9% (875/1755)</td>
<td>75.0% (57/76)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Oral contraception</td>
<td>38.1% (363/952)</td>
<td>36.1% (634/1755)</td>
<td>19.7% (15/76)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Bide douche at intercourse</td>
<td>15.4% (147/952)</td>
<td>14.0% (246/1755)</td>
<td>5.3% (4/76)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Douché requested from the partner</td>
<td>94.3% (909/964)</td>
<td>96.3% (1704/1769)</td>
<td>86.8% (66/76)</td>
<td>0.001</td>
</tr>
<tr>
<td>History of skin or genital warts</td>
<td>86.0% (832/968)</td>
<td>89.6% (1585/1768)</td>
<td>78.9% (60/76)</td>
<td>0.001</td>
</tr>
<tr>
<td>History of previous CIN</td>
<td>58.0% (580/956)</td>
<td>62.1% (127/204)</td>
<td>12.1% (7/58)</td>
<td>0.018</td>
</tr>
<tr>
<td>Ever had Pap smear</td>
<td>35.5% (302/851)</td>
<td>63.4% (501/794)</td>
<td>34.7% (25/72)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Time since the last Pap test (months)#</td>
<td>11.35 (±11.69)</td>
<td>12.21 (±12.92)</td>
<td>12.44 (±7.61)</td>
<td>0.594</td>
</tr>
<tr>
<td>Previous Pap test normal</td>
<td>72.3% (219/302)</td>
<td>71.2% (501/704)</td>
<td>73.1% (19/26)</td>
<td>0.923</td>
</tr>
<tr>
<td>Current smoker</td>
<td>30.9% (301/974)</td>
<td>23.9% (430/1796)</td>
<td>21.8% (17/78)</td>
<td>0.0001</td>
</tr>
<tr>
<td>If yes, for how long (no. of yrs)</td>
<td>6.63 (±4.92)</td>
<td>9.58 (±7.04)</td>
<td>9.54 (±5.07)</td>
<td>0.0001</td>
</tr>
<tr>
<td>If not current, ever been smoker</td>
<td>22.4% (147/655)</td>
<td>19.2% (250/1300)</td>
<td>11.7% (7/60)</td>
<td>0.055</td>
</tr>
<tr>
<td>How long did you smoke (yrs)#</td>
<td>4.57 (±3.66)</td>
<td>5.43 (±4.41)</td>
<td>10.8 (±8.61)</td>
<td>0.003</td>
</tr>
<tr>
<td>Time since stopped smoking (months)#</td>
<td>31.49 (±37.73)</td>
<td>54.59 (±86.53)</td>
<td>81.60 (±93.10)</td>
<td>0.004</td>
</tr>
<tr>
<td>Sexual partner regular smoker</td>
<td>61.5% (575/935)</td>
<td>55.9% (951/1701)</td>
<td>43.5% (30/69)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ever had cervical erosion</td>
<td>37.9% (589/1500)</td>
<td>62.0% (1108/1787)</td>
<td>55.1% (43/78)</td>
<td>0.420</td>
</tr>
<tr>
<td>If yes, was erosion treated</td>
<td>42.6% (339/796)</td>
<td>53.5% (775/1449)</td>
<td>64.2% (34/53)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

#Kruskal-Wallis test; 'Age group with peak HR-HPV prevalence; *Age groups with progressively declining HR-HPV prevalence; **Age groups with sharply increasing HR-HPV prevalence; '0/7 were SCC; '16/54 were SCC; '10/11 were SCC; Negative response includes women with no current partner.
Table 2. — Significant determinants of HR-HPV infection in the three groups.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Women under 25 years¹</th>
<th>Women between 26 and 55 years¹</th>
<th>Women over 55 years¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) p</td>
<td>OR (95% CI) p</td>
<td>OR (95% CI) p</td>
</tr>
<tr>
<td>SCR</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>STD</td>
<td>1.53 (1.15-2.03) 0.008</td>
<td>2.39 (1.82-3.12) 0.0001</td>
<td>0.054</td>
</tr>
<tr>
<td>GYN</td>
<td>1.41 (1.04-1.91)</td>
<td>1.90 (1.48-2.44)</td>
<td>5.00 (1.35-18.41)</td>
</tr>
<tr>
<td>HSIL, PAP</td>
<td>NC 0.238</td>
<td>39.33 (12.0-128.5) 0.0001</td>
<td>34.3 (6.26-187.86) 0.0001</td>
</tr>
<tr>
<td>CIN3 or above</td>
<td>0.75 (0.08-6.74) 0.579</td>
<td>7.99 (1.87-34.16) 0.001</td>
<td>1.12 (0.08-16.30) 0.931</td>
</tr>
<tr>
<td>Ever been pregnant</td>
<td>0.76 (0.57-0.98) 0.041</td>
<td>0.77 (0.58-0.99) 0.048</td>
<td>0.93 (0.18-4.98) 0.940</td>
</tr>
<tr>
<td>No. of deliveries</td>
<td>0.86 (0.73-1.01) 0.068</td>
<td>0.84 (0.73-0.95) 0.007</td>
<td>1.95 (0.97-3.94) 0.060</td>
</tr>
<tr>
<td>Sexual habits regular since onset</td>
<td>0.94 (0.73-1.22) 0.689</td>
<td>0.78 (0.62-0.97) 0.029</td>
<td>8.84 (1.09-71.64) 0.028</td>
</tr>
<tr>
<td>Partner’s good sexual hygiene (bide)</td>
<td>0.81 (0.56-1.17) 0.270</td>
<td>0.67 (0.48-0.94) 0.024</td>
<td>1.08 (0.26-4.41) 0.911</td>
</tr>
<tr>
<td>Ever had genital warts</td>
<td>1.08 (0.90-1.20) 0.588</td>
<td>0.93 (0.76-1.14) 0.502</td>
<td>2.33 (1.03-5.24) 0.045*</td>
</tr>
<tr>
<td>Previous CIN</td>
<td>1.08 (0.60-1.95) 0.789</td>
<td>1.44 (0.96-2.15) 0.081</td>
<td>5.62 (1.01-31.48) 0.033*</td>
</tr>
<tr>
<td>Previous Pap normal</td>
<td>1.01 (0.60-1.67) 0.985</td>
<td>0.56 (0.38-0.81) 0.002</td>
<td>1.45 (0.22-9.61) 1.000</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1.14 (0.86-1.50) 0.349</td>
<td>1.39 (1.09-17.8) 0.009</td>
<td>2.78 (0.83-9.27) 0.103</td>
</tr>
<tr>
<td>Cervical erosion treated</td>
<td>0.80 (0.60-1.06) 0.148</td>
<td>0.75 (0.59-0.96) 0.022</td>
<td>0.65 (0.15-2.77) 0.706</td>
</tr>
</tbody>
</table>

¹Age group with peak HR-HPV prevalence; ²Age groups with progressively declining HR-HPV prevalence; ³Age groups with sharply increasing HR-HPV prevalence; NC, non computable; *Pearson Chi-square.

Table 3. — Viral loads, individual HR-HPV* types, and physical state of HPV16 in the three groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Women under 25 years¹</th>
<th>Women between 26 and 55 years¹</th>
<th>Women over 55 years¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) p</td>
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</tr>
<tr>
<td>HPV positive (HCII test)</td>
<td>48.8% (522/1069)</td>
<td>24.5% (474/1938)</td>
<td>21.3% (17/80) 0.0001</td>
</tr>
<tr>
<td>Viral load HCII test***</td>
<td>207.4 (95% CI 177.0-237.7)</td>
<td>84.9 (95% CI 69.4-100.5)</td>
<td>120.8 (95% CI 31.3-210.2) 0.0001</td>
</tr>
<tr>
<td>HPV positive (TaqMan assay)</td>
<td>40.3% (420/1042)</td>
<td>26.6% (493/1856)</td>
<td>20.3% (16/79) 0.0001</td>
</tr>
<tr>
<td>Viral load¹(TaqMan assay):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV16</td>
<td>-0.90 (-1.49 -0.32)</td>
<td>-1.16 (-1.65 -0.68)</td>
<td>2.32 (-0.96-5.62) 0.070)</td>
</tr>
<tr>
<td>HPV18/45</td>
<td>-0.63 (-1.32-0.06)</td>
<td>-1.85 (-2.67-0.103)</td>
<td>0.88 (-53.4-55.22) 0.065)</td>
</tr>
<tr>
<td>HPV31</td>
<td>-1.21 (-1.97 -0.45)</td>
<td>-2.39 (-3.00 -1.77)</td>
<td>0.06 (-1.76-1.77) 0.100)</td>
</tr>
<tr>
<td>HPV33</td>
<td>0.98 (0.25-1.70)</td>
<td>0.51 (-0.25-1.27)</td>
<td>4.72 (-0.92-9.47) 0.204)</td>
</tr>
<tr>
<td>HPV35</td>
<td>1.12 (-1.09-3.34)</td>
<td>2.35 (-0.09-4.79)</td>
<td>NC 0.549)</td>
</tr>
<tr>
<td>HPV39</td>
<td>2.16 (1.04-3.28)</td>
<td>1.61 (0.37-2.86)</td>
<td>NC 0.464)</td>
</tr>
<tr>
<td>HR-HPV Types:</td>
<td>No. Per Cent</td>
<td>HPV+</td>
<td>No. Per Cent</td>
</tr>
<tr>
<td>HPV-negative</td>
<td>622</td>
<td>59.7</td>
<td>1363</td>
</tr>
<tr>
<td>HPV16</td>
<td>117</td>
<td>11.2</td>
<td>27.9</td>
</tr>
<tr>
<td>HPV18/45</td>
<td>61</td>
<td>5.9</td>
<td>14.5</td>
</tr>
<tr>
<td>HPV31</td>
<td>45</td>
<td>4.3</td>
<td>10.7</td>
</tr>
<tr>
<td>HPV33</td>
<td>51</td>
<td>4.9</td>
<td>12.1</td>
</tr>
<tr>
<td>HPV35**</td>
<td>2</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>HPV39</td>
<td>15</td>
<td>1.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Multiple</td>
<td>129</td>
<td>12.4</td>
<td>30.7</td>
</tr>
<tr>
<td>HPV16 Integration Status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episomal</td>
<td>112</td>
<td>50.3%</td>
<td>145</td>
</tr>
<tr>
<td>Mixed</td>
<td>100</td>
<td>44.8%</td>
<td>151</td>
</tr>
<tr>
<td>Integrated</td>
<td>11</td>
<td>4.9%</td>
<td>33</td>
</tr>
</tbody>
</table>

| Integration: |                       |                               |                       |
| Yes | 111 | 49.8% | 184 | 55.9% | 7 | 100.0% | 0.009 |
| No | 112 | 50.2% | 145 | 44.1% | 0 | 0.0% |

¹Integration load: 10.5 (95% CI 9.3-11.7) 17.5 (95% CI 11.3-23.7) 0.019

*HR-HPV types determined by real-time PCR (TaqMan) analysis; **HPV35 analysed in 1,500 samples only; ***HCII index values; #HPV-negative cases included; @HPV-negative cases excluded; Integration load in logarithmic scale; ²Kruskal-Wallis test; ³Log-transformed copy/cell values; NC, no cases.

College Station, TX, USA). To adjust for the differences in age distribution in the three NIS countries, we calculated age-standardised HR-HPV prevalence for 14 five-year age groups (15–84 years) of the European standard population [44]. Logistic regression modelling with a curve estimation procedure was used to assess the age profile in each three countries, by fitting a logistic regression model with either i) linear, ii) quadratic or iii) cubic terms for 14 five-year age groups. Curves with a significant (p < 0.05) quadratic term were classified as non-linear (U-shaped), those with significant cubic term as non-linear (bi-phasic or S-shaped), to distinguish from those with only a linear age term. All curve fit procedures were controlled by scatter plots, where the fit parameters (= predicted parameters) were plotted against the residuals.

Frequency tables for categorical variables were analysed using the chi-square test, with likelihood ratio (LR) or Fisher's exact test.
exact test for significance. Differences in the means of continuous variables were analysed using non-parametric tests (Mann-Whitney, Kruskal-Wallis) or ANOVA, after careful control of the normal distribution. Logistic regression was used to analyse the power of different covariates as predictors of the outcome variables (CIN2/3, HR-HPV), calculating crude odds ratios (OR) and 95% confidence interval (CI). Significant variables in univariate analysis were entered into the multivariate regression models to calculate adjusted ORs (95% CI). Con founding was also controlled by calculating the weighted-average of the stratum-specific estimates using the Mantel-Haenszel test for common OR (95% CI). In all tests, the values \( p < 0.05 \) were regarded as statistically significant.

Results

The age-standardised prevalence rate (ASPR) of HR-HPV infections was very similar in Russia (18.3/100 women; 95% CI, 16.6-19.9), and Belarus (17.2/100 women; 95% CI, 14.1-20.3), but in Latvia as high as 24.6/100 women (95% CI, 20.60-28.65).

In the whole cohort, the HPV prevalence curve was clearly U-shaped, steadily declined from 55.6% among women < 20 years of age, down to 10.1% among those aged 51-55 years, followed by a deep increase among women > 55 years (Figure 1). In the whole cohort, the F statistic for model fit was significant both in the linear and quadratic equation (\( p = 0.0001 \), but substantially higher (\( R^2 = 0.966 \)) for the quadratic model (U-shape curve) than (\( R^2 = 0.809 \)) for the linear model. In the curve of Russia, the results mimic those for the whole cohort; \( R^2 = 0.806 \) for the linear model and \( R^2 = 0.968 \) for the quadratic model (\( p = 0.0001 \) for both). In the curve of Belarus, there was not much difference between the linear and quadratic models; \( R^2 = 0.952 \) and \( R^2 = 0.995 \), respectively. The age-specific HPV curve of Latvia showed the least obvious linearity and the most accentuated second peak; \( R^2 = 0.647 \) for linear and \( R^2 = 0.915 \) for the quadratic model.

These three groups differed at the \( p = 0.0001 \) level with regard to the majority of the recorded epidemiological variables (Table 1). Many of these variables can be directly explained by the age difference between the three age categories. On the other hand, however, there are some interesting variables that do not show any difference between the three groups; e.g., history of skin and genital warts, time since the last Pap smear, previous Pap normal, and ever had cervical erosion.

Of the determinants of HR-HPV infection in the three groups, patient category was significant only in the two groups of younger women, but not among the older ones (Table 2). HSIL Pap predicted HR-HPV only in the two older groups, whereas the CIN3 cut-off was a significant predictor only in women between 25-55 years of age. The same holds true with the number of deliveries, which had a protective effect among this age group (a surrogate of regular family life?). A history of previous CIN was significant only among the older women (OR = 5.62; 95% CI, 1.01-31.48).

HPV prevalence was highest among the youngest age groups, but not significantly different between the two older ones, either in HCII or TaqMan assay (Table 3). The quantitative viral loads for HPV16, 18/45, 31 and 33 were markedly higher among the older women. The most interesting is the curve of HPV16 loads, as shown in Figure 2. It shows the best fit with the cubic model (\( R^2 = 0.714 \)), resulting in a distinct biphasic S-shaped curve (Figure 3), with a sharp second rise among women > 50 years.

The distribution of individual HPV types was significantly different among the three age categories (Table 3). As compared with the youngest age groups, there was a marked shift from multiple-type infections (from 30.7% to 6.3%) to the accumulation of HPV16 (37.5% of HPV+ cases) and HPV31 (31.3%) among the older women. There was a transition from episomal to mixed and integrated state from the youngest age groups to the women over 55 years, in whom, all HPV16 positive lesions
showed viral integration ($p = 0.009$). Similarly, the viral load of integrated HPV16 was significantly higher (17.5) in the older women, as compared with the two other age categories, with practically identical loads of integrated HPV16.

There was no difference in the clinical course of the cervical disease as determined by the repeated Pap tests (Table 4). In contrast, the outcome of HR-HPV infections was significantly different between the three groups. As compared with the age group 26-55, in which a sharp decline of HR-HPV prevalence was characteristic (Figure 1), women over 55 years of age show i) higher proportion of incident infections, ii) higher rate of viral persistence, and particularly iii) lower rate of HR-HPV clearance ($p = 0.0001$).

**Discussion**

As emphasised in a recent editorial on this subject (35), several key questions await clarification to explain the observed increase in HPV prevalence among older women [19-22, 24-28]. These unanswered questions are: 1) Is the increased prevalence among elderly women due to i) viral persistence, or ii) acquisition of new infections? 2) How much of this increase is attributable to the cohort effect? 3) What is the role of changing sexual habits and other risk factors by age as determinants of acquisition or persistence of HPV infections? 4) Are the age-related differences between oncogenic- and non-oncogenic HPV types a potential cause of these differences? 5) Is there an age-dependence of other viral factors, particularly i) viral load, and ii) viral integration, and what is their contribution to increased prevalence among older women? 6) What is the influence of early (i.e., intrauterine, perinatal or early childhood) HPV exposure on the subsequent risk of HPV persistence in adult age? 7) Are there any age-specific differences in the outcome (persistence, progression, clearance) of HPV infections? In the present study, we provide answers to most of these questions, except for no. 6, which is being explored in our ongoing study on HPV transmission within families [45].

The age-specific prevalence curve for the entire cohort from the three different NIS countries was shown to be clearly U-shaped. This U-shaped curve fits almost perfectly (96.6%) with the quadratic model in logistic regression. This observation is consonant with the data reported in several other populations [19-22, 24-28]. However, the shape of these age-specific prevalence curves differed substantially among the three neighbouring countries. While the linear model fits best (95.2%) with the age-specific curve of Belarus, the quadratic model (U-curve) shows by far the closest fit in the two

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**Figure 1.** — Age-specific prevalence of HR-HPV infections in the three NIS countries.
others. Such a declining linear curve has been reported for a variety of populations in other geographic regions [29-34].

As to the implicated cohort effects [22, 35], our three birth cohorts (women born after 1974; those between 1973-1945; and those between 1914-1944) differed at the p = 0.0001 level with regard to the majority of the recorded epidemiological variables, including the patient category, Pap smear abnormalities and CIN lesions in the biopsy. These data clearly confirm that women born before 1945 did demonstrate a sexual behaviour and other risk factors markedly different from women born after 1974. Women between 26 and 55 years of age fall between these two extremes in many of the recorded variables, and it is frequently difficult to visualise whether they are closer to their younger or older counterparts. Yet, the age-specific HPV profile in these three groups was completely different. Our results lend support to the concepts discussed recently by Winer et al. [35], as to i) the different sexual habits in different birth cohorts (Table 1), and ii) the role of these divergent risk factors as determinants of HR-HPV among the different age groups. There was not a single predictive variable common to all three age categories, and few such predictors that were significant even in two of these categories. However, we could not provide direct evidence to support the notion that changing a sexual partner later in life might be the reason for increased HPV prevalence [25, 35]. In fact, the number of recent (past 24 months) sexual partners was almost identical (1.53 vs 1.33) among women between 26 and 55 years and those > 55 years, respectively. Similarly, no previous data are available on the physiological state and integration load of HR-HPV types in different age groups [35]. Such age-dependence of HPV integration was first suggested by us, while detecting that women with purely integrated HPV16 were almost ten years older than those with episomal HPV16 [44]. This was fully confirmed in the present analysis, where the physical state of HPV16 was significantly different among the three age categories (p = 0.005). There seems to be a distinct transition from episomal to integrated state with progressing age, and in women > 55 years, all HPV16 positive lesions showed viral integration. Importantly, also the quantitative load of integrated HPV16 seems to be significantly higher in these older women as
Epidemiological, clinical and viral determinants of the increased prevalence of high-risk human papillomavirus (HPV) infections etc.

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Acknowledgements

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References


compared with the two other age categories (p = 0.009). This implicates that not only is viral integration increased, but also the load of the integrated virus is of different order of magnitude among the women > 55 years.

Finally, we demonstrated that the outcome of HR-HPV infections is significantly different between the three age categories. As compared with the age group 26-55 years, characterised by a sharp decline in HR-HPV prevalence, women over 55 years of age showed: i) higher proportion of incident infections, ii) higher rate of viral persistence, and particularly, iii) significantly lower rate of HR-HPV clearance. All this contributes to the fact that the prevalence of HR-HPV (21.3%) among women above 55 years is almost similar to that (24.5%) of the 26-55-year age group.

The present study casts more light on most of the unanswered questions to explain the differences in the age-specific prevalence of HR-HPV infections [35]. Accordingly, 1) the second peak in prevalence among women over 55 years seems to be equally contributed to by i) an increased viral persistence, ii) acquisition of new infections, and iii) decreased clearance of these infections. As to 2) the possible cohort effect, our data implicate that women born before 1945 did demonstrate a sexual behaviour and other risk factors markedly different from the women born after 1974. There is little doubt that 3) these changing sexual habits and other risk factors by age contribute to the different age-specific prevalence of HR-HPV infections. The present study fully confirmed 4) the age-dependence of the viral factors, i.e., i) type prevalence (shift from multiple- to single-type), ii) viral load, and iii) viral integration as explanatory factors of increased prevalence among the older women.

Taken together, the present results feasibly explain what was suggested by our in vitro studies some years back [42, 43, 46]. The rapid acquisition of HR-HPV infections after onset of sexual activity [12, 15] leads to an early peak of both HR-HPV prevalence and viral loads between 20 and 25 years of age. This is followed by a constant clearance (reduced viral loads) [13, 15] of the infections between 25 and 55 years of age. In women > 55, a sharp increase in both HPV prevalence and viral loads follows, shown by the U-shaped and S-shaped age-specific curves, respectively. These data implicate that in women who fail to eradicate their HR-HPV infection by menopause, selection of an integrated viral clone has likely taken place, driving the process towards an aggressively progressing disease. Consequent to this, most of the HR-HPV infections in women older than 55 years were associated with high-grade CIN or invasive carcinoma in the present cohort.
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Comparison of conization and limited excision of the transformation zone (LETZ) in the treatment of squamous intraepithelial lesions (SIL) of the uterine cervix

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Summary

Objective: To compare the treatment of squamous intraepithelial lesions of the uterine cervix using conization with limited excision of the transformation zone (LETZ).

Material and Methods: A retrospective study of 285 women who received surgical treatment for cervical SIL between 2003 and 2006 was carried out. Prior to treatment, all the women underwent cervicovaginal cytology, colposcopy, and HPV testing. The women whose histology showed the presence of high-grade SIL were then divided into two groups for purposes of comparison: those treated by conization, and those treated by LETZ.

Results: In group 1 (treatment by conization), 92 women met the selection criteria, and in group 2 (treatment by LETZ) 33 women met the selection criteria. Histology results showed high-grade SIL involvement of the cone biopsy surgical margins for 22 cases (23.9%) in group 1, and high-grade SIL involvement of the LETZ surgical margins for six cases (18.1%) in group 2. In 13 of the women in group 2, the indication for LETZ was persistent low-grade SIL.

Discussion: The percentage of surgical margins involved was similar in the two groups in our study, and comparable to that reported in the literature (16.2 to 26.6%). Our study, like other published studies, thus supports the possibility in certain cases of treating high-grade cervical SIL conservatively with LETZ or minicones. In the 13 women with a diagnosis of persistent low-grade SIL, 11 of whom (84.6%) were infected with a high-risk HPV genotype, LETZ made a diagnosis of occult high-grade SIL.

Conclusion: LETZ may be an alternative to conization in young women, and it is advisable in cases of persistent low-grade SIL with high-risk HPV infection.

Key words: Conization; LETZ; SIL; Human papillomavirus.

Introduction

In 1989, Prendiville et al. [1] introduced the use of the diathermy electrode into the treatment of high-grade SIL. Subsequently, other authors have confirmed its efficacy in treating high-grade SIL by comparison with cold-knife biopsy [2, 3], which until the introduction of large loop excision was considered the standard treatment [4].

The prevalence of high-grade SIL has increased in recent decades [5]. This development may be a result of an increase in human papillomavirus (HPV) infection and other risk factors (earlier initiation of sexual relations, tobacco use, and HIV infection). It has also been observed that high-grade SIL is appearing more often in younger women, who then become candidates for treatment by conization, with the negative repercussions this may have later on for their reproductive lives (higher risk of spontaneous abortion and preterm delivery) [6-8].

In this study, we compared the standard treatment for high-grade cervical SIL by large loop excision of the transformation zone (LLETZ) with limited excision of the transformation zone (LETZ) also performed with a diathermy electrode.

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Results

Of the 285 women surgically treated for SIL, 161 were treated by conization, but only 92 of these met the selection criteria of treatment by LLETZ and histological confirmation of the presence of high-grade SIL. Prior to conization, 61 (66%) of these women also underwent a colposcopically guided biopsy that yielded a diagnosis of high-grade SIL. These 92 women constituted group 1.

Group 2 was comprised of women who had undergone LETZ. Of the 102 LETZ procedures performed, 33 cases met the inclusion criterion of histological confirmation of the presence of high-grade SIL. The indications for LETZ in these patients were as follows: discordant cytology results in 18 cases, in some of which high-grade SIL was also present but not confirmed by colposcopically guided biopsy; a diagnosis of persistent (longer than 1 year) low-grade SIL confirmed cytologically and/or by colposcopically guided punch biopsy; and in two cases a colposcopically guided biopsy confirmed the presence of high-grade SIL.

In the first group (treated by LLETZ) histological study revealed involvement of the surgical margins in 22 cases (23.9%), as compared with six cases (18.1%) of involvement of surgical margins in group 2 (treated by LETZ).

A detailed analysis of the 22 cases in group 1 treated by LLETZ shows that a second conization was performed in eight cases, of which six resulted in a diagnosis of high-grade SIL. In eight cases a hysterectomy was performed, in four of which a high-grade SIL lesion was found. In the two cases in which LETZ was performed the results were negative. In the four cases in which the cytology, colposcopy and biopsy results showed no high-grade SIL, we opted for follow-up only. Involvement of the surgical margin was confirmed in only 10 cases (45.5%) of the 22 women.

In group 2, conization was performed on four of the six women with positive surgical margins, and high-grade SIL was found in only one case. One hysterectomy was performed, with a negative result for high-grade SIL. In one case in which the cytology and colposcopy results were negative, we opted for follow-up only. High-grade SIL involvement of the surgical margin was found in only one case (16%).

In group 1, high-risk HPV infection was detected in 90.2% of cases, and the most frequently isolated genotype was type 16 (40.9%). In 19 cases (22.8%) more than one genotype was detected. In group 2, 90.9% of the women were infected by a high-risk HPV genotype, most frequently type 16 (46.6%), and nine cases (30%) were infected by more than one genotype.

Discussion

As other studies reported in the literature have observed [9, 10] the presence of high-grade SIL is significantly related to HPV infection, especially by high-risk genotypes. This was the case for both groups in our study, in which the incidence of HPV infection was 90.2-90.9%, similar to that observed in these studies (92.2-93.3%).

The percentage of high-grade SIL cases in which there was involvement of the surgical margins is reported in the literature as ranging from 16 to 26.6% [11, 12]. In our study, this percentage was 23.9% for group 1, although subsequently it was confirmed in only 10.8%. This percentage is similar to that observed in group 2 (treated with LETZ): involvement of surgical margins in 18.1% of cases, and confirmation of only one case of high-grade SIL in the remaining cervical tissue in 3% of cases.

These data suggest that treatment of high-grade SIL by LETZ may be sufficient, especially in young women who wish to have children, without a significant increase in the number of cases in which the surgical margins of the cone biopsy are involved. This result was observed by Mints et al. [13] using a miniconization procedure individualizing the size of the cone and limiting excision to the transformation zone. They report a 12% rate of incomplete resection of the lesion in cases of grade 2 cervical intraepithelial neoplasia (CIN II), and 17% in women diagnosed with CIN III.

It is also important to note that in the 13 cases in group 2 with a diagnosis of persistent low-grade SIL, the LETZ procedure detected occult high-grade SIL not found by cytology screening, colposcopy or biopsy. In these 13 women, 11 (84.6%) cases of infection by a high-risk HPV genotype were identified. This finding confirms the need to treat women with persistent low-grade SIL, especially when associated with infection by a high-risk HPV genotype, using non-destructive techniques to make a histological diagnosis [12]. LETZ offers the advantage that it can be performed on an outpatient basis and is associated with lower morbidity [12, 14].

In conclusion, LETZ may be an alternative to LLETZ in young women who plan to have children, and it is advisable for women with persistent low-grade SIL and high-risk HPV infection, in order to rule out occult high-grade SIL.

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Estrogen receptor α and β expression in a case matched series of serous and endometrioid adenocarcinomas of the ovary

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Summary

Objective: The purpose of this study was to analyze estrogen receptor α and β (ERα, ERβ) expression in a stage and grade matched cohort of patients with serous and endometrioid adenocarcinoma of the ovary. Methods: Forty-two patients from 1991 to the present were found to have the diagnosis of endometrioid adenocarcinoma of the ovary and have tissue available for analysis. Of these 42, ten were selected for analysis. These were stage and grade matched with ten patients having serous adenocarcinoma of the ovary during the same time period. ERα and ERβ mRNA was detected by a multiplex RT-PCR and amplification of random hexamer generated cDNA using a housekeeping gene (G3PD) as a control for mRNA quality and quantity. Methylation specific PCR (MS-PCR) was used to correlate methylation of the ERα and ERβ CpG islands with mRNA expression status. Results: ERα expression was present in ten of ten endometrioid adenocarcinomas but in only five of ten serous carcinomas (χ², p = 0.01). ERβ expression was present in six of ten endometrioid adenocarcinomas and in four of ten serous carcinomas (χ², p = 0.65). Methylation of the ERα and ERβ CpG islands was found in tumors without mRNA expression but not in the tumors with mRNA expression (p = 0.005). Conclusions: ERα expression, but not ERβ expression, is significantly more common in endometrioid than serous adenocarcinomas of the ovary when controlled for stage and grade. The role of methylation in ER silencing may lead to potential therapeutic interventions.

Key words: Methylation; Estrogen receptor; Ovarian cancer; Serous; Endometrioid.

Introduction

In the United States, ovarian cancer is the most deadly of all gynecologic malignancies accounting for only 4% of newly diagnosed cancers annually, but 5% of deaths from cancer in women. In 2003 alone, an estimated 25,400 women were diagnosed with ovarian cancer and 14,300 would die from their disease [1]. More and more of the basic biology of these deadly cancers is beginning to be understood.

Histologically, multiple subtypes of epithelial ovarian cancer exist. Although it is somewhat controversial as to whether certain subtypes have different prognoses, it is believed that different histologies have different genetic alterations [2, 3, 4]. Buller demonstrated that clear cell carcinomas have a higher rate of BRCA2 dysfunction than is present in other ovarian cancers [4]. Others have shown that significant differences in p53 overexpression occur among serous, endometrioid, and clear cell carcinomas [5, 6]. In fact, some of these differences have led to the classification of clear cell carcinomas as “high-risk” [7].

The objective of this study was to look at the expression of both estrogen receptors (ERα and ERβ) in the tumors of women with endometrioid adenocarcinoma of the ovary and compare the results to a matched cohort of patients with serous carcinomas. A further aspect of the study was to try and determine if lack of expression was related to CpG promoter methylation.

Materials and Methods

This study was performed in accordance with the standards of our institutional committee for the Protection of Human Subjects. Patient selection was solely on the basis of the availability of snap frozen tissue for RT-PCR/cDNA amplification. Most of these tumors were 100% tumor with none being less than 90% tumor.

mRNA expression by RT-PCR

The techniques for RNA isolation and cDNA synthesis by RT-PCR were as previously described starting from snap frozen tumor samples stored at −140°C [8]. Failure to amplify a product in the cDNA reactions (despite appropriate amplification of a housekeeping gene sequence such as glycerol 3-phosphate dehydrogenase [G3PD]) provided candidate tumors where epigenetic phenomenon including promoter silencing may be operational. ERα and ERβ were amplified in a multiplex reaction [9]. A buffer with increased magnesium concentration (6.7 mM MgCl₂) [10] was used with 20 pMoles of the joint ERα/β forward primer and 10 pMoles of each reverse primer, 5 units, of Taq polymerase and 3 μl cDNA. G3PD expression was measured in a separate, concurrent reaction [11].

Methylation specific PCR

After EcoR1 restriction, methylation specific PCR (MS-PCR) was performed on NaHSO₃ converted DNA. The NaHSO₃ reaction has been previously described by Clark and others [10-14].
Succinctly, DNA (0.5-5 μg) was incubated first with 0.3 M NaOH at 37°C. The alkalized mixture was exposed to 3.6 M NaHSO₃, and 1 mM hydroquinone at 55°C for 14 hours before recovering the products and desalting with Promega® Wizard Prep (Promega®, Madison, WI). Desalting was performed per manufacturer’s recommendation except for the last elution in which 75°C deionized H₂O was incubated on the column at room temperature for 5 min before the final centrifuging. The solution was then incubated with 0.3 M NaOH at 37°C again before the addition of 3 M ammonium acetate and 95% ethanol. The mixture was next incubated at -20°C for 20 min and then centrifuged at 18,620 x g (4°C) for 30 min. The supernatant was removed, the DNA lyophilized, and finally re-suspended in 100 μl of ddH₂O.

MS-PCR for ERα and ERβ was carried out on the converted DNA using the primers and conditions described previously [15, 16]. Both the ERαA and ERβB regions were examined. The same buffer used for the multiplex PCR was used for all MS-PCR reactions [10]. CpGenome™ - Universal Methylated DNA (Intergen Company, Gaithersburg, MD) was used as the methylated control after NaHSO₃ conversion. Non-neoplastic ovarian tissues corresponding CpG island.

expression did correlate with methylation of the corresponding CpG island.

Discussion
Down-regulation of ER expression has been shown to be correlated with methylation in the promoter site [17, 18]. In ovarian cancer cell lines, methylation of the ERα promoter was only shown in tumors not expressing ER [19]. Methylation has been shown to be a common cause of gene down-regulation or lack of expression in ovarian malignancies [20-22].

Li and colleagues demonstrated that multiple alterations in steroid receptors are present in ovarian cancer cell lines [23]. The differences were more apparent in estrogen receptor subtypes than in progesterone receptor subtypes.

Although stage-matched endometrioid and serous carcinoma patients have equivalent five-year survivals, studies have shown different rates of gene expression and/or gene defects [2, 24]. Geisler et al. has shown that in optimally cytoreduced Stage IIIc serous ovarian carcinoma patients, decreased ER status was correlated with increased survival [25].

In this series, stage-matched controls demonstrated different expression of both ERα and β. ERα and β expression was much more common in endometrioid carcinomas than in serous carcinomas of the ovary. This correlates with what has been previously shown by immunohistochemical staining [25]. CpG promoter island methylation occurred in the promoter region in genes that were not expressed but not in the promoters of genes that were expressed.

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Results
Forty-two patients with endometrioid adenocarcinomas of the ovary were found to have banked frozen tissue. Ten of these samples were randomly chosen and then matched by stage and grade with the tumors from ten patients with ovarian serous carcinoma (Table 1). No peritoneal or fallopian tube carcinomas were used.

ERα expression was present in ten of ten endometrioid adenocarcinomas but in only five of ten serious carcinomas (χ², p = 0.01). Using MS-PCR, methylation of the A and B promoter regions was demonstrated in all samples not expressing ERα.

ERβ expression was present in six of ten endometrioid adenocarcinomas and in four of ten serious carcinomas (χ², p = 0.65). Methylation of the ERβ CpG island was found in tumors without mRNA expression but not in the tumors with mRNA expression (p = 0.005).

No correlation between stage, and ERα or ERβ expression could be demonstrated however the series was small. When looking at both histologies, loss of ERα or ERβ expression did correlate with methylation of the corresponding CpG island.

Table 1. — Clinical characteristics of matched patients.

<table>
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Histologic grade

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NS = not significant

References


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Uterine sarcoma: a report of 57 cases over a 16-year period analysis

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Summary

Uterine sarcomas comprise approximately 4-9% of all uterine malignant tumors with a poor prognosis. We report 57 cases of sarcoma originating in the uterus treated from 1990 to 2006 at the Department of Obstetrics and Gynecology of Democritus University of Thrace, Greece and the Department of Obstetrics and Gynecology of Aschaffenburg Hospital, Germany. The median age of occurrence was 49 years with the commonest symptom being abnormal uterine bleeding. Forty-nine patients underwent a total hysterectomy and bilateral salpingo-oophorectomy whereas 17 cases underwent radical lymphadenectomy. During the last follow-up (December 2006), six patients were alive and well with no evidence of disease, 23 patients had died of undercurrent disease, and 28 were alive with recurrence of disease. These rare cancers can be aggressive, and account for a greatly disproportionate number of deaths from uterine cancers. Treatment for this rare disease should be performed according to international protocols in order to have the most updated information.

Key words: Uterine sarcoma; Surgical; Postoperative treatment; Follow-up.

Introduction

Cancer of the uterine corpus accounts for about 6% of cancers in women [1]. Uterine sarcomas are extremely rare and comprise approximately 4-9% of all invasive uterine cancers and account for less than 3% of all female genital tract malignancies [2,3]. In various studies the average incidence of the three main histological sarcoma-subgroups, respectively, were reported as 41.7%-50% for leiomyosarcoma (LMS), 30% for mixed müllerian tumors (MMT), 7-15% for endometrial stromal sarcoma (ESS) and about 5% for others [4-6]. The last group includes liposarcoma, rhabdosarcoma and fibrosarcoma. LMS, which comprises only 1% of gynecologic malignancies, has a notoriously poor prognosis [7]. In contrast to MMT, which contains both epithelial and mesenchymal elements, LMS occurs almost always as a pure homologous tumor. Rarely, heterologous leiomyosarcomas such as rhabdomyosarcoma, osteogenic sarcoma, and chondrosarcoma of the uterus have been described [8]. Endometrial stromal sarcomas are rare uterine malignancies accounting for less than 1% of all uterine cancers [9]. ESS is characterized by cells that resemble those of the endometrial stroma during the proliferative phase of the menstrual cycle and have traditionally been classified as either low-grade or high-grade. Low-grade ESS is generally a slow growing malignancy with an indolent clinical course, but with a tendency for late recurrences. Pure uterine sarcomas of the homologous type arise from native elements, as in endometrial stromal sarcoma and leiomyosarcoma. A mixed müllerian tumor has histologic features of carcinoma and sarcoma. MMT with an incidence of 1.5% of all malignant diseases of the uterus is a rarity among the malignancies of the female genital tract [10]. Primary locations of MMT may be the endometrium, the cervix and the ovary. Development of endometrial hyperplasia, endometriosis, endometrial polyps and endometrial adenocarcinomas has been described [11]. All sarcomas carry a poor prognosis with an overall survival of less than 50% at two years, even when presenting at an early stage [12].

Approximately 33% of patients seen are already in advanced stages of disease [5], and distant metastases are frequent. The rarity of these tumors as well as their pathologic diversity, has made it difficult to define optimal management. This study analyzes retrospectively the treatment results of adjuvant radiotherapy and chemotherapy after the initial surgical investigation.

Materials and Methods

This is a retrospective study of women during the time period 1/9/90-31/12/06, who were treated at the Department of Obstetrics and Gynecology of Democritus University Alexandroupolis, Greece and the Department of Obstetrics and Gynecology of Aschaffenburg Hospital, Germany. Data were extracted by chart review that included patient information. The following variables were included: age, menopausal status, family history of cancer, histological subtype, tumor stage, tumor grade, operative procedure, adjuvant radiotherapy, adjuvant chemotherapy, disease-free survival, site of recurrence and current disease status. A pathologist at each institution reviewed the histopathology at the time of surgery. We received the final histological diagnosis a few days postoperatively. All patients in both institutions had primary sur-
gical management. The main indication for surgery was uterine myoma. Other indications for surgery were history of abnormal bleeding and recurrent abdominal pain despite conservative treatment. Patients with any abnormality such as bleeding or atypical smears were evaluated histologically. Total abdominal hysterectomy with bilateral salpingo-oophorectomy is the gold standard for the surgical procedure of uterine sarcoma in cases of tumor limited to the uterine corpus. The surgical procedures were removal of as much tumor as possible in cases with pelvic and/or abdominal spread. Omentectomy was performed and any suspiciously enlarged lymph node was biopsied when malignancy was recognized pre- or intraoperatively. The records of 57 patients treated postoperatively were examined retrospectively.

All patients had regular follow-up visits until the end of the study and were evaluated with a mean follow-up of 48 months. During the first year the patients were followed up at three-month intervals, and then at six-month intervals. Pelvic examination, abdominal and vaginal ultrasonography, and serum CA125 determination were performed at each check-up, and in case of any suspicion of recurrence or metastasis, magnetic resonance imaging (MRI) was carried out. The clinical course of the disease was recorded from the patients’ notes by three independent clinical physicians. Follow-up for all surviving patients ranged a minimum of three months postoperatively to a maximum of 13 years with a median follow-up observation time of three years (SD 3.714). All examined study parameters (pre- and intraoperative) were retrospectively analyzed and correlated with recurrence and survival-rate.

Results

A total of 57 women with uterine sarcomas (Group A = 8 from Alexandroupolis hospital and Group B = 49 from Aschaffenburg hospital) were identified during the period from 1/9/1990 to 31/12/2006. The characteristics of the 57 subjects are presented in Table 1. The mean age was 51.14 ± SD 11.682 years (range 30-81 years). The mean parity of the women was 1.73 ± SD 1.027 (range 0-4). None of the women was receiving hormone replacement therapy (HRT) nor had had any gynecological malignancy in the past. Although no prior malignancies had occurred in our patients and none had a family history of gynecological cancer, endometriosis was surgically documented in two cases. Five patients had severe medical conditions such as heart, pulmonary or renal disease. Two cases had had a cerebral insult nine years before and diabetes mellitus for 20 years. In the study patients, LSM cases accounted for 33 (57.89%), MMT cases for 17 (29.82%), ESS for six (10.53%) and other sarcomas and angiosarcoma one case (1.75%).

Table 1. — Patient characteristics and presenting symptoms.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Mean ± SD, Range</th>
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<tr>
<td>Age</td>
<td>51.14 ± 11.68 (30-81)</td>
</tr>
<tr>
<td>Parity</td>
<td>1.73 ± 1.02 (0-4)</td>
</tr>
<tr>
<td>Mass</td>
<td>51.45 ± 30.27 (17-115)</td>
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<table>
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<tr>
<th>Presenting symptoms</th>
<th>Frequency</th>
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<tr>
<td>Abnormal vaginal bleeding</td>
<td>80.7% (46/57)</td>
</tr>
<tr>
<td>Pelvic mass</td>
<td>14.03% (8/57)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.26% (3/57)</td>
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</table>

The most common presenting symptom was abnormal vaginal bleeding, occurring in 46 patients (80.7%). Other features such as a vaginal ultrasound of a pelvic mass and recurrent abdominal pain were observed in eight (14.03%) and three (5.26%) patients, respectively (Table 1). The masses were located in the uterine wall (n = 5) and three presented as a polypoid mass penetrating the endometrial cavity from the myometrium. In all patients myomas were detected preoperatively at clinical and vaginal ultrasound examination. By mass we refer to the largest length of the tumor involved. The mean mass length was 51.45 ± 30.27 range (17-115). Most of the uterine myomas showed several calcifications at ultrasound and were always associated with sarcoma. Especially concerning vaginal bleeding, hypermenorrhoea occurred in 33 cases (33/46, 57.89%), metrorrhagia in nine cases (9/46, 19.56%) and spotting in the last four (4/46, 8.69%). Fractional curettage was performed in all patients (46) with abnormal uterine bleeding. Histological diagnosis was made through fractional curettage in 15 patients (32.7%). In the other 31 (67.3%) sarcomas were diagnosed by hysterectomy.

Forty-nine patients underwent total abdominal hysterectomy and salpingo-oophorectomy, and in 17 cases with advanced disease pelvic lymphadenectomy and omentectomy were performed. In five of them paraaortal lymph node sampling was carried out. In these 17 radically operated (FIGO Stage I/II) patients, three patients with ESS (FIGO Stage II) and two with MMT (FIGO Stage I) had lymph node metastases. One patient with MMT (FIGO Stage III) had lymph node and ovarian metastases in both ovaries and another case with ESS (FIGO Stage III) had omental metastases. In four women (30-36 years) the surgical procedure was only total hysterectomy without salpingo-oophorectomy. The remaining four cases with FIGO Stage III were treated with subtotal hysterectomy, salpingo-oophorectomy and biopsy of the pelvic tumor mass. According to FIGO classification, Stage I, II, and III tumors were identified in 51, four, and two patients, respectively. The classification of uterine sarcomas, histological type, tumor stage and histological grade are shown in Table 2. Thirty-five patients (61.40%) were postmenopausal. No statistically significant correlation was found concerning menopausal status nor any of the patients’ characteristics (histological type, stage, grade of sarcomas (Table 3). The frequency of tumor histological type concerning menopause is shown in Table 4. Adjuvant treatment with radiotherapy was administrated in 52 cases. Chemotherapy was used with consistency for adjuvant therapy in 36 patients. No
additional treatment was recommended in three patients because they had other severe diseases. Two patients with Stage I sarcoma refused treatment. After three and five years, recurrence rates of 54.54% and 70.96%, respectively, were recorded for patients who had received postoperative radiation, no adjuvant treatment and adjuvant chemotherapy (Tables 5 and 6). The results of correlation between tumor recurrence and the following parameters: tumor-stage, grade, histological type, treatment and CA125 values are presented in Tables 5 and 6. Serum samples were analyzed for CA125 and the results were correlated to the course of the primary disease. The values of CA125 correlated positively in observed patients (total 31) with recurrence of the disease especially in histological subtype MMT (6/9 = 66.6%). From eight study patients sera were not available at the exact follow-up time but rather two months later. At the time of final analysis, 40.35% of patients (23/57) had died due to progressive sarcoma disease; 49.12% (28/57) were alive with disease recurrence and 10.52% (6/57) were alive without evidence of disease. At the same time 64.28% of the patients had an isolated local recurrence (18/28) and 35.71% (10/28) pelvic recurrence with distant metastases. Three patients recurred after seven months. In a total of 15, recurrence was limited to the pelvis. Metastatic disease was detected in ten patients; four had pulmonary metastases, four in the abdomen, one in the brain and one in the spine, respectively. Recurrent disease in the pelvis was treated by combination chemotherapy and surgery, while in cases of distant metastatic diseases only chemotherapy was used. In one case recurrence in the vulva was treated with external local radiotherapy only. The small number of patients does not permit statistical analysis of individual grades. Overall survival for the 57 patients was 70.17% at three years and 38.7% at five years (Tables 7 and 8). With respect to histology, ESS predicted the worst prognosis, followed by MMT and LMS with a survival rate at five years of 0%, 22.22%, and 52.63%, respectively (Table 8). After treatment no second

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<th>B</th>
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<tr>
<td>III</td>
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<tr>
<td>3</td>
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<th>2</th>
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<tbody>
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<td>40.0%</td>
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<tr>
<td>Radiation Therapy + Radiotherapy</td>
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<th>66.6%</th>
<th>2</th>
<th>33.3%</th>
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<td>&gt; 30 Uml</td>
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<td>20.0%</td>
<td>4</td>
<td>80.0%</td>
<td>5</td>
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Table 4. — Frequency of histological type to menopause. A: Premenopausal 22: 38.5%; B: Postmenopausal 35: 61.40%.

Table 5. — Recurrence rate at 3 years by histological type, stage and grade. A) Recurrence negative 5 (45.46); B) Recurrence positive 6 (54.54%).
malignancy has been reported in our series. When we compared postoperative treatment versus no adjuvant treatment, we observed that postoperative treatment (radiotherapy or radiotherapy + chemotherapy) did not improve local recurrence, and it did not give any long-term survival benefit (Tables 7 and 8).

Discussion

Up to 30% of women with leiomyomas will experience abnormal uterine bleeding [13]. The most common pattern is menorrhagia, although other abnormal bleeding patterns may also be seen. The reason why uterine myomas cause abnormal bleeding is essentially unknown, although there are several theories that have been offered as an explanation [14]. Leiomyosarcomas represent neoplasms that arise entirely independently from benign leiomyomas. Further, there is no evidence that women with uterine myomas are at increased risk for this malignant neoplasm. Therefore, labelling leiomyosarcoma as a misnomer. Most leiomyosarcomas occur later in life (the fifth or sixth decade) than benign myomas [15]. Abnormal uterine bleeding and rapid growth of the uterus in a postmenopausal woman are the typical initial features. Abdominal pain and uterinethelargement may occur [15, 16]. As previously noted, these neoplasms are quite uncommon, particularly among women undergoing surgery for presumed leiomyomas [17]. Surgery has always been described as the most effective treatment in uterine sarcoma [18, 19]. Taking away all the tumor mass seems to optimize the chance of survival for patients with sarcoma. Removal of the ovaries is recommended in all cases despite tumor stage. Haberal et al. reported that retained ovaries had a recurrence rate of 100%, but the recurrence rate was 43% for patients who had oophorectomies at the initial surgery [20, 21].

Removal of the ovaries in young women is controversial. In our study no significant difference in recurrence rates in patients receiving surgery (3/7 = 2.5%) (salpingo-oophorectomy) versus total hysterectomy alone (2/5 = 40%) was noted. In cases of young women undergoing either removal of the ovaries or premature ovarian failure (in cases of retained ovaries) cryoconservation of the ovarian tissue is recommended to avoid a postmenopausal status.

Cryoconservation of ovarian tissue is currently proposed as an experimental alternative to oocyte and embryo freezing, in the hopes of restoring future fertility in young women before treatment with radiation or chemotherapy [22]. This procedure is a unique opportunity for young patients with malignant diseases to store their gametes before gomadotoxic treatments [23].

Surgical staging using the 1988 FIGO system for endometrial carcinoma was applied retrospectively. Clinical staging was based on clinical examination, fractional curettage and in recent years on MRI. Extirpative surgery is the primary treatment for patients with uterine sarcoma and may be curative in cases where the tumor is confined to the uterus. Unfortunately, the overall prognosis is poor regardless of the stage; the use of adjunctive therapy such as irradiation and chemotherapy in conjunction with hysterectomy does not appear to significantly alter the prognosis. Due to the high incidence of recurrence and poor prognosis of these tumors, they should be studied and managed by a multidisciplinary team composed of surgeons, oncologists, radiotherapists and pathologists. Radio- and chemotherapy are always administrated in the adjuvant setting. In advanced stages of the disease radio- and chemotherapy are the primary treatments. Berchuk et al. reported an overall survival of 22% with none of their patients with extraterine disease (Stages III and IV) surviving more than 20 months [24]. A higher survival probability is often reported for patients with low-grade endometrial stromal sarcoma [25]. In our study, 52 patients (91.22%) received radiotherapy as part of their primary postoperative therapy and 36 patients (63.15%) received additional chemotherapy either after the radio-

| Table 7. — Survival rate at 3 years by histological type, stage, grade and treatment. A) Alive 7 (70.17%); B) Dead 4 (29.82%). |
|-----------------|--------|--------|--------|
| Histological type | A      | B      |        |
| LMS             | 5      | 83.33% | 1      | 16.66% |
| MMT             | 2      | 50.00% | 2      | 50.00% |
| ESS             | 0      | 0.00%  | 1      | 100.00%|
| Other           | 0      | 0.00%  | 0      | 0.00%  |
| Stage |        |        |        |        |
| I    | 7      | 77.77% | 2      | 22.22% |
| II   | 0      | 0.00%  | 1      | 100.00%|
| III  | 0      | 0.00%  | 1      | 100.00%|
| Grade |        |        |        |        |
| 1    | 6      | 75.00% | 2      | 25.00% |
| 2    | 1      | 50.00% | 1      | 50.00% |
| 3    | 0      | 0.00%  | 1      | 100.00%|
| Treatment |        |        |        |        |
| No treatment | 0      | 0.00%  | 3      | 100.00%|
| Radiotherapy | 10     | 62.50% | 6      | 37.50% |
| Chemotherapy + Radiotherapy | 2     | 20.00% | 10    | 83.33% |

| Table 8. — Survival rate at 5 years by histological type, stage, grade and treatment. A) Alive 12/31 (38.70%); B) Dead 19/31 (61.29%). |
|-----------------|--------|--------|--------|
| Histological type | A      | B      |        |
| LMS             | 10     | 52.63% | 9      | 47.36% |
| MMT             | 2      | 22.22% | 7      | 77.77% |
| ESS             | 0      | 0.00%  | 3      | 100.00%|
| Stage |        |        |        |        |
| I    | 11     | 37.93% | 18     | 62.06% |
| II   | 1      | 50.00% | 1      | 50.00% |
| III  | 0      | 0.00%  | 0      | 0.00%  |
| Grade |        |        |        |        |
| 1    | 12     | 42.85% | 16     | 57.14% |
| 2    | 0      | 0.00%  | 3      | 100.00%|
| 3    | 0      | 0.00%  | 0      | 0.00%  |
| Treatment |        |        |        |        |
| No treatment | 0      | 0.00%  | 3      | 100.00%|
| Radiotherapy | 10     | 62.50% | 6      | 37.50% |
| Chemotherapy + Radiotherapy | 2     | 20.00% | 10    | 83.33% |
therapy or at the time of recurrence. The role of adjuvant radiotherapy in the treatment of uterine sarcoma is still unclear. Some authors have reported no benefit from postoperative irradiation [25-28]. Other studies confirmed the limited role of chemotherapy [29-32]. The benefit of chemotherapy by controlling subclinical distant disease is unproven and not generally accepted or recommended [33]. In our study the recurrence rate of the tumor after radio- or chemotherapy decreased compared to patients with no postoperative treatment (Tables 5 and 6). The length of time from the date of surgery to commencement of irradiation did not seem to affect outcome. We noted no major difference when patients within 30 days of surgery were compared with those of more than 40 postoperative days. Our experience with chemotherapy was very limited. In our patients the chemotherapy response was not determined by histological tumor type, stage or grade. During the chemotherapy diarrhea was only transitory. Survival rates for uterine sarcoma patients have been uniformly poor. Most series report a 5-year survival of 30-48%, which is in agreement with our study (12/31 = 38.7%) [34-37]. Our study emphasized stage and grade as prognostic factors but revealed age as the most important prognostic factor. This has also been confirmed in other studies [38-41]. Piver et al. reported an estimated 5-year survival rate of 36% in surgically treated patients with Stage I uterine sarcoma [42]. Gadducci et al. obtained a 5-year survival rate of 33% for 23 patients with early-stage uterine sarcoma, the majority of whom were treated with a combination of surgery and pelvic irradiation [43]. The recurrence rate in post-menopausal study women was less than that in pre-menopausal women (p = 0.01599) and is statistically significant. Age is often quoted as an independent prognostic factor. The recurrence rate was positively correlated with decreasing age (p = 0.0302). Histopathological classification (ESS) is positively correlated with recurrence rate and survival rate, but is not a statistically significant influencing parameter.

Histological tumor stage and grade lost statistical significance. Postoperative treatment was not significant when evaluated for local recurrence and survival rate. The frequent development of distant metastases is the main reason for the less favorable survival rates observed in uterine sarcoma compared with other uterine malignancies [44]. During the past few years, occasional cases of raised serum CA125 levels have been observed in patients with uterine sarcoma [45]. We confirmed in our series that elevated CA125 levels were related to the extent of the tumor, and high serum CA125 levels were observed in the majority of patients with recurrent or progressive disease of sub-histological type MMT.

Our study is limited by the relative rarity of the sarcomas. Due to the small patient number rigorous statistical analysis was not performed. In the absence of effective systemic treatment, we favor immediate surgery. Prospective multi-institutional studies are necessary to determine the optimal choice of therapy, both for primary disease and metastasis.

References


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Magnetic resonance imaging in the preoperative staging of endometrial carcinoma

S. Cabrita¹, H. Rodrigues², R. Abreu¹, M. Martins², L. Teixeira², C. Marques², F. Mota¹, C. Freire de Oliveira¹

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Summary

Purpose of Investigation: Magnetic resonance imaging (MRI) has emerged as an important imaging modality in the evaluation of the extension of endometrial carcinoma which is essential in planning treatment and predicting prognosis. This study aimed to assess the value of MRI in the preoperative staging of endometrial carcinoma. Methods: We included in this study 162 patients with a histological diagnosis of endometrial carcinoma who underwent MRI pelvic imaging and surgical staging. MRI images were compared with pathological findings to measure MRI's sensitivity, specificity, positive and negative predictive values and diagnostic accuracy in what concerns myometrial, cervical and lymph node invasion. Results: MRI differentiation of deep myometrial invasion from superficial disease agreed with pathological findings in 77% of cases, with a sensitivity of 83%, a specificity of 72% and a diagnostic accuracy of 77%. Concerning cervical invasion, MRI had a sensitivity, specificity and diagnostic accuracy of 42%, 92%, 81% respectively. In assessing lymph node invasion, MRI presented a sensitivity of just 17%, a specificity of 99% and a diagnostic accuracy of 89%. Conclusion: Our study confirmed the high accuracy of MRI imaging in assessing myometrial and cervical invasion in endometrial carcinoma. When evaluating lymph node invasion, micrometastases are responsible for the low sensitivity of MRI.

Key words: Magnetic resonance; Endometrial carcinoma; Preoperative staging; Surgical planning.

Introduction

Endometrial carcinoma is the most common gynecologic cancer and the fourth most frequent malignancy in women [1]. In Portugal, it has an incidence of 17.6/100,000 per year with a mortality rate of 3.4/100,000 per year [2]. Based on the inaccuracy of the clinical staging [3], the International Federation of Gynecology and Obstetrics (FIGO) proposed a surgicopathological staging adopted since 1988 [4]. Besides histological tumor grade, the prognosis is primarily correlated to tumor stage, for which the depth of myometrial and cervical invasion and the presence or not of lymph node metastases are essential [3]. In most institutions, patients with more than 50% of myometrial invasion are offered pelvic and paraaortic lymphadenectomy. Furthermore, cervical invasion also affects the extension of surgery. All these enlarged procedures have risks, namely resulting from increased time of anesthesia and increased blood loss [5]. Preoperative staging seems, therefore, essential in planning treatment, reducing surgery risks and predicting prognosis.

Magnetic resonance imaging (MRI) has emerged as an important imagiologic modality in the evaluation of the extension of endometrial carcinoma [6-9], showing to be important in assessing myometrial and, to a lesser extent, also cervical and lymph node infiltration.

Materials and Methods

Population: This study considered 183 women with a histological diagnosis of endometrial carcinoma by endometrial biopsy, who performed preoperative MRI. Given the extent of the disease, nine women were treated with chemotherapy or radiotherapy prior to surgery and were excluded from the study, as were three women with medical contraindications to surgery. Patients whose final histological diagnosis was not endometrial carcinoma were also excluded (3 with carcinosarcoma and 6 with leiomyosarcoma). Our population included, therefore, 162 patients with a mean age of 64.6 years (range 22-94 years), being mostly postmenopausal (91%).

Imagiologic investigation: All patients were imaged with a 1.5-T system prior to surgery. MRI was performed with axial T1-weighted images, axial and sagittal T2-weighted images and also dynamic gadolinium-enhanced T1-weighted imaging. Disease was staged according to imagiologic established criteria.

Surgicopathologic investigation: All women underwent hysterectomy. Lymph node dissection was performed when one of the following was present: histology of serous, clear cell or squamous carcinoma; differentiation grade 3; MRI evidence of cervical deep myometrial invasion. Histological examination revealed 146 (90%) endometrioid adenocarcinomas, seven (4.3%) serous carcinomas, four (2.5%) clear cell carcinomas, four (2.5%) adenocarcinomas with squamous differentiation and one (0.7%) mucinous carcinoma. Concerning histological differentiation, 120 (74%) were found to be grade 1, 37 (23%) grade 2 and 5 (3%) grade 3.
Data analysis: Pathology analyzed surgical specimens with no knowledge of MRI results. Both pathology and MRI classified the findings according to the International Federation of Gynecology and Obstetrics staging system for endometrial carcinoma.

MRI findings were compared with pathologic findings (regarded as the gold standard) concerning myometrial, cervical and lymph node invasion. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of each of those parameters was calculated.

Results

After comparing MRI findings with pathologic findings of the 162 cases, final results were achieved. Overall staging concordance was 44% (71/162) with 50 cases of understaging and 41 of overstaging. MRI staging of myometrial disease (inner or outer half) accurately assessed 62% of cases (100/162), overestimating 23% (38/162) and underestimating 15% (24/162). From the erroneously staged cases, 57% (35/61) were noted to have leiomyomata or adenomyosis disturbing uterine zonal anatomy. MRI differentiation between superficial disease (stages IA and IB) and deep myometrial invasion (IC) agreed with pathological findings in 77% (125/162) of cases, making the correct assessment in 72% of patients with less than half of myometrial infiltration and in 83% of patients with more than half of myometrial infiltration. Regarding this differentiation, MRI showed a sensitivity of 83%, a specificity of 72%, a PPV of 71%, a NPV of 84% and a diagnostic accuracy of 77%. Finally, we found a positive correlation between MRI findings and pathologic findings in characterizing myometrial invasion (p < 0.001).

Concerning cervical invasion (Stages IIA and IIB), MRI presented 15 true-positive, 116 true-negative, ten false-positive and 21 false-negative results. Analyzing this parameter, we found a sensitivity of 42%, a specificity of 92%, a diagnostic accuracy of 81%, a PPV of 60% and a NPV of 85%. From the 21 false-negative MRI results, 16 were histologically classified as IIA and only five as IIB, one of which with MRI reference to profuse cervical secretion.

In assessing lymph node invasion, MRI showed two true-positive, 90 true-negative, one false-positive and ten false-negative of the possible 103 comparable results as in 59 cases there was no surgical specimen. All 12 cases of histologic node invasion had a MRI staging with deep myometrial invasion. Considering lymph node invasion, MRI demonstrated a sensitivity of just 17%, a specificity of 99%, a diagnostic accuracy of 89%, a PPV of 66% and a NPV of 90%.

Overall, MRI sensitivity, specificity, diagnostic accuracy, PPV and NPV are depicted in Table 1.

Discussion

It is well known that treatment and prognosis of endometrial carcinoma depends greatly on tumor staging. Considering endometrial cancer treatment, pre-operative knowledge of the depth of myometrial invasion, the presence of cervical infiltration and lymph node invasion or disseminated disease has potential advantages as it should obligate to a pelvic and paraaortic lymphadenectomy, to a radical hysterectomy and eventually to adjuvant treatment. Also, a less invasive surgical technique (i.e., laparoscopy, vaginal approach) represents an option in early endometrial cancer. On the other hand, the prognostic value of tumor size, myometrial infiltration (essentially of the external half), cervical infiltration (cervical stroma) and lymph node metastasis has been established. Better presurgical assessment may contribute to the decreasing endometrial cancer morbidity and mortality by allowing optimization of the primary treatment. For planning treatment and drawing a prognosis, a preoperative work-up with an accurate staging seems fundamental.

In evaluating myometrial invasion, MRI has shown to offer a considerable higher sensitivity and specificity than transvaginal ultrasound or computed tomography, being the only modality to accurately assess cervical involvement. When multifactorial evaluation is required, MRI seems the only modality to accurately estimate myometrial, cervical and lymph node invasion [6, 11, 12]. Further, the accuracy and the cost of MRI have proven to be comparable to surgical staging with intraoperative uterine gross evaluation, also decreasing the number of unnecessary lymphadenectomies [7]. Without this last procedure, a decrease in patient morbidity and mortality should be expected as it is associated, for example, with increased time under general anesthesia or increased blood loss [5].

Our group evaluated the role of MRI in the preoperative staging of endometrial carcinoma by analyzing the results of the institution. Concerning the differentiation between superficial disease (IA, IB) and deep myometrial invasion (IC), our results (Table 1) show an accuracy comparable to those reported in previous literature [9, 11, 13] with more than half of the erroneously staged cases presenting myometrial pathology (i.e., leiomyomata, adenomyosis) disturbing uterine zonal anatomy and thus complicating MRI classification. Myometrial compression by an endometrial lesion also biased accurate staging because it produced a distortion of the zonal anatomy difficult to evaluate even with contrast. We also found a positive correlation between MRI and pathologic findings (p < 0.001). It is also noteworthy that MRI results present a higher negative than positive predictive value (84% vs 71%) as it contributes to fewer resurgeries.

Table 1. — Overall MRI results concerning deep myometrial, cervical and lymph node invasion.

<table>
<thead>
<tr>
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<th>Myometral (%)</th>
<th>Cervical (%)</th>
<th>Lymph node (%)</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>83</td>
<td>42</td>
<td>17</td>
</tr>
<tr>
<td>Specificity</td>
<td>72</td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>Positive Predictive Value</td>
<td>71</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>Negative Predictive Value</td>
<td>84</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>Diagnostic Accuracy</td>
<td>77</td>
<td>81</td>
<td>89</td>
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</table>
As for cervical invasion, our results are inferior than those achieved by some centers [9, 14] being comparable to other Portuguese series [16]. A 42% sensitivity, resulting from the 21 false-negative results, may be attributed to the 16 histologically classified IIA cases as they are impossible to categorize by MRI. This results from the difficulty in differentiating cervical secretions from a superficial lesion, because both have the same signal intensity on T2 images. Contrast could have a role in this chapter, producing mucosa enhancement, but this point still has some pitfalls.

Lymph node invasion analysis showed the poorer results of our series as MRI only diagnosed two of 12 cases of ganglionar infiltration. This may be explained by the presence of micrometastases, only histologically detected, as MRI suspicion of lymph node invasion is based on node enlargement (> 1 cm) or central necrosis (more frequent with lymph nodes larger than 2 cm). Nevertheless, it is important to take into account that all 12 cases with histological node invasion, including the ten false-negative MRI cases, showed deep myometrial invasion on MRI. Hence, all patients had indications for lymphadenectomy, which they did.

Conclusion

Our study confirmed the high accuracy of MRI imaging in the locoregional staging of endometrial cancer. Despite the fact that MRI lymph node evaluation has shown a low sensitivity, all cases with histological ganglionar infiltration presented MRI deep myometrial invasion therefore being submitted to an adequate procedure.

Even with the limitations of the technique, MRI has proved to be a valuable contribution in the presurgical assessment of endometrial cancer.

References


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Does the localisation of tumour at Stage I endometrial endometrioid adenocarcinoma have an impact on invasion of the tumour and individualisation of the surgical procedure?

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Summary

Objective: To detect whether the localisation of the tumour has an impact on the dissemination of the tumour and whether or not surgical procedures should be individualised according to the localisation of the tumour. Material Method: 106 clinically surgically stage I endometrial endometrioid carcinoma cases treated multi-institutionally at Gulhane Military Medical Academy (GATA) and Dr. Zekai Tahir Burak (ZTB) Women’s Health Education and Research Hospital Gynecologic Oncology Units in the last five years were evaluated retrospectively. The tumours localised near the internal cervical os and not invading the cervical canal were accepted as lower uterine segment (LUS) localisation and the corporal location as upper uterine segment (UUS) localisation. Results: Tumour localisation was more frequent in the upper segment than LUS (85.9% vs 14.1%). There was no statistically significant difference between only endometrial and only serous invasion rates. Myometrial invasion less than one-half was significantly higher in the UUS group than the LUS group (p < 0.05). Lymph vascular space involvement rate was significantly higher in the LUS group (60%, 9/15) than the UUS group (23 %, 21/91), (p < 0.01). Positive peritoneal cytology rate was 20% (3/15) in the LUS group and 6.6% (6/91) in the UUS group (p > 0.05). Conclusion: Patients with LUS involvement should be considered as high-risk patients. Thus more expanded surgery must be taken into consideration. In this study a limitation was the low number of patients with LUS involvement. Larger prospective studies are necessary to confirm our results.

Key words: Endometrial cancer, Tumour invasion, Surgical procedure.

Introduction

Endometrioid adenocarcinoma constitutes approximately 8.4% of endometrial carcinoma cases [1]. Myometrial invasion rate and the grade of the disease are important indicators in these histopathologic types due to the extent of the surgical procedure and dissemination of the disease [2]. Histologic and nuclear grades can be accurately diagnosed in the preoperative period by endometrial sampling [3]. Histologic and nuclear grades are equally accepted and used by FIGO and WHO pathology committees [4, 5]. Although an accurate myometrial invasion rate can be detected by magnetic resonance imaging (MRI), the gross and pathologic intraoperative examination of the specimen is cheaper and more effective [6]. The relation among tumour grade, rate of myometrial invasion and lymph node involvement has been reported previously. Moreover myometrial invasion and nodal involvement rates increase by indifferentiation of the tumour [2, 7-10].

The endometrial cavity can be divided into two segments: lower uterine segment (LUS) and the upper uterine segment (UUS) (corpus mucosa proper) [7]. Endometrial carcinomas usually arise in the US, though some cases appear to originate from the LUS [11].

According to some authors, localisation of the tumour may be a prognostic factor and it is postulated that localisation near the cervical canal shows early cervical involvement and rapid dissemination. Moreover isthmic tumours tend to have more pelvic-paraaortic lymph node involvement [2, 12, 13]. Lower uterine segment localization of the tumour may be related to more myometrial invasion, more lymph node involvement rates and more positive peritoneal cytology and higher grade than UUS localization [12, 13].

LUS and UUS tumors can be regarded as different tumours due to different immunohistochemistry, clinico-pathology and microsatellite involvement [12].

The aim of the study was to detect whether localisation of the tumour has an impact on the dissemination of the tumour and whether or not the surgical procedure should be individualised according to the localisation of the tumour.
Material and Method

One hundred and six clinically surgically Stage I endometrial endometrioid carcinoma cases treated multi-institutionally at Gülhane Military Medical Academy (GATA) and Dr. Zekai Tahir Burak (ZTB) Women’s Health Education and Research Hospital Gynecologic Oncology Units in the last five years were evaluated retrospectively. Preoperative evaluation results, operation notes, and postoperative pathology reports were recorded carefully. Cases other than endometrioid adenocarcinoma subtype were excluded. Cases that had undergone a standard surgical-pathologic staging procedure (total abdominal hysterectomy + bilateral salpingo-oophorectomy + peritoneal washing and peritoneal biopsies and omentectomy, pelvic-paraortic lymph node dissection) and without macroscopic extraterine tumour according to the operation notes were included in the study. Invasion of the disease was defined by the pathology notes. Tumours localised near the internal cervical os and not invading the cervical canal were accepted as LUS location and corporal location as UUS localisation.

Suspicious and disseminated tumours were excluded from the study. Cases were assessed for tumour localisation, clinical and pathologic predetermined factors. Fisher’s exact test was used and multivariate analyses were done for analyses of stratified groups for grade, myometrial invasion depth and lymph vascular involvement plus tumour localisation.

Results

Mean age of the 106 cases was 57 (34-76) and mean body mass index (BMI) was 27.6 kg/m² (21-42). Mean parity was 3.5 (0-10). Twenty percent of patients (21/106) had diabetes mellitus and 49% of patients (51/106) had hypertensive disorders. Ninety-four percent of cases were recorded carefully. Cases other than endometrioid carcinoma (80%) and the most of the cases can be diagnosed at early stage [14]. The high nodal invasion rate, high-grade cytology and deep myometrial invasion are the generally accepted poor prognostic factors. The surgical procedure can be individualised preoperatively or intraoperatively based on tumour grade and myometrial invasion. Localisation of these tumours in the uterine cavity intraoperatively may have predictive value for tumour invasion and may direct the surgical procedure.

Lymph vascular space involvement rate was significantly higher in the UUS group (60%, 9/15) than the US group (23%, 21/91), (p < 0.01). The positive peritoneal cytology rate was 20% (3/15) in the UUS group and 6.6% (6/91) in the UUS group (p > 0.05).

The pelvic lymph node invasion rate was significantly higher in UUS cases – 20% (3/15) compared with 4.4% (4/91) of UUS cases (p < 0.05). Although there was no paraortic, pelvic + paraortic lymph node invasion in LUS cases, the rate was 1% in UUS cases. Omental invasion was not detected in any patients.

Discussion

Endometrioid adenocarcinoma is the most frequent type of endometrial cancer (80%) and the most of the cases can be diagnosed at early stage [14]. The high nodal invasion rate, high-grade cytology and deep myometrial invasion are the generally accepted poor prognostic factors. The surgical procedure can be individualised preoperatively or intraoperatively based on tumour grade and myometrial invasion. Localisation of these tumours in the uterine cavity intraoperatively may have predictive value for tumour invasion and may direct the surgical procedure.

LUS involvement ranges from 4.8 to 31% [15, 16]. In our study the LUS involvement rate was 14.1%. Hachisuga et al. [17] observed higher grade, deeper myometrial invasion, and less favourable histologies with LUS involvement. Jiko et al. [18] reported that p53 mutation, which occurs predominantly in high grade tumours, was found in 38% of LUS patients. Mayr et al. [19] also noted deep myometrial invasion, grade 3 disease, and lymph vascular invasion in patients with LUS involvement. Furthermore, several studies have confirmed these high-risk factors for LUS localisation with increased

<table>
<thead>
<tr>
<th>Localisation of positive lymph nodes</th>
<th>Rate (%)</th>
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<tr>
<td>Only pelvic</td>
<td>6.8 (7/106)</td>
</tr>
<tr>
<td>Only paraortic</td>
<td>0.9 (1/106)</td>
</tr>
<tr>
<td>Pelvic+paraortic</td>
<td>0.9 (1/106)</td>
</tr>
<tr>
<td>Total</td>
<td>8.6 (9/106)</td>
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</table>

Tumour localisation was more frequent in the UUS than the LUS (85.9% vs 14.1%). Except for the increased age in the LUS group, other clinical characteristics did not show statistically significant differences between the groups (p < 0.05). Nuclear and histologic grades tended to be higher in the LUS group. The grades and tumour localisation are summarised in Table 2.

| Table 2. — Histologic grade and tumour localisation. |
|---------------------------------|-------------------|-----------------|
| Grade                          | Lower segment (%) | Upper segment   | p    |
| Histologic grade (HG) 1        | 26.7 (4/15)       | 69.2 (63/91)    | < 0.01 |
| HG2                            | 53.3 (8/15)       | 27.6 (25/91)    | < 0.05 |
| HG3                            | 20 (3/15)         | 3.2 (3/91)      | < 0.01 |
| Nuclear grade (NG)a            | 20 (3/15)         | 56 (51/91)      | < 0.05 |
| NG2                            | 80 (12/15)        | 41.6 (38/91)    | < 0.01 |
| NG3                            | 0 (0/15)          | 2.4 (2/91)      | > 0.05 |

There was no statistically significant difference between only endometrial and only serous invasion rates. Myometrial invasion less than one-half was significantly higher in the UUS group than the LUS group (p < 0.05) (Table 3).

| Table 3. — Myometrial invasion localisation. |
|---------------------------------|-------------------|-----------------|
| Invasion | Lower segment (%) | Upper segment   | p    |
| Endometrial | 0 (0/15)       | 3.3 (3/91)      | > 0.05 |
| < 1/2 myometrial | 33.4 (5/15) | 60.4 (55/91) | < 0.05 |
| > 1/2 myometrial | 66.6 (10/15) | 35.1 (32/91) | < 0.05 |
| Serous  | 0 (0/15)         | 1.2 (1/91)      | > 0.05 |
recurrence rate [15, 16, 20-22]. Our data are consistent with the studies mentioned above. However, the role of the extent of surgical staging and adjuvant therapies is not obvious.

Phelan et al. [23] concluded that LUS involvement was not correlated with a worse outcome in the absence of adverse pathologic features and that adjuvant radiotherapy should not be used in Stage I endometrial carcinoma by analysing 98 cases with 42% LUS involvement. In another study by Irwin and colleagues [16] the significance of LUS involvement was lost after control for pathologic factors on multivariate analysis. In contrast with these findings, several other studies imply a more aggressive behaviour of LUS involvement [8-12]. Lower segmental localised tumours are seen in older ages, have higher grade, deeper myometrial invasion and more lymph vascular space and pelvic lymph node involvement rates. Patients with LUS involvement should be considered as high-risk patients. Therefore more expanded surgery must be taken into consideration. In this study a limitation is the low number of patients with LUS involvement, thus larger prospective studies are needed.

References

Tunneled central venous catheters in a gynecologic oncology service: operative and short-term complications

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Summary

Purpose: To determine the difference in the immediate complication rate between placement of long-term central venous catheters (LTCVCs) by the percutaneous versus jugular venous cutdown method. Method: Case lists were examined to determine the number of LTCVCs placed during the designated time period. Medical records, operative reports, and chest roentgenograms were examined to extract pertinent information. Immediate complications included complications occurring in the operating room until 30 days postoperatively. Complications included misplacement of the catheter requiring an adjustment or a repeat procedure, pneumothorax, hydrothorax, or hemothorax, operative site or tunnel infection, and line migration requiring removal. Results: Five hundred and one patients had LTCVCs placed during the period of this study. This included 399 totally implantable venous access devices (TIVADs) and 102 free access venous access devices (FAVADs) with 163 placed percutaneously into subclavian veins and 338 placed by cutdown into jugular veins. There was a significant increased risk in the overall immediate complication rate for the percutaneous placement compared to venous cutdown (p < 0.001). Also, pneumothorax was more common with the percutaneous approach compared to the venous cutdown approach (p < 0.001). Conclusions: Immediate complications, especially pneumothorax, were more common when placing catheters by the percutaneous approach as compared to the venous cutdown approach.

Key words: Implanted catheters; Central venous catheters; Gynecologic oncology, Percutaneous; Venous cutdown.

Introduction

Over 20,000 gynecologic cancer patients per year will require chemotherapy for treatment of their malignancies. As Roy et al. found over three decades ago, many of these patients will need long-term central venous catheters (LTCVCs) for convenience and ease of administration [1]. The long-term side-effects of these catheters are well documented [2, 3]. Minassian and colleagues showed that thrombotic complications were much less common when low-dose prophylactic anti-coagulation was utilized [4]. They further showed that the overall rate of long-term complications was lower by venous cutdown as compared to percutaneous access [4]. Minassian did not find any long-term differences in complication rates between totally implantable venous access devices (TIVADs) and a free-access venous access device (FAVADs); however, Gleeson and colleagues at the Moffitt Cancer Center found that FAVAD had a higher rate of complications [4, 5]. Mirro et al. found that there was not a significant difference in long-term catheters placed by the percutaneous approach as compared to cutdown, but TIVADs had fewer complications than FAVADs [6]. Furthermore, there is conflicting data as to whether the internal jugular or subclavian approach has a lower risk of complications including thrombosis [7, 8]. However, the percutaneous approach to the internal jugular can be associated with unique complications such as carotid puncture, stroke, and Horner’s syndrome [9-12]. Although long-term complication rates are known, it is not known whether differences in short-term complications differ between the percutaneous subclavian approach and the internal jugular cutdown method.

The purpose of this study was to retrospectively determine whether operative and short-term complications were more common by the percutaneous or cutdown approach and to secondarily see if differences existed between TIVADs and FAVADs.

Materials and Methods

The operative records, roentgenograms, and case lists were examined for the period July 1, 1997 to December 31, 2003 to extract all cases of tunneled LTCVC placed by the Gynecologic Oncology Service at St. Vincent Hospital, Indianapolis and the University of Iowa Hospitals and Clinics. The types of catheters used were as follows: TIVAD (Port-a-Cath®, Sims Deltec Inc., St. Paul, MN; BardPort®, Bard Access Systems, Salt Lake City, UT) and FAVAD (Hickman®, Bard Access Systems, Salt Lake City, UT). All LTCVCs were placed and removed by the Gynecologic Oncology Service. No perioperative antibiotics were used. Initially, povidone-iodine solutions were routinely used for skin preparation unless otherwise contraindicated until January 2002 when a chlorhexidine-based preparation became standard. With the percutaneous method, postoperative roentgenograms in the operative suite were used for evaluation of placement. Internal and external jugular venous cutdown was performed through a supravacuvicular incision on the appropriate side with direct access to the vein through a venotomy. Postoperative roentgenograms in the operative suite were used for evaluation of placement initially and fluoroscopic examination has been used more recently. TIVADs were routinely sewn to the pectoralis fascia to prevent line migration or rotation/flipping of the hub.
Results

From July 1, 1997 to December 21, 2003, 501 LTCVCs were placed (Table 1). This included 399 TIVADs and 102 FAVADs with 163 placed into subclavian veins percutaneously and 338 placed into jugular veins by the venous cutdown method. The type of placement was at the surgeon’s discretion. On the anatomic left side, 92.5% of the catheters were placed percutaneously as opposed to 13.9% catheters on the right side (p < 0.001). The anatomic side influenced type of catheter used. For instance, on the left, 66 of 120 (55.0%) catheters were TIVADs while on the right side 333 of 381 (87.4%) catheters were TIVADs (p < 0.001). The choice of method (percutaneous vs cutdown) also influenced type of catheter used. Ninety-five of 163 (58.3%) percutaneously placed catheters were TIVADs while 304 of 338 (89.9%) catheters placed by cutdown were TIVADs (p < 0.001). Table 1 documents the perioperative complications. The rate of total complications, as well as the rate of three specific complications (pneumothorax, line malposition/migration, and operative site infection) was examined. Overall complications were highest with the percutaneous approach (p < 0.001). Pneumothorax was significantly more common by the the percutaneous approach as compared to cutdown (p = 0.001).

Table 2 presents the complications associated with the placement of LTCVC by type of catheter used. Again the rate of total complications, as well as the rate of three specific complications (pneumothorax, line malposition/migration, and operative site infection) was examined. No differences were found in short-term complications based on the type of catheter (all p > 0.05) (FAVAD or TIVAD) used.

Discussion

Minassian and colleagues found that long-term complications such as thromboembolic events and infection were more common with the percutaneous approach as compared to cutdown [4]. This study found that the rate of the most worrisome short-term complication, pneumothorax, was more common by the percutaneous approach as compared to cutdown again documenting the safety of this approach.

In gynecologic oncology patients, the percutaneous approach has been shown to have a low rate of complications [13]. Nelson et al. found the rate of pneumothorax to be 4.3%, similar to the 3.7% found in the present series. Ruesch and colleagues found, in intensive care patients, that the pneumothorax rate in percutaneously placed catheters was less than 2% (subclavian or internal jugular) in experienced hands [14]. Although these rates are low, they are still much higher than the rate of pneumothorax by cutdown (0.0% in the present series).

Di Carlo et al. demonstrated the safety of the cutdown approach in their case series [15]. The jugular veins were only used in one of 346 patients. All of their patients had malignancies although not specifically gynecologic malignancies. The documented rate of both short- and long-term complications in their patient population was only 1.8% (not including malposition/migration) compared to a short-term complication rate of 0.6% in this series.

Two separate series from our services have now demonstrated lower complication rates with the venous cutdown versus the percutaneous approach. Although both series were retrospective, they covered different time periods and demonstrated that the cutdown approach was superior both in short-term and long-term complication rates.

References

Tunneled central venous catheters in a gynecologic oncology service: operative and short-term complications


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Frequency of infectious agents for vaginitis in patients with a cytological diagnosis of atypical squamous cells of undetermined significance

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¹Research Institute of Oncology (IPON)/Discipline of Gynecology and Obstetrics
²Discipline of Immunology, Federal University of Triangulo Mineiro (UFTM), Uberaba, MG (Brazil)

Summary

Aim: To evaluate the presence of infectious agents for vaginitis in patients with ASCUS. Methods: 33,388 patients who underwent cervical-vaginal cytology from 08/1993 to 05/2002 were included in the study, and 1,104 (3.4%) presented positive ASCUS. The appraised infectious agents were Coccobacilli, Candida sp, Trichomonas vaginalis, and clue cells (Gardnerella vaginalis). Results: In the group with ASCUS a larger frequency of Coccobacilli (22.37%) and Trichomonas vaginalis (5.25%) was found when compared with the group with negative ASCUS (17.79% and 3.98%, respectively; p < 0.05). Cytolysis occurred more frequently in patients with ASCUS (3.8 vs 6.3%, first phase and 4.5 vs 10%, second phase). Conclusions: We believe that some diagnoses of ASCUS can be induced by the presence of infectious agents for vaginitis, mainly cocci and coccoides. ASCUS occurs more frequently in the first phase of the menstrual cycle, therefore in less acid vaginal pH.

Key words: ASCUS; Infectious agents; Vaginitis; Papanicolaou smears.

Introduction

One of the methods for diagnosing preneoplastic lesions of the uterine cervix may begin with abnormal results from cervicovaginal material collected on a slide and stained using the Papanicolaou method. Various cytological classifications for these lesions have been used. The Bethesda system for cervicovaginal cytological diagnosis was introduced in 1988 and had the objective of furnishing uniform terminology. After using this system for a period of time, it was observed that findings of atypical squamous cells of undetermined significance (ASCUS) were the most commonly encountered diagnosis from cervicovaginal cytology [1]. This category relates to cellular squamous abnormalities that are not diagnostic for inflammatory reaction or preneoplasia, or that represent conditions that qualitatively and quantitatively are insufficient to be interpreted as cervical intraepithelial neoplasia (CIN) [2, 3].

The National Cancer Institute of the United States has concluded that a diagnosis of ASCUS is expected in around 5% of the patients, and that greater frequency may indicate misuse of the term [4]. The American College of Obstetrics and Gynecology suggests that patients with at least two consecutive diagnoses of ASCUS, or one diagnosis of ASCUS with the presence of a high-risk factor (such as infection by human papillomavirus, smoking or multiple sexual partners) should undergo complementary assessment [5].

An extensive and diverse spectrum of pathogenic and nonpathogenic organisms can be observed in the vaginal microflora [6]. Different studies carried out with the objective of establishing the frequencies of the most common infectious agents for vaginitis have shown a variety of results. The prevalence found for Gardnerella vaginalis has ranged from 8% to 75%, Candida albicans from 2.2% to 30% and Trichomonas vaginalis from zero to 34% [6-14].

Previous studies by our group have demonstrated that the frequency of infectious agents for vaginitis may be influenced by the presence of the uterine cervix, or may even vary according to the different decades in which the tests were performed [15, 16]. This leads us to wonder whether the frequency of these agents might be related to a diagnosis of ASCUS.

Another point is the difference in vaginal pH that is found between the first and second phase of the menstrual cycle. The second phase is more acidic than the first phase [17]. The question that arises is whether this greater acidity in the second phase of the menstrual cycle might influence a cytologist’s interpretation of a diagnosis of ASCUS.

One of the difficulties in interpreting cytological tests is the presence of inflammation. The few studies available in the literature have demonstrated that infectious agents have a strong influence on cell alterations, thereby producing different interpretations. In a study by our group comparing the cytological findings proposed by two different protocols (Bethesda and Emilia-Romagna), bacterial vaginosis was found more frequently in women whose cytological tests revealed ASCUS [18].

Our aim in the present study was to contribute towards this topic, to lead to a better understanding and comprehension of women with a cytological diagnosis of...
ASCUS. The term ASCUS is controversial and the question needs to be asked as to whether the presence of infectious agents might contribute towards making this interpretation. To address this question, our objective was to analyze the age group, phase of the menstrual cycle and frequency of infectious agents (as seen on Papanicolaou smears) among women with a cytological diagnosis of ASCUS.

Material and Methods

Patients

A retrospective study covering the period between August 1993 and May 2002 was conducted. Evaluations were made on the results from 33,388 patients who underwent routine cervicovaginal cytological tests at the cytopathology service of the Federal University of the Triângulo Mineiro (UFTM). Of these, 1,104 (3.4%) presented ASCUS (i.e. ASCUS-positive) and 32,284 (96.6%) did not present atypia corresponding to a diagnosis of ASCUS (i.e., ASCUS-negative). All the patients were assessed for the presence of coccobacilli, Candida sp, Trichomonas vaginalis, clue cells (Gardnerella vaginalis) and cytolysis.

Samples of endocervical material (brush) and cervical and vaginal material (spatula) were obtained from patients who did not undergo hysterectomy. The material collected was fixed in ethyl alcohol and stained using the Papanicolaou method. The interpretations were performed by doctors specializing in cytopathology, all using the same diagnostic criteria in relation to Doderlein bacilli, cytolysis, bacteria, and coccoids, clue cells, Trichomonas vaginalis and Candida sp.

Women were excluded from the study if they presented bacterial vaginosis or had had active vaginal bleeding or sexual relations, or had used vaginal douches or medication, within the 48 hours preceding sample collection.

This study was granted approval by the Research Ethics Committee of the Federal University of the Triângulo Mineiro.

Cytological criteria [19, 20, 21]

The diagnosis of ASCUS was based on the Bethesda criteria: karyomegaly with an increased nucleus/cytoplasm ratio; slight irregularity of the nucleus with mild hyperchromasia and chromatin, without granulation; binucleation and mild dyskariosis; keratosis and atypical parakeratosis.

The following criteria were used as cytological diagnostic parameters: clue cells – squamous cells covered with coccobacilli, for which the cytoplasmic margins presented as stain; Candida sp – pseudohyphae seen, weakly stained with eosin or sometimes with hematoxylin, and/or small spores (diameters of 2-4 nm), stained pale pink; Trichomonas vaginalis – single-cell organism of ovoid or rounded shape (diameter of 8-20 nm), with pale or grayish cytoplasm, possibly with eosinophilic granules at the center of the cytoplasm, and a vesicular nuclear format or half-moon shape that was clearly stained using hematoxylin; Cytolysis – defined as a pale coloration, with a vesicular nucleus and little or no cytoplasm in intermediate cells from the cervicovaginal material; Coccobacilli – bacillary and coccoid organisms, diffusely scattered in groups or microcolonies; and Lactobacilli – presence of elongated bacillary structures.

Statistical analysis

The chi-square test was used for statistical analysis, with the significance level set at less than 0.05.

Results

In the group of women with a diagnosis of ASCUS, greater frequencies of Coccobacilli (22.37%) and Trichomonas vaginalis (5.25%) were found than in the ASCUS-negative group (17.79% and 3.98%, respectively): p < 0.05 (Table 1).

Table 2 shows the patients divided according to the phase of the menstrual cycle, taking the first phase as the first to the 15th day and the second phase as the 16th to the 30th day. The majority of the women with a diagnosis of ASCUS (56.5%) were in the first phase of the menstrual cycle, although this finding did not have statistical significance (p = 0.53). Thus, there was a greater frequency of Trichomonas vaginalis (6.7%; p = 0.0358) among the ASCUS-positive patients presenting the first phase of the cycle than among the ASCUS-negative patients presenting the first phase of the cycle.

There were no differences in the frequencies of coccobacilli and cytolysis when the groups were divided according to the phase of the cycle. Coccobacilli remained a more frequent finding among ASCUS-positive patients in both the first and second phase, and cytolysis in the ASCUS-negative patients in both the first and second phase.

When divided by age (Table 3), the women in the ASCUS-positive group aged between 31 and 40 years presented a greater frequency of Trichomonas vaginalis (6.8% vs 4.4%; p = 0.0437) than did the same age group in the ASCUS-negative group. There were also higher numbers of lactobacilli (80.4%; p < 0.0001) than the 70.5% presented by the ASCUS-negative group.

Table 1. — Total number of patients with positive ASCUS, negative ASCUS and frequency of infectious agents.

<table>
<thead>
<tr>
<th>Infectious Agent</th>
<th>Positive ASCUS (N = 1,104)</th>
<th>Negative ASCUS (N = 32,284)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Cytolysis*</td>
<td>47 4.25</td>
<td>2,592 8.02</td>
</tr>
<tr>
<td>Coccobacilli*</td>
<td>247 22.37</td>
<td>5,744 17.79</td>
</tr>
<tr>
<td>Clue cells</td>
<td>196 17.75</td>
<td>5,968 18.48</td>
</tr>
<tr>
<td>Candida sp</td>
<td>216 19.56</td>
<td>6,072 18.80</td>
</tr>
<tr>
<td>Trichomonas vaginalis**</td>
<td>58 5.25</td>
<td>1,288 3.98</td>
</tr>
<tr>
<td>Lactobacilli</td>
<td>789 71.46</td>
<td>23,007 71.26</td>
</tr>
</tbody>
</table>

* p < 0.0001, ** p = 0.0358.

Table 2. — Distribution of patients in the first phase (1st-15th day) and second phase (16th-30th day) of the menstrual cycle.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Positive ASCUS (N = 624)</th>
<th>Negative ASCUS (N = 17,155)</th>
<th>Positive ASCUS (N = 14,969)</th>
<th>Negative ASCUS (N = 48,335)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
<td>N %</td>
</tr>
<tr>
<td>Cytolysis</td>
<td>24 3.8</td>
<td>1,092 6.3</td>
<td>22 4.5</td>
<td>1,501 10.0</td>
</tr>
<tr>
<td>Coccobacilli</td>
<td>138 22.1</td>
<td>3,208 18.5</td>
<td>107 22.4</td>
<td>2,538 16.9</td>
</tr>
<tr>
<td>Clue cells</td>
<td>102 16.3</td>
<td>3,330 19.2</td>
<td>93 19.3</td>
<td>2,639 17.6</td>
</tr>
<tr>
<td>Candida sp</td>
<td>110 17.6</td>
<td>2,904 16.7</td>
<td>105 21.8</td>
<td>3,169 21.1</td>
</tr>
<tr>
<td>Trichomonas vaginalis</td>
<td>42 6.7</td>
<td>751 4.3</td>
<td>15 3.1</td>
<td>538 3.5</td>
</tr>
<tr>
<td>Lactobacilli</td>
<td>452 72.4</td>
<td>12,316 71.1</td>
<td>336 70.0</td>
<td>10,692 71.4</td>
</tr>
</tbody>
</table>

Comparison among positive and negative ASCUS: * p = 0.0124, † p < 0.0001, ‡ p = 0.0238, † † p = 0.0002, ‡ ‡ p = 0.0358.

Note: some patients had more than one infection.
Table 3. — Distribution of patients by age.

<table>
<thead>
<tr>
<th>Positive ASCUS</th>
<th>Negative ASCUS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 1,104)</td>
</tr>
<tr>
<td>Age (N)</td>
<td></td>
</tr>
<tr>
<td>&lt; 20 (109)</td>
<td>20 (348)</td>
</tr>
<tr>
<td>21-30 (314)</td>
<td>16 (337)</td>
</tr>
<tr>
<td>31-40 (330)</td>
<td>9 (251)</td>
</tr>
<tr>
<td>&gt; 41 (251)</td>
<td>3.6</td>
</tr>
</tbody>
</table>

Comparison among women with positive and negative ASCUS: p = 0.0061 (< 20 years), p = 0.0233 (31-40 years), p = 0.0333 (> 41 years). Women in the ASCUS-positive group aged between 21 and 30 years presented a greater frequency of coccobacilli (p = 0.0210). Women in the ASCUS-positive group aged between 31 and 40 years presented a greater frequency of coccobacilli (p = 0.0006). Women in the ASCUS-positive group aged > 40 years presented a greater frequency of Candida sp. (p = 0.0159). Women in the ASCUS-positive group aged between 31 and 40 years presented a greater frequency of Trichomonas vaginalis (p = 0.0437). In the ASCUS-positive group aged between 31 and 40 there were also higher numbers of lactobacilli (p < 0.0001) than in the ASCUS-negative group.

Note: some patients had more than one infection.

In the ASCUS-positive group over the age of 40 years, there was a higher frequency of Candida sp (19.9%; p = 0.0006) than in the same age group of the ASCUS-negative group (14.4%).

Discussion

The diagnosis of ASCUS is still a term leading to much discussion, given that the interpretation differs among pathologists. One large difficulty in interpreting cytological tests when a diagnosis of ASCUS is given is the inflammation caused by infectious agents such as Candida sp and Trichomonas vaginalis that lead to the development of vaginitis. This discussion is longstanding. In one study published in 1996, in which 50 cervicovaginal smears were analyzed, 16 were initially interpreted as ASCUS and 34 as normal. After reviewing the Bethesda criteria for ASCUS, and identifying the changes associated with the presence of Candida sp (focal hyperchromasia, orangeophilia and perinuclear halos), ten of the 16 cases of ASCUS were reclassified as normal [22]. Thus, it was demonstrated that the infectious agents had a strong influence on cell alterations that produced erroneous interpretations and diagnoses.

Our findings demonstrated that coccobacilli were more frequently found among ASCUS-positive women. This may reinforce the possibility that there might be a relationship between ASCUS and bacterial vaginosis. According to the discussion in a review of the Bethesda criteria (Bethesda System 2001), one modification to the nomenclature would be removal of flora with Coccobacilli, which would be replaced by suggestions of vaginosis [23]. A previous study by our group found greater frequency of bacterial vaginosis in patients with a diagnosis of ASCUS, thus favoring neoplasia [18]. Another interesting finding was the greater presence of T. vaginalis in ASCUS-positive women. Findings of T. vaginalis in cytological tests have dropped in frequency over recent decades to around 3% [6]. It seems that this finding is much greater among ASCUS-positive women (5%) although, because of the low numbers, it is improbable that the presence of this infectious agent for vaginitis would lead to a cytological interpretation of ASCUS.

These affirmations demonstrate that there is a strong relationship between the presence of infectious agents and the presence of ASCUS. The basis for this is studies that have demonstrated classifications for bacterial vaginosis [24, 25], in which all the classes demonstrated that the presence of coccobacilli was one of the factors involved in bacterial vaginosis. Our suggestion is that the simple presence of coccobacilli may be a factor to be considered in cell alterations, and it may influence the interpretation of the results regarding ASCUS.

Vaginal pH is related to the phase of the menstrual cycle, and it is known that it is higher during the menstruation phase (1-5 days) and proliferative phase (8-12 days) of the cycle than in the secretory phase (18-22 days) [26]. Our results showed that a greater number of women with a diagnosis of ASCUS were in the first phase of the cycle (1st-5th day; 56.5%), versus 43.4% in the second phase (16th-30th day), which leads us to suggest a hypothesis that the lower vaginal pH that occurs in the secretory phase of the cell cycle does not influence the cytological alterations associated with ASCUS. Another fact that reinforces this finding is that cytology (an event that is related to lower pH) occurred almost twice as often among the ASCUS-negative women.

In the United States, it has been estimated that 3.5 million colposcopic tests give rise to a diagnosis of some abnormality every year, of which approximately 2.5 million are interpreted as ASCUS [27]. The estimates have suggested that 10-20% of the women with ASCUS have high-grade intraepithelial lesions, and that one in every 1,000 has invasive cancer [23]. Because of this
undetermined nature, diagnoses of ASCUS create great doubt for doctors, since this category may represent some lesion, and delaying the diagnosis could alter the prognosis for the patient. It also creates anxiety for the patients, because the possibility of malignant disease has not been discarded. Our results demonstrated that there was greater frequency of coccobacilli and \textit{T. vaginalis} in the women with a diagnosis of ASCUS; the greatest number of women with Trichomonas were in the group aged between 31 and 40 years; and \textit{Candida sp} was most frequent among ASCUS-positive women aged over 40 years, as we had already shown in another study by our group [16]. These results lead us to believe that it is possible that many diagnoses of ASCUS are being induced by the presence of infectious agents for vaginitis, particularly cocci and coccoids, and that ASCUS findings are more frequent in less acidic vaginal pH. Treatment of these alterations is recommended for better interpretation of ASCUS.

**Acknowledgement**

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**References**


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e-mail: eddiemurta@mednet.com.br
Knowledge about and attitudes to Pap smears, cervical cancer and human papillomavirus among women in Slovenia

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Institute of Oncology, Ljubljana (Slovenia)

Summary
High-risk human papillomaviruses (HPV) play a vital role in the development of precancerous changes or cancer in the uterine cervix. Prophylactic vaccination has proven to be an effective measure to reduce the incidence of precancerous changes in the uterine cervix and thereby also of cervical cancer. A population investigation was performed in Slovenia with the aim of determining the level of knowledge and awareness of women about cervical cancer, Pap test, HPV infection and preventive vaccination. The investigation was executed by computer-aided telephone inquiry in the period from 5-22 September 2006 on a sample of 500 women aged from 18 to 55 years from all regions of Slovenia. From the results it may be concluded that, in Slovenia, there is an urgent need to provide the lay population and medical community with relevant and accurate information on HPV infection, on early detection of cervical cancer and preventive vaccination.

Key words: Knowledge; HPV infection; Pap test; HPV vaccination.

Introduction
Cervical cancer is ranked second among the most frequent female cancers in the world. Every year, half a million women of the worldwide female population develop cervical cancer and half of them die of cervical cancer. In developed countries, the incidence of cervical cancer is significantly lower than elsewhere in the world, which is mainly due to screening programs using the Pap test. Screening for cervical cancer has considerably reduced the disease-related death rate. Cervical cancer screening utilizing the cervical smear test is one of the oldest methods of cervical cancer prevention; however, it has some shortcomings that may result from inadequate sampling of a cervical smear, inadequate smear preparation and fixation, and from biased slide reading. Evidence that high-risk human papillomavirus (HPV) plays a vital role in the development of precancerous changes or cancer of the uterine cervix is important and has had a strong influence on the execution of a number of research studies on cervical cancer detection by using HPV testing as well as on the prevention by HPV vaccination [1, 2]. From epidemiological research studies of HPV prevalence and from clinical studies of infections with high-risk HPV and related diseases of the uterine cervix, the following conclusions may be drawn: (i) high-risk HPV is present in more than 99% of all cervical cancer cases; (ii) persistent infection with high-risk HPV is the main cause of invasive cervical cancer development; (iii) the negative prognostic value of the HPV test is rather high, particularly in cases of negative Pap test results (> 99%); (iv) the HPV test has higher sensitivity for detecting pathologic changes in the uterine cervix than the Pap test; and, (v) flow-cytometry methods also allow the determination of high-risk HPV.

The above statements were used as criteria for controlling the applicability of the HPV test in primary screening for cervical cancer (as an independent test or in combination with the Pap smear test), in triaging the women with initial pathologic abnormalities in cervical smears and after the treatment of precancerous changes in the uterine cervix to detect the symptoms of persistent or recurrent disease. Prophylactic vaccination against HPV 6, 11, 16 and 18, which has been already introduced in Slovenia and in several countries worldwide, has proven to be an effective measure to reduce the incidence of precancerous changes in the uterine cervix and thereby also cervical cancer [4]. Currently, licenses for medical use of bivalent vaccine against HPV 16 and 18 are in the process of being granted by appropriate authorities. According to the research results, this vaccine is a promising agent in the prevention of pathologic abnormalities in the uterine cervix [5]. News about preventive vaccination against cervical cancer and HPV infection has aroused great interest in HPV in general, in the influence of HPV infection on the development of precancerous changes, of cancer of the uterine cervix and other diseases, and in the risk of sexually transmitted HPV infection and its incidence. Due to the lack of information, curious questions arise among women, doctors and other medical staff. From the research results that have been published so far, it could be noted that the level of knowledge and awareness of the population about HPV varies from country to country; there is thus an urgent need to determine this level of knowledge and awareness in each country to be able to provide the population in each individual country with adequate information that is lacking and to select the proper target group which is most in need of information.

The investigation on the population was performed in Slovenia with the aim of determining the level of knowledge and awareness of women about cervical cancer, the Pap test, HPV infection and preventive vaccination.
Materials and Methods

Our investigation was executed by computer-aided telephone inquiry in the period from 5-22 September, 2006 on a sample of 500 women aged from 18 to 55 years from all regions of Slovenia (Table 1). They were divided into four age groups: 18-24 years (17%), 25-34 years (26%), 35-44 years (27%), and 45-55 years (30%). Out of the total of 500 women, 76% were married or had a permanent relationship with a man, 19% had completed primary school or had obtained vocational qualification, 50% had completed secondary school and 31% had a college or university degree: 34% were nulliparous, while others had one, two or three children, mainly two (37%).

The data were processed by descriptive epidemiological methods. The Mantel-Haenszel chi-square and Fischer’s p tests were used to evaluate statistical significance.

Table 1. — Epidemiologic characteristics of the women under investigation.

<table>
<thead>
<tr>
<th>Epidemiologic characteristics of the women under investigation</th>
<th>Total number</th>
<th>Percentage (no. = 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>84</td>
<td>16.8%</td>
</tr>
<tr>
<td>25-34</td>
<td>131</td>
<td>26.2%</td>
</tr>
<tr>
<td>35-44</td>
<td>135</td>
<td>27%</td>
</tr>
<tr>
<td>45-55</td>
<td>150</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/living with a partner</td>
<td>380</td>
<td>76%</td>
</tr>
<tr>
<td>Single</td>
<td>105</td>
<td>21%</td>
</tr>
<tr>
<td>Divorced/widowed</td>
<td>15</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary school or vocational education</td>
<td>93</td>
<td>18.6%</td>
</tr>
<tr>
<td>Secondary school</td>
<td>250</td>
<td>50%</td>
</tr>
<tr>
<td>College, university degree or higher degree</td>
<td>157</td>
<td>31.4%</td>
</tr>
<tr>
<td><strong>Number of children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>169</td>
<td>33.8%</td>
</tr>
<tr>
<td>1</td>
<td>101</td>
<td>20.2%</td>
</tr>
<tr>
<td>2</td>
<td>187</td>
<td>37.4%</td>
</tr>
<tr>
<td>3 or more</td>
<td>43</td>
<td>8.6%</td>
</tr>
</tbody>
</table>

Results

Knowledge about the Pap test and cervical cancer

The question on what the Pap test is used for was correctly answered by 78% of the women included in the investigation. One third or almost half of the women believed that the Pap test was also used to detect other gynecological diseases; 59.8% were convinced that the Pap test was a method to detect any gynecological cancer in general, 42.6% claimed that the test detected inflammation and/or infections of the sexual organs, and 37.4% were convinced that the Pap test could also detect sexually transmitted infections. As much as 12.2% of the women did not know at all what the Pap test was used for. The women from the 45-55-year age group were better informed about the Pap test than the women from the 18-24 year age group (p = 0.008). The percentage of women who believed that the test could also detect inflammation and/or infections of the sexual organs was higher among those with a primary school education than among those with a university education (p = 0.005).

The women included in the investigation said that of all female cancers they were most aware of breast cancer (99.4%), followed by cervical cancer (98.8%), ovarian cancer (95.2%), uterine cancer (89.2%), cancer of the external genitals (66.0%), vaginal cancer (46.2%), and other diseases (0.4%). According to the women in our study, the strongest risk factors for developing cervical cancer were familial, poor genital hygiene, poor genital hygiene of a male partner, and three or more pregnancies (and childbirths). Weaker risk factors included – according to their viewpoint – smoking, old age, poor nutrition habits, sexual intercourse, sexual intercourse without penetration, neglecting regular physical training, long-term use of contraceptive drugs, and the least risk was posed by changing sexual partners.

From the women interviewed in our study, 50.1% were convinced that they were not at risk or at very low risk of developing cervical cancer (Figure 1). Only 10.9% of women assumed that they were at high risk for developing cervical cancer and added that, most likely, the risk was the highest in the 36-45-year age group whereas 12.7% of women replied that they were not at all at risk for cervical cancer. This last belief prevailed in the women of the 45-55-year age group (16.2%).

From the women interviewed in our study, 50.1% were convinced that they were not at risk or at very low risk of developing cervical cancer (Figure 1). Only 10.9% of women assumed that they were at high risk for developing cervical cancer and added that, most likely, the risk was the highest in the 36-45-year age group whereas 12.7% of women replied that they were not at all at risk for cervical cancer. This last belief prevailed in the women of the 45-55-year age group (16.2%).

The question as to whether they knew what the causes of cervical cancer were, was imprecisely answered by 67.7% of women with a primary school (72.7%) or vocational education (85.1%) who said that they did not know exactly. The causes of cancer most frequently mentioned by the women in the study were: changing sexual partners (22.3%), non-defined infections (19.6%), heredity (13.5%), HPV (10.8%), and untreated inflammations (10.1%). Possible protection measures to be used against cervical cancer were known to 42.7% of women (mostly to those with a university education), whereas the remaining 66.3% of women had never heard of such measures.

Out of the total of 500 women in the study, 78 had never had a Pap test. Of these 78 women, 39 were aged between 18 and 24 years, 14 between 25 and 34, 15 between 35 and 44, and ten between 45 and 55; as may
be seen, 6.7% of the women from the 45-55-year age group had never had a Pap test. The women from the 18-24-year age group (51.3%) said as an excuse that they were too young to undergo the test, that they did not have any gynecological problems (20.5%), that they were not sexually active, or did not have a permanent partner. For the women over 25 years of age, the most frequent pretexts for evading a Pap test were that they did not have a permanent partner, that they did not have any gynecological problems, or that they were not sexually active, and the women from the 45-55-year age group stated, in addition to other excuses, that they were too old.

Out of the 500 women included in the study, 422 had had a Pap test; 46% of these had had the first test before the age of 20, 38.3% before the age of 30, 11.7% before the age of 40, and 3.7% after the age of 40. From the women who decided to have Pap tests performed, 67.9% did so because of their belief that the test was a necessary health measure, 27.3% on the advice of their family doctor, 3.6% upon official recommendations, and 1.2% upon the advice of a friend or family member. Almost half of the women were informed that Slovenian gynecologists recommended having the Pap smear test every three years and 20% did not know how often the test should be performed. A comparison of age and education of the women did not reveal any significant differences. Of the women who had had the Pap test, 34.7% discussed the test results with their gynecologist or other medical specialist; 30.2% fully understood the information on the test results, 13.4% declared that the information was not clear, and 5.5% did not understand the information at all. During the gynecological examination and collection of cervical smear sample, 59.7% of the women did not experience any discomfort, 33.6% reported minor discomfort, and 6.7% complained of serious discomfort.

Of 477 women who had already had sexual intercourse, 4% experienced the first intercourse with a man before the age of 15, 59.1% between the age of 16 and 18 years, 34.0% between 19 and 25 years, and 1.3% between the age of 26 and 35 years; 1.7% of the women did not wish to answer that question; 35.3% of the women had had only one sexual partner, 18.3% two, 16.4% three, 7.6% four, and 16.6% of the women had had five or more partners. Among the women who had five or more partners, the majority were nulliparous, aged between 25 and 34 years. Of the interviewed women, 4.4% did not wish to answer that question. In the previous two years, 85.5% of women had had a single partner, 5.7% had two, and 1.8% had three or more partners, whereas 3.4% of the women did not wish to answer that question.

Knowledge about HPV

Among the viruses that the women interviewed in the study were informed of, the best known were HIV, influenza virus, herpes simplex virus, and HPV, which was known to around two-thirds of the women in the study (Figure 2). HPV was best known by the women in the 25-34-year age group (51.9%) and to those with a university education (64.9%). The answer to the question as to what HPV could cause, posed to 198 women who claimed that they understood HPV, was cervical cancer (37.9%), genital warts (21.2%), endometrial cancer, ovarian cancer or herpes (less than 10%). The percentage of women who knew that HPV could cause cervical cancer was the highest among the women with a university education (54.1%) and the lowest among those who had obtained vocational qualification or completed secondary school (28.4%); 36.4% of the women who knew that HPV could cause genital warts had a primary education. Considering the ages of the interviewed women, there were no significant differences among their answers. A little less than half of them (44.8%) were informed that there are several types of HPV. Out of 47 women who knew what the cause and effect relation was between HPV and cervical cancer, 88.9% – predominantly those of younger age and with university education – were acquainted with the data that cervical cancer is caused only by a particular HPV, and 11.1% believed that all HPV types could cause cervical cancer. As much as 59.8% of the women did not know at which age women were most susceptible to HPV infection, with more than 10% of the answers claiming that these were the women in the following three age groups: under 14 years of age, between 26 and 35 years, and between 36 and 45 years. The question as to whether they knew that vaccines against HPV infection were being developed was answered positively by 36.5% of women.
testing was obvious. A lack of knowledge was evident in accurate answers to the question about the use of Pap in Slovenia by using the Pap test, a high percentage of 8%. Considering long-term screening for cervical cancer of women, i.e., those aged between 18 and 55 years [6-8], our research included responses from a wider age group—centenarians, students and young people in general, the results of which reflect the level of knowledge and awareness of adolescents among their beliefs as to which source was the most important. In general, women could get the relevant information at a gynecologist’s office at the age of 25 or over, whereas the information from the press, internet or family members was usually sought by younger women aged between 18 and 24 years.

As a rule, women preferred to have more information from their gynecologist than from women’s magazines and, lastly, from TV programs (Figure 5). The most frequent topics of the talks between gynecologists and their patients are the need for regular gynecological examinations (92.4%), contraception (90.2%), pregnancy (80.2%), menstrual problems (72.2%), Pap test results (70.6%), other gynecological problems (43.8%), sexually transmitted infections (37.0%) and menopause (25.6%). Age distribution corresponded to the health topics typical for each particular age group of patients.

During the session with their gynecologist, 46.8% of the women in the study asked questions about the procedure of the HPV test, 12.4% about the causes of the development of cervical cancer, and 6.2% about HPV infection.

**Discussion**

In comparison to the majority of published data that reflect the level of knowledge and awareness of adolescents, students and young people in general, the results of our research included responses from a wider age group of women, i.e., those aged between 18 and 55 years [6-8]. Considering long-term screening for cervical cancer in Slovenia by using the Pap test, a high percentage of accurate answers to the question about the use of Pap testing was obvious. A lack of knowledge was evident in the group of individuals who answered that the Pap test is used to detect a number of other diseases. In our study as well as other studies, the level of education proved to be a significant indicator of knowledge and awareness about the Pap test. It may be alarming that girls aged over 18 years are less interested in the importance of the Pap test than women aged over 45 years, which might be a proof of inadequate education of young women about the importance of the test. A similarly high importance may be attached to the fact that the majority of interviewed women were convinced that they were not at all at risk of developing cervical cancer and only 10% thought that they could be at high risk of developing cervical cancer. In a recently published study performed on 204 Brazilian women aged between 16 and 23 years, 42% considered themselves as being at high risk for sexually transmitted infections and thereby also for cervical cancer [9]. As much as two-thirds of the interviewed women from our investigation did not know what the possible causes of cervical cancer were and which risk factors were most influential. Nevertheless, the majority of Slovenian women (over 90%) were aware that it is urgent to have gynecological checkups and Pap smear tests performed regularly, though barely half of them knew how often the smear test should be performed. A considerably large percentage of the women from our investigation, who were insufficiently aware of the high risk for developing cervical cancer or virtually convinced of its absence, might serve as an explanation as to why the responsiveness to the formally organized screening program for the detection of cervical cancer has been and is still not satisfactory, particularly among the women in the 45 to 55-year age group. This is also further supported by a recent estimation that 6.7% of women in the same age group had not had a Pap test. Their main excuses for declining a Pap test were discomfort and fear of pain during the gynecological examination [9].

Of the woman interviewed in our study, 39% knew what HPV was, and of these, 59.1% were informed that HPV could cause the development of cervical cancer and/or genital warts. The majority of women who were informed about HPV vaccination were those with a higher education, whereas no statistical significance was
noted among the age groups of the women who were acquainted with HPV. This smaller half of the interviewed women who were informed about HPV also knew that there were several types of HPV, each targeting a different age group of women. Only one-third of all women from the study knew that a vaccine against HPV infection was being developed. The results of analogous interviews made elsewhere reported similar results [6, 9]. A great majority of parents who are considering whether or not to protect their children against HPV infection by vaccination are most interested in learning more about HPV and cervical cancer. However, even though it appears that they lack information, this should not be the key factor on which their decision regarding vaccination would depend [10, 11].

Sources of information about cervical cancer, HPV and related issues are of paramount importance [12]. Articles in women’s magazines, a talk with the gynecologist, TV and radio educational programs are the major sources of information available to Slovenian women. The articles in magazines and radio and TV programs have a key role in spreading information among the lay population. Although recently numerous articles on HPV and vaccination against it have appeared in magazines intended for the lay public, it has been often noted that articles dealing with the association of HPV and cervical cancer appear to be missing [13]. The data accessible on the Internet may sometimes be misleading; however, the Internet as a source of information is gaining in importance, particularly for young women aged over 18 years.

The results of our investigation show that the information on HPV supplied by schools is scarce; this should certainly be a challenge to all those preparing school curriculum in Slovenia. According to our results, women would like to have more information from their gynecologist or general practitioner – again a challenge to this group of medical doctors to spare more time for talking with female patients about HPV and/or vaccination against HPV, thereby also highlighting the need of further instruction for general practitioners and gynecologists about these matters. The results of the investigation on the level of the knowledge of Slovenian women about the Pap test also indicate that gynecologists spare too little time to talk with patients about cervical cancer. Less than half of the women from our study had the chance to talk about the Pap test with their gynecologists, and only a third of these women discussed the last test results with their doctor. Moreover, the value of the quality of information may be realized from the following data obtained from the study: the gynecologist’s report based on the Pap test results was understood by only one-third of the patients; one-fifth of the patients considered the report as partly understandable or completely incomprehensible. Surprisingly, some women neither expected nor wished to be informed by nurses, pharmacists, or by family members or friends; likewise, some women did not wish to talk about the most intimate details, e.g., how many sex partners they had had or when they had had the first sexual intercourse. Therefore, the answers to these kinds of questions should be considered as possibly biased, particularly if they are included in the mere core of the investigation.

Conclusions

From the results of our investigation and of other studies on HPV it may be concluded that there is an urgent need to provide the lay population and medical community with relevant and accurate information on HPV infection, on early and effective detection of precancerous changes of the uterine cervix, and thereby also on cancer [6], safe sex practices, prevention of HPV infections, genital warts and preventive vaccination. The key point is to achieve a high-level of knowledge and awareness of HPV risk among women as well as men. Particularly women often associate HPV infection with inexorable development of cervical cancer. They refuse to understand that HPV infection is a transient infection and often does not distinguish between the roles of HPV and Pap tests. They often mistakenly consider that the Pap test that detects precancerous changes of the uterine cervix is a predictive factor for HPV infection and that it can differentiate among different HPV subtypes and genotypes. Hence, there is no excuse for the reluctance and unnecessary doubts, accusations and fear that young women are experiencing in relation to HPV infections, not even that the time is too short to supply them with adequate advice, education and important facts about HPV and being simply negligent in respect to warning them about the risk of sexually transmitted infection with HPV [7, 8].

Care should be taken that healthcare staff should also be additionally trained and educated to obtain a higher level of knowledge and awareness of the risk of HPV infection [6, 14]. We will gather fresh data on the awareness of the risk of HPV infection with further and more extensive investigations. By launching the information to target groups and also the data that have been missed we can achieve a higher responsiveness to the screening program, thus also assuring better success of prophylactic vaccination against HPV infection [15, 16].

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References


Knowledge about and attitudes to Pap smears, cervical cancer and human papillomavirus among women in Slovenia


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Evaluation of acute and late radiation morbidity in patients with gynaecologic malignancy using the RTOG criteria and Franco-Italian glossary

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Summary

Purpose: The purpose of this study was to evaluate acute and late radiation morbidity in patients with gynaecologic malignancy using the RTOG criteria and Franco-Italian glossary, and to compare the usefulness and disadvantages of each system. Materials and Methods: Between February 2001 and February 2003, 107 patients with gynaecologic malignancy who received either radical or adjuvant external radiotherapy ± intracavitary brachytherapy or radiochemotherapy were enrolled in this study. The patients were evaluated before radiotherapy and weekly during radiotherapy for acute morbidity using the RTOG grading system and Franco-Italian glossary. Postradiotherapy evaluation was done one month after radiotherapy and at 3-month intervals thereafter. Median follow-up duration was 17 months. Morbidity was graded and recorded according to each scoring system. Results: Median age was 46 years (range 37-82). Sixty-four patients (59.8%) had endometrial cancer. Radical radiotherapy was applied to 26 patients because of inoperability and 81 patients received postoperative radiotherapy. Biologically effective doses for the bladder, rectum and vagina were 98.39, 103.54 and 121.81, respectively, for late morbidity (BED 3); 70.88, 72.84 and 80.92, respectively, for acute morbidity (BED 2). According to the RTOG grading system acute morbidity rate for the genitourinary and gastrointestinal systems, and skin were 52.3%, 83.2% and 63.5%, respectively. Late morbidity rate for the bladder, colon-rectum, skin and vagina were 16.8%, 20.6%, 47.7% and 51.4%, respectively. The morbidity rate for the bladder, nonspecific abdominal, hematopoietic system, uterus-vulva-vagina, skin and rectum were 35.4%, 29.9%, 5.6%, 60.8%, 40.1% and 32.7%, respectively using the Franco-Italian glossary. In patients with carcinoma of the vulva – whose treatment fields were wider – acute morbidity rate according to RTOG criteria was higher (p = 0.057); photon energy (6 MV rather than 1.25 MV) (p = 0.01) and treatment interruption of more than eight days (p = 0.019) were correlated with decreased long-term morbidity. According to the Franco-Italian glossary morbidity rates were higher in patients who received chemotherapy (p = 0.047), both external radiotherapy and brachytherapy (p = 0.022) and treatment interruption of less than eight days (p = 0.019). Conclusion: There is no common language between the RTOG grading system and Franco-Italian glossary for defining and scoring radiation morbidity. Up to date no standard and well-defined system has been developed for recording and reporting acute and late radiation morbidity in gynaecologic malignancy, but rather it depends on the subjective evaluation and experience of a radiation oncologist and subjective complaints of the patient, and sometimes on clinical findings. A standard and well-defined user friendly objective scoring system is needed to define and predict the morbidity rate more properly.

Key words: Radiation therapy; Collateral effects; RTOG; Franco-Italian glossary.

Introduction

In recent years, survival rates of cancer patients have improved significantly due to the progress in cancer treatment. Therefore postoperative care, rehabilitation, attempts to decrease treatment complications and to improve quality of life have gained importance. From this point of view preservation of normal tissues or organs has become an important aspect of radiotherapy. Although there are various studies reporting acute and late radiation morbidity a uniform toxicity scoring system is still lacking. At present the major national or international toxicity scoring systems include RTOG (Radiation Therapy Oncology Group), EORTC (European Organization for Research and Treatment of Cancer), ECOG (Eastern Cooperative Oncology Group), CCGS (The Crohn’s and Colitis Support Group), Franco-Italian Glossary for gynaecologic malignancies and MRC (Medical Research Council) [1-4].

In the present study we evaluated the acute and late effects of treatment in patients with gynaecologic malignancy using the RTOG grading system and Franco-Italian glossary to determine the compatibility and the sufficiency of the two different grading systems.

Materials and Methods

Between February 2001 and February 2003, 107 patients with gynaecologic malignancy who received either radical or adjuvant external radiotherapy (ERT) ± intracavitary brachytherapy (IBRT) or radiochemotherapy were enrolled in this study. Radiotherapy portals were AP/PA pelvic, four-field pelvic box, paraaortic + pelvic or paraaortic + pelvic + inguinal portals depending on the type and the stage of the disease. ERT was delivered with megavoltage beams (Co60 in 27.1% of the patients and 6 MV photon beam in 72.9%) using 1.8 Gy per fraction, five fractions per week. Median total ERT dose was 50.4 Gy in operable patients and 59.4 Gy in inoperable patients (with parametrial boost after 54 Gy). Midline shielding was performed at 50.4 Gy. Two fractions of 6.5 Gy were given to a depth of 7 mm from the vaginal surface in operable patients with the ovoids of the Rotterdam applicator and three fractions...
of 6 Gy with weekly intervals were applied to point A in inoperable patients with the Rotterdam applicator via microSelectron-HDR remote afterloader Ir-192. Weekly cisplatin (40 mg/m²) was given concurrently with radiotherapy to inoperable or high-risk patients.

The patients were evaluated before radiotherapy and weekly during radiotherapy for acute morbidity using the RTOG criteria and Franco-Italian glossary. Postradiotherapy evaluation was done one month after radiotherapy and at 3-month intervals thereafter.

Statistical analyses were done using the SPSS V. 10.0 computer programme. The Mann-Whitney U test was used for comparison of the median values between independent variables and the Kruskal-Wallis test was used for comparison of the median values in more than two groups. Values of p ≤ 0.05 were considered statistically significant.

Results

Median age of the patients was 46 (range 37-82). Most of the patients had endometrial carcinoma and most of them were operated on. General characteristics of the patients are shown in Table 1.

Biologically effective doses for early (BED₁₀) and late (BED₃) effects for the bladder, rectum and vagina are indicated in Table 2.

Early morbidity was defined as complications occurring during or within three months after radiotherapy and late morbidity as those complications occurring later than three months. According to the RTOG grading system gastrointestinal toxicity was the most frequent early morbidity (Table 3). Late morbidity is indicated in Table 4.

Toxicity grading according to the Franco-Italian glossary is listed in Table 5.

Table 1. — General characteristics of the patients.

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Median 56 (range 37-82)</td>
</tr>
<tr>
<td>Operation type</td>
<td></td>
</tr>
<tr>
<td>TAH+BSO</td>
<td>50 (46.7)</td>
</tr>
<tr>
<td>Wertheim</td>
<td>28 (26.2)</td>
</tr>
<tr>
<td>Simple vulvectomy</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Inoperable</td>
<td>26 (24.3)</td>
</tr>
<tr>
<td>Primary tumour type</td>
<td></td>
</tr>
<tr>
<td>Carcinoma of the endometrium</td>
<td>64 (59.8)</td>
</tr>
<tr>
<td>Carcinoma of the uterine cervix</td>
<td>33 (30.8)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>5 (4.7)</td>
</tr>
<tr>
<td>Vulvar cancer</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td>Vaginal carcinoma</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Treatment portals</td>
<td></td>
</tr>
<tr>
<td>AP/PA pelvic</td>
<td>65 (60.7)</td>
</tr>
<tr>
<td>Four-field pelvic</td>
<td>24 (22.5)</td>
</tr>
<tr>
<td>Paraaortic + pelvic</td>
<td>10 (9.3)</td>
</tr>
<tr>
<td>Paraaortic + pelvic + inguinal</td>
<td>8 (7.5)</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79 (73.8)</td>
</tr>
<tr>
<td>No</td>
<td>28 (26.2)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29 (27.2)</td>
</tr>
<tr>
<td>No</td>
<td>78 (72.8)</td>
</tr>
</tbody>
</table>

Table 2. — BED₁₀ and BED₃, values for the bladder, rectum and vagina.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Median total dose (Gy)</th>
<th>BED₁₀ (Gy)</th>
<th>BED₃ (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>58.59</td>
<td>70.88</td>
<td>98.39</td>
</tr>
<tr>
<td>Rectum</td>
<td>59.72</td>
<td>72.84</td>
<td>103.54</td>
</tr>
<tr>
<td>Vagina</td>
<td>63.40</td>
<td>80.92</td>
<td>121.81</td>
</tr>
</tbody>
</table>

Table 3. — Acute morbidity according to the RTOG grading system.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Gastrointestinal</th>
<th>Genitourinary</th>
<th>Skin</th>
<th>Subcutaneous tissue</th>
<th>Bladder</th>
<th>Small/large mucosa tissue</th>
<th>Rectum</th>
<th>Vaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 (15.9%)</td>
<td>27 (25.2%)</td>
<td>35 (32.7%)</td>
<td></td>
<td>18 (16.8%)</td>
<td>2 (1.9%)</td>
<td>20 (18.7%)</td>
<td>27 (25.2%)</td>
</tr>
<tr>
<td>2</td>
<td>71 (66.4%)</td>
<td>26 (24.3%)</td>
<td>32 (29.9%)</td>
<td></td>
<td>11 (10.3%)</td>
<td>14 (10.3%)</td>
<td>2 (1.9%)</td>
<td>16 (15.0%)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.9%)</td>
<td>3 (2.8%)</td>
<td>1 (0.9%)</td>
<td></td>
<td>3 (2.8%)</td>
<td>2 (1.9%)</td>
<td>12 (51.4%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>89 (83.2%)</td>
<td>56 (52.3%)</td>
<td>58 (63.5%)</td>
<td></td>
<td>32 (29.9%)</td>
<td>18 (16.8%)</td>
<td>22 (20.6%)</td>
<td>55 (51.4%)</td>
</tr>
</tbody>
</table>

Table 4. — Late morbidity according to the RTOG grading system.

Table 5. — Toxicity grading according to the Franco-Italian glossary.

Potential factors which could influence the toxicity rate included age, diabetes, obesity, prior surgery, total ERT dose, BED, and BED₃; treatment portals, photon energy, chemotherapy, brachytherapy, and treatment interruption. Parameters such as age (p = 0.167), diabetes (p = 0.589), obesity (p = 0.07), prior surgery (p = 0.615), total ERT dose above 50.4 Gy (p = 0.145), administration of chemotherapy (p = 0.772), application of brachytherapy (p = 0.159), the photon energy used-1.25 MV or 6 MV (p = 0.7), and treatment interruption more than eight days (p = 0.979) had no significant correlation with the development of acute morbidity according to the RTOG system whereas there was a trend with extended treatment fields including paraaortic or inguinal lymph nodes (p = 0.057). The significant factors influencing late morbidity rate were the photon energy (p = 0.01) and treatment interruption more than eight days (p = 0.019) which were correlated with a decreased long-term morbidity rate.

The Franco-Italian system does not categorize morbidity as acute or late, rather it evaluates it more detailed as a whole. Factors such as age (p = 0.694), operation type (p = 0.178), total ERT dose (p = 0.967), the photon energy used (p = 0.821), and the treatment portal (p = 0.488) had no significant impact on the development of morbidity according to the Franco-Italian glossary.
Administration of chemotherapy (p = 0.047), and brachytherapy application (p = 0.022) increased the morbidity rate while treatment interruption of more than eight days (p = 0.019) decreased it.

Discussion

Although the aim of radiotherapy is to achieve maximum local control with minimum treatment related complications, specific acute and late complications involving different systems and organs in different degrees of frequency and severity can be seen either during or after radiotherapy. Especially late morbidity has a great influence on the patient’s quality of life. There are many factors such as total dose, irradiation technique, fractionation and daily dose, use of midline shielding, etc., which influence the likelihood of complications both for ERT and IBRT [5-8].

Acute toxicity due to pelvic radiotherapy has not been reported well in the literature. Most studies were retrospective reviews which did not provide enough information about toxicity, especially grade 1 and 2 acute toxicity, hence they were not mentioned by the patient and required a detailed clinical examination on daily practice. Kapp et al. analysed the complications after primary external beam radiation and Ir-192 HDR brachytherapy in 161 patients with carcinoma of the cervix. The acute sequelae rate was 41.6% (9). The most frequent side-effects were diarrhea (63%) followed by nausea (30%) and cystitis. The incidence of late complications were as follows: grade 1-50.9%; grade 2-11% and grade 3-3.7%. Yalman et al. reported a 41.5% acute morbidity rate in 771 patients with gynaecologic malignancy, grade 1 and 2 bladder morbidity being the most frequent type [5]. In the present study acute morbidity rates for the genitourinary and gastrointestinal system and skin were 52.3%, 73.2% and 63.5%, respectively, according to the RTOG grading system. Due to the prospective design of this study, a detailed clinical examination and documentation might be the reason for more higher acute toxicity rates when compared with the literature.

Corn and associates evaluated late morbidity in 235 patients who received a median dose of 46.2 Gy ERT to the whole pelvis or ERT combined with IBRT with a vaginal cylinder (median vaginal surface dose was 32.4 Gy). At the end of the fifth year the severe morbidity rate was 5.5% [10]. Barillot et al. used the Franco-Italian glossary to determine the morbidity rate in 642 patients treated with radiotherapy alone for carcinoma of an intact uterine cervix [11]. The total morbidity rate was 51%. The five-year actuarial toxicity rate per grade was: G1 - 42%; G2 - 23.5%; G3 - 10%; G4 - 3%. The gynaecological tract (31%) and rectum (21.5%) were the most frequent sites of treatment sequelae and complications followed by the pelvic soft tissues (18%), bladder (13%) and small bowel (4%). In the present study, late complication rates according to the RTOG scale were as follows: 16.8% genitourinary, 20.6% gastrointestinal, 49.7% skin, 29.9% subcutaneous tissue, 51.1% mucosa-vagina, and 47.7% skin The complication rates according to the Franco-Italian glossary were as follows: 35.4% bladder-genitourinary, 29.9% non-specific abdominal-gastrointestinal, 60.8% uterus-vulva-vagina, 40.1% subcutaneous tissue, and 32.7% rectum. Our experience with the Franco-Italian glossary was quite different from the RTOG rates in terms of late effects.

There is no common language between the RTOG and Franco-Italian scoring system in terms of evaluation and rates of toxicities. However, both scoring systems have different difficulties and incompetence regarding toxicity evaluation. There is no scoring in the RTOG system for an anal fissure as it is a common acute toxicity in our experience. Additionally RTOG late toxicity scoring for the vagina is not detailed as demanded regarding vaginal stenosis and telangiectasias. Although RTOG defined severe telangiectasia as a grade 3, in our experience multiple telangiectasias are not as severe as grade 3. Ultimately, asymptomatic telangiectasias scoring as Grade 3 would cause a false-positive increase in grade 3 vaginal toxicity. RTOG late urinary system toxicity scoring has limitations regarding urinary incontinence, cystocele and asymptomatic leukocyturia. Although, the Franco-Italian scoring system is more detailed compared to RTOG, no definition of acute and late toxicity might cause an underestimation of acute toxicity in daily practice. As a result of the present study, we concluded that a standard and a well-defined user-friendly objective scoring system is needed to define and predict the morbidity rate more properly.

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Plasma lipid profile in gynecologic cancers

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Summary

Background: Lipids are associated with cancer because they play a key role in the maintenance of cell integrity. We studied the relationship of plasma lipids with gynecologic cancer. Methods: A total of 196 female individuals were included in the study. Of these 50 were normal subjects. The remaining were cancer patients: 80 breast cancer, 40 ovarian cancer and 26 patients with other gynecologic cancers. Plasma levels of triglycerides, total cholesterol, LDL-cholesterol and HDL-cholesterol were estimated by using spectrophotometer. Results: In breast cancer patients there is moderate increase in the plasma levels of triglycerides (18%) and cholesterol (21%), and a high increase in LDL-cholesterol (43%), while there is a moderate decrease in HDL-cholesterol levels (30%) when compared with normal subjects. In ovarian cancer patients, there is a high increase in the plasma levels of triglycerides (31%) and HDL-cholesterol (39%), while a moderate decrease in cholesterol (28%) and LDL-cholesterol levels (11%) when compared with normal subjects. In gynecologic cancers other than breast and ovarian cancer, there is a moderate decrease in plasma levels of the triglycerides (25%), cholesterol (21%), and HDL-cholesterol levels (27%), while a non-significant decrease in LDL-cholesterol (6.2%) when compared with normal subjects. Conclusions: Plasma lipid levels, except HDL-cholesterol, are raised in breast cancer and are decreased in other gynecologic cancers. HDL-cholesterol is decreased in all gynecologic cancers. As there is an alteration in the plasma lipid profile during gynecologic cancers, it may be helpful for diagnosis of the disease.

Key words: Plasma lipids; Gynecologic cancers.

Introduction

Breast cancer and ovarian cancer are the major gynecologic cancers [1]. Lipids are carried in body fluids with the help of lipoproteins [2, 3]. Chylomicrons transport triglycerides from the intestine to all cells. Very low density lipoproteins (VLDL) are involved in the transportation of triglycerides from the liver to other cells. Low density lipoproteins (LDL) are responsible for the transport of cholesterol from the liver to the cells and high density lipoproteins (HDL) are involved in the transport of cholesterol from cells to the liver. Chylomicrons and very low density lipoproteins are rapidly catabolized [4, 5]. Thus triglycerides, cholesterol, LDL-cholesterol and HDL-cholesterol constitute the plasma lipid profile.

Researchers have reported an association of plasma/serum lipids and lipoproteins with different cancers. As neoplastic disease is related to new growth, there is a greater utilization of lipids including total cholesterol, lipoproteins, and triglycerides for new membrane biogenesis. Cells fulfill these requirements either from circulation, by synthesis through the metabolism or from degradation of major lipoprotein fractions like VLDL, LDL or HDL. The plasma concentrations of lipids are not the single additive function of intake, utilization and biosynthesis because of the continuous cycling in and out of the blood stream [6]. Our study was designed to evaluate the relationship between the plasma lipid profile (triglycerides, cholesterol, LDL-cholesterol and HDL-cholesterol) and gynecologic cancers.

Materials and Methods

Subjects

A prospective study was carried out on 196 women. Of these, 50 were normal subjects who had no complaint nor any major illness in the last few years. They were close relatives of the patients who were hospitalized. The remaining subjects were cancer patients: 80 breast cancer, 40 ovarian cancer and 26 patients with other gynecologic cancers. No patient had a history of thyroid disease, diabetes or any other major illness that could affect lipid metabolism. The patients were not treated with any chemotherapy, radiation or surgery before the sample collection.

Fasting blood samples were collected from the Combined Military Hospital, Rawalpindi, Pakistan and NORI Hospital, Islamabad, Pakistan. The plasma was stored at -20°C until used for estimation of the plasma lipid profile.

Estimation of plasma lipid profile

Plasma levels of triglycerides, total cholesterol, LDL-cholesterol and HDL-cholesterol were estimated by using a spectrophotometer.

Triglycerides

Triglycerides were determined by an enzymatic method (GPO-PAP method) using the commercially available kit manufactured by Human, Germany.

Procedure

Three cuvettes were washed with distilled water and labelled blank, standard and sample; 20 ml of distilled water, 20 ml of standard, and 20 ml of sample were pipetted into each cuvette, respectively. Chromogen reagent (2 ml) was added to each cuvette. Contents of all the cuvettes were mixed thoroughly and incubated for five minutes at room temperature. The wavelength of the spectrophotometer was set at 500 nm and after some time the results were displayed. Blood triglyceride levels were calculated by applying the following formula.
Triglycerides mg/dl = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 200

Total cholesterol
Rapid enzymatic determination of the total cholesterol by the CHOD-PAP method [7] was performed using the commercially available kit (Human, Germany).

Procedure
Three cuvettes were washed with distilled water and labelled blank, standard or sample; 20 ml of distilled water, 20 ml of standard, and 20 ml of sample were pipetted into each cuvette, respectively. Chromogen reagent (2 ml) was added to each cuvette. Contents of all the cuvettes were mixed thoroughly and incubated for five minutes at 37°C. The wavelength of the spectrophotometer was set at 500 nm and after some time the results were displayed. Blood cholesterol levels were calculated by applying the following formula.

Cholesterol mg/dl = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times 200

LDL-cholesterol
LDL-cholesterol was determined by the precipitation method. Tests were performed by using the commercially available kit manufactured by Randox, Germany.

Procedure
For sample preparation 100 ml of sample and 1000 ml of precipitant were placed in a tube. After thorough mixing, the tube was allowed to stand for 15 min at room temperature and then was centrifuged at 1500 rpm for 15 min. Supernatant was separated from the sediment and cholesterol was measured by the CHOD-PAP method. LDL-cholesterol levels were calculated by applying the following formula.

LDL-cholesterol mg/dl = \text{Total cholesterol} - \text{Cholesterol in supernatant}

HDL-cholesterol
HDL-cholesterol was determined by using the commercially available kit (Human, Germany).

Procedure
For sample preparation 200 ml of sample and 500 ml of precipitant were placed into a tube. After thorough mixing, the tube was allowed to stand for ten minutes at room temperature and then was centrifuged at 4000 rpm for ten minutes. Supernatant was separated from the sediment and cholesterol was measured by the CHOD-PAP method.

Statistical Analysis
The computer program SPSS 11.0 version was used for statistical analyses. The Student’s t-test was performed to compare mean values of the parameters; p value < 0.05 was considered as statistically significant.

Results
In the present study plasma levels of triglycerides in control subjects ranged from 120-189 mg/dl (mean 158.29 ± 6.31), plasma levels of cholesterol ranged from 158.29 ± 6.31, plasma levels of LDL-cholesterol ranged from 29-92 mg/dl (mean 66.12 ± 6.41), and plasma levels of HDL-cholesterol ranged from 13-59 mg/dl (mean 33.33 ± 7.54) (Table 1).

Discussion
Several studies of plasma lipid alterations in animals with neoplasms have been conducted [8-10]. In the past few years there have been reports related to general
cancer, hematological cancers, and head and neck cancer [11, 12, 6]. The return of plasma lipids and lipoproteins towards normal limits during remission in leukemia patients confirms the correlation of lipid alterations with primary disease activity [12, 13].

In the present study, plasma triglycerides, cholesterol and LDL-cholesterol showed a highly significant (p < 0.01) increase in breast cancer patients when compared with normal control subjects, while HDL-cholesterol levels showed a highly significant (p < 0.01) decrease. In ovarian cancer all the plasma lipid components showed a highly significant (p < 0.01) decrease except for LDL-cholesterol which was significantly decreased (p < 0.05). In gynecologic cancers other than breast and ovarian cancer, all the plasma lipid components showed a significant (p < 0.05) decrease except for HDL-cholesterol which was highly significantly decreased (p < 0.01).

The pathophysiologic mechanism implicated in plasma lipid alterations during neoplasm has not been determined. Lipids are major cell membrane components essential for various biological functions including cell growth and division of normal and malignant tissues. Low levels of cholesterol in the proliferating tissues and in blood compartments could be due to the process of carcinogenesis. The raised plasma concentrations of these parameters in patients with breast cancer may be due to an increased rate of lipid absorption as the fat-splitting enzymes, lipases, were also found to be increased in the patients [15].

Briefly we conclude that plasma lipid levels, except HDL-cholesterol, are raised in breast cancer and are decreased in other gynecologic cancers. HDL-cholesterol is decreased in all gynecologic cancers. As there is an alteration in the plasma lipid profile during gynecologic cancers, this profile may be helpful for diagnosis of the disease.

Acknowledgment

We are thankful to the Higher Education Commission of Pakistan for their financial support. We are also indebted to the director and clinicians, clinical assistants, and nursing staff of the Oncology Department of CMH, Rawalpindi and NORI Hospital, Islamabad Pakistan for their support and guidance.
References


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Sodium Phosphate (NaP) versus polyethylene glycol-electrolyte lavage solution (PEG-ELS) tolerability: a prospective randomized study in patients with gynecological malignancy

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¹Department Obstetrics and Gynecology, ²Department Physiology, Gaziantep University Faculty of Medicine, Gaziantep (Turkey)

Summary

Purpose: The aim of the study was to evaluate patient tolerability and compliance to two bowel cleansing agents (PEG-ELS and NaP) as well as to compare the cost effectiveness. Methods: Three hundred and forty-three consecutive patients were randomized to receive either the standard 4 l of polyethylene glycol and electrolyte lavage solution (PEG-ELS) or 90 ml of sodium phosphate (NaP). All patients were advised to be on a clear liquid diet one day before starting the bowel cleansing regimen and to take ornidazole orally (3 x 2 tablets) 24 hours before surgery. Patient tolerability and compliance to the regimens were assessed based on complaints of nausea, vomiting and the need of antiemetics. In addition completion of the regimens was evaluated in both groups. Results: The need for antiemetics because of nausea and vomiting was statistically higher in the PEG-ELS group than the NaP group (p = 0.000). Regimen completion rate was statistically higher in the NaP group than in the PEG-ELS group (p = 0.000). NaP is more cost effective than PEG-ELS. Conclusion: NaP was rated superior to PEG-ELS in terms of patient tolerability, compliance, completion of the regimen and cost effectiveness and should be the first-choice treatment.

Key words: PEG-ELS; NaP; Tolerability; Regimen completion; Cost effectiveness.

Introduction

Bowel cleansing before gynecological malignancy surgery is important because of the risk of bowel injury. Recently polyethylene glycol-electrolyte lavage solution (PEG-ELS) and oral sodium phosphate (NaP) are the preferred agents in bowel preparation regimens. The bowel cleansing efficacy of PEG-ELS and NaP have been studied widely in patients who underwent colonoscopic evaluation, and a similar efficacy of the two agents has been suggested. The main disadvantage of PEG is that large volumes have to be ingested, and this is not well tolerated by some patients. The advantage of NaP preparations is that smaller volumes are administered which are more tolerable for the patient [1].

The aim of this study was to evaluate patient tolerability and compliance to two bowel cleansing agents (PEG-ELS and NaP) as well as to compare the cost effectiveness. This is the first study on the tolerance of bowel cleansing regimens in abdominal gynecological malignancy rather than an evaluation of the efficacy of the two regimens.

Materials and Methods

A prospective randomized study at the Obstetrics and Gynecology Department of Gaziantep University Faculty of Medicine was carried out between 2000 and 2006 on 343 consecutive patients with gynecological malignancies with normal clinical histories and biochemical parameters.

The patients were randomized to receive either 4 l of standard PEG-ELS or 90 ml of NaP.

Exclusion criteria for the study included electrolyte and fluid disturbances, heart disease, and impaired kidney function. Moreover patients experiencing nausea and vomiting secondary to malignancy and other gastric problems were excluded from the study.

One hundred and sixty-one patients were diagnosed with ovarian carcinoma; 135 had endometrial carcinoma and 47 had cervix carcinoma. Patient ages ranged between 25 and 72 (Table 1).

One hundred and seventy-three patients in the PEG-ELS group were instructed to drink 4 l of the solution (PEG-ELS) 24 hours before surgery.

In the NaP group 170 patients received 90 ml of the solution (a 2.4 g monobasic and 0.9 dibasic solution) in a split regimen of two 45-ml doses separated by 12 hours prior to surgery. All patients were advised to be on a clear liquid diet one day before starting the bowel cleansing regimen and to take ornidazole (3 x 2 tablets) orally 24 hours before surgery.

The primary endpoints included the tolerance and acceptability assessed by complaints of nausea, vomiting, and the need for antiemetics (parenteral metoclopramide). The secondary endpoint was completion of the regimen.

Statistical analysis

Data were analyzed with SPSS software (version 10.0, SPSS Inc., IL, USA) using the chi-square test. Differences were considered as statistically significant for p values < 0.05.
Table 1. — Patient characteristics.

<table>
<thead>
<tr>
<th>Tumor types</th>
<th>PEG-ELS</th>
<th>NaP</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian carcinoma</td>
<td>82</td>
<td>79</td>
<td>25-72</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>73</td>
<td>62</td>
<td>53-68</td>
</tr>
<tr>
<td>Cervix carcinoma</td>
<td>18</td>
<td>29</td>
<td>38-70</td>
</tr>
<tr>
<td>Total</td>
<td>173</td>
<td>170</td>
<td></td>
</tr>
</tbody>
</table>

Results

In the PEG-ELS group, 163 patients vomited more than three times during the regimen. All of the 173 PEG-ELS group patients needed antiemetic therapy because of severe nausea. Only 113 patients in this group were able to completed the procedure, whereas in the NaP group 90 patients needed antiemetics during the regimen and 30 of these patients vomited more than three times. All the 170 patients completed the intake of the NaP solution. Regimen completion rates were statistically different between the two groups (Table 2, p = 0.000).

The need for antiemetics was higher in the PEG-ELS group than the NaP group (Table 2, p = 0.000). Antiemetic usage in the ovarian carcinoma group was significantly higher than for the cervical and ovarian carcinoma groups (Table 3, p = 0.046).

The cost of PEG-ELS for one patient is $10.00 (US) versus $3.00 (US) for NaP.

Table 2. — Patient tolerability.

<table>
<thead>
<tr>
<th></th>
<th>PEG-ELS</th>
<th>NaP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting more than 3 times</td>
<td>163</td>
<td>30</td>
<td>0.000</td>
</tr>
<tr>
<td>Need for antiemetics (3 ampuls of metoclopramide)</td>
<td>173</td>
<td>80</td>
<td>0.000</td>
</tr>
<tr>
<td>Regimen completion</td>
<td>113</td>
<td>170</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Table 3. — Metoclopramide use in PEG-ELS and NaP regimens.

<table>
<thead>
<tr>
<th>Metoclopramide</th>
<th>Over</th>
<th>Endometrium</th>
<th>Cervix</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoclopramide 253 (3 ampuls)</td>
<td>125</td>
<td>100</td>
<td>28</td>
<td>0.046</td>
</tr>
<tr>
<td>Met+PEG-ELS 173</td>
<td>82</td>
<td>73</td>
<td>18</td>
<td>0.17</td>
</tr>
<tr>
<td>Met+NaP 80</td>
<td>43</td>
<td>27</td>
<td>10</td>
<td>0.37</td>
</tr>
<tr>
<td>PEG-ELS only 0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>NaP only 90</td>
<td>36</td>
<td>35</td>
<td>19</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Discussion

Bowel preparation before a surgical procedure for abdominal gynecological malignancy is crucial. Large-volume polyethylene glycol-electrolyte lavage solution (PEG-ELS) and oral sodium phosphate (NaP) preparations are the most popular regimens for colon cleansing worldwide [2].

PEG, a non-absorbable and osmotically balanced lavage solution, has proven to be safe as there is virtually no net absorption or excretion of water and electrolytes because of its electrical neutrality and iso-osmolality with plasma. However the unpleasant taste and large volume of PEG-ELS frequently lead to poor compliance with recommended dosing regimens, often causing patients significant dissatisfaction with the procedure.

NaP acts via an osmotic effect, drawing plasma water into the gastrointestinal tract. It has been shown to be effective as a cleansing preparation in many randomized trials [1].

The primary aim of our study was not to compare the efficacies of NaP vs PEG-ELS but rather the tolerability and cost effectiveness in patients with gynecological malignancies. The similar effect of these two agents has already been reported by numerous studies in the literature [1-4]. Nonetheless there has been no trial in the literature about the efficacies and tolerability of the two regimens in gynecological malignancies.

The bowel cleansing efficacy of PEG-ELS and NaP has been studied widely in patients who underwent colonoscopic evaluation. Comparison of these two regimens has yielded conflicting results, although a recent meta-analysis favored NaP [3]. The meta-analysis was based on the data of 1,286 subjects in eight trials. NaP and PEG-ELS were equivalent in terms of quality of preparation, but excellent quality of preparation and ability to complete the cleansing were more likely with NaP [4].

In a meta-analysis of the 16 trials in the PEG vs NaP group, nine concluded that NaP was superior in terms of bowel cleansing ability. Six trials reported that both PEG and NaP were comparable in efficacy, and one trial was in favor of PEG [5].

In this study two groups were evaluated on complaints of nausea, vomiting and need of antiemetics. It has been suggested that the PEG-ELS regimen is highly correlated with more than three times the vomiting and antiemetic use compared with NaP (p = 0.000). The emesis rates (> 3) for PEG-ELS and NaP were 94% and 17%, respectively. Antiemetic usage in the ovarian carcinoma group was significantly higher than in the cervical and endometrial carcinoma groups.

In the study the PEG-ELS group cessation rate of the regimen was 34%, whereas in the NaP group it was 0% (p = 0.000).

In many studies physical complaints have mainly been reported by patients taking PEG-ELS, and significantly more patients reported moderate to severe complaints of nausea, abdominal distension and anal irritation than patients taking NaP [4]. All the patients on NaP completed the intake of the solution and significantly fewer patients did so in the PEG-ELS group.

In a recent meta-analysis, it was shown that significantly more patients were able to complete the NaP preparation when compared with PEG (94.4% vs 70.9%). Therefore it has been noted that this would have an impact on the quality of bowel cleansing, and the superior cleansing ability of NaP may be partly due to a greater rate of completion of bowel preparation by patients [1].

In a study by Vanner et al. [6] the use of oral sodium phosphate preparation was found to be more effective than a PEG lavage solution and also better tolerated. In addition it has been shown that sodium phosphate makes no clinically significant changes in intravascular volume and is more cost-effective than other solutions [7].
On the other hand when cost effectiveness was compared, NaP was more favorable than PEG-ELS as the cost of PEG-ELS for one patient is $10.00 vs $3.00 for NaP. Moreover more metachlopramide use in the PEG-ELS group than the NaP group is important to cost effectiveness.

Conclusion

Bowel cleansing before surgery for gynecological malignancies with NaP was found to be superior to PEG-ELS in terms of patient tolerability, compliance, completion of the regimen and cost effectiveness. As NaP is more effective in bowel cleansing than PEG and is comparable in terms of number of adverse events like severe nausea and vomiting, it should be considered as the first-choice treatment.

References


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Can “chromohysteroscopy” help target endometrial biopsy in postmenopausal bleeding?

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¹Department Obstetrics and Gynecology, ²Department Pathology, GATA School of Medicine, Ankara (Turkey)

Summary

Summary: A preliminary study was conducted to evaluate the value of endometrial dying during diagnostic hysteroscopy. Twenty-two postmenopausal bleeding cases without hysteroscopic findings were included in the study. Before the random endometrial biopsy 5 ml of methylene blue (1%) was instilled into the uterine cavity. Staining was observed in 19 of the cases. Tissues were obtained from both stained and non-stained areas with grasping forceps. “Chromohysteroscopy” led the diagnosis of three more endometrial pathologies; two more cases of endometritis and one more case of endometrial hyperplasia. In conclusion, chromohysteroscopy seems like a new avenue worth pursuing for better diagnoses of unexplained endometrial pathologies.

Key words: Postmenopausal bleeding; Hysteroscopy; Chromohysteroscopy; Methylene blue.

Introduction

Postmenopausal vaginal bleeding is an alarming condition both for the patient and physician. About 10% of women with postmenopausal bleeding are subsequently found to have endometrial carcinoma [1]. Because of the high incidence of malignancy as a cause of postmenopausal bleeding, all women presenting with this complaint should be thoroughly evaluated until a final diagnosis is reached. Following physical examination and lab work, imaging techniques are warranted for endometrial evaluation. Transvaginal sonogram (TVS) is the most readily applied. When this is sufficient to diagnose a pathology, subsequent endometrial sampling is performed to establish a histopathologic diagnosis.

Traditionally, suspected endometrial pathologies have been investigated with blunt biopsy techniques like dilatation & curettage or Pipelle biopsy. Since hysteroscopy allows visualization of the endometrial cavity, hysteroscopy with directed biopsy has been valued as the “gold standard” for endometrial assessment for the last two decades [2, 3].

When there are gross abnormal hysteroscopic findings like endometrial polyps, submucous myoma or focal outgrowing/ingrowing abnormalities (as in focal endometrial hyperplasia or endometrial carcinoma) it is easy to aim the biopsy. However when there are no abnormal visual findings to direct biopsy (as in diffuse endometrial hyperplasia) a random biopsy is obtained. Without established hysteroscopic criteria even visually directed biopsy can miss atypical lesions. In this case the reliability of diagnosis and the tissue obtained are related to the experience of the physician, which can be extremely variable.

Chromoendoscopy is a widely used technique in gastrointestinal imaging [4]. Over the last decade, endoscopic systems have acquired great power due to high resolution images owing to CCD chip technology and narrow band imaging techniques [5]. Besides imaging enhancement, gastroenterologic endoscopists use chemical agents either to identify specific epithelia, contrast or highlight subtle mucosal irregularities, or tattoo a specific mucosal site.

Unlike the gastrointestinal mucosa the endometrium is not an absorptive epithelium. Endometrium is not supposed to take any dye in under normal circumstances. However Marconi et al. [6] reported that endometrium is stained by methylene blue except in the periovulatory phase. The reason for endometrial staining is explained by apoptosis. They noted that structural damage of the cell during apoptosis would allow passage of the methylene blue dye into the cell.

The aim of the current study was to assess the value of “chromohysteroscopy” (endometrial death during hysteroscopy) in postmenopausal bleeding as an indicator of biopsy site.

Materials and Methods

Twenty-seven postmenopausal bleeding patients were included in the study. They were initially evaluated with complete physical examination and TVS. When no diagnosis could be established they were offered diagnostic hysteroscopy. Hysteroscopy was performed after 7-20 days following cessation of the bleeding. In five patients hysteroscopy revealed an endometrial pathology and they were excluded from the study. Conventional hysteroscopy did not show any endometrial pathology and they were excluded from the study. Institutional review board approval and signed informed consents were obtained.

When no direct abnormality was seen in the endometrial cavity (Figure 1), before taking a random biopsy, distending medium flow was stopped. Then 5 ml of 1% methylene blue dye was introduced through the hysteroscopic inlet. After five minutes distending medium flow was started again to wash the endometrial cavity. The cavity was visualized for staining (Figure 2). Biopsy was obtained from the stained sites and non stained sites and sent for pathologic examination in separate bottles.
to the diagnosis of the case, except possibly when endometritis is present. Our small series contradicts this suggestion; in addition to two endometritis cases we found one more case of hyperplasia using chromohysteroscopy.

A negative hysteroscopic view does not warrant the omission of endometrial sampling. Due to the risk of missing the correct site of biopsy in a small tissue sample, gynecologists prefer aspiration curettage in these cases to feel more comfortable about the diagnosis.

**Table 1. — Raw data of the cases.**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Years since menopause</th>
<th>Hysteroscopic finding</th>
<th>Histopathology</th>
<th>Chromohysteroscopic staining</th>
<th>Histopathology</th>
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<tr>
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</tr>
</tbody>
</table>

NNE: Non-neoplastic endometrium.
However in that case a vaginal speculum and a tenaculum are used and possibly anesthesia is required, but then, the philosophy of performing a no-touch diagnostic hysteroscopy is broken.

The diagnosis of endometrial hyperplasia is challenging for hysteroscopists [8, 9]. There is no established diagnostic criteria for the diagnosis of endometrial hyperplasia, and there is overlap with the normal late secretory endometrium. An attempt of establishing hysteroscopic criteria for endometrial pathologies has been made [10]. Garuti et al.'s study to correctly diagnose endometrial hyperplasia using his own criteria failed [11]. Thus the final diagnosis is still established with histopathologic examination.

Cicinelli et al. reported on correct diagnoses of endometritis in hysteroscopy [12]. The observation of micropolyps at fluid hysteroscopy was associated with a 94% probability of chronic endometritis. However, in patients with confirmed endometritis, micropolyps were only observed in 54% of cases. The addition of endometrial dying to the diagnostic criteria in hysteroscopy will possibly increase the accuracy of hysteroscopic diagnoses.

Dying of the endometrium with methylene blue was first reported by Marconi et al. [6]. They used methylene blue in various phases of the endometrial cycle in 20 premenopausal women. Although epithelium is “non-absorptive” they showed staining of endometrium except in the periovulatory phase. There is only one possible explanation for staining of the endometrial cells: disruption of the integrity of the cell membrane. Membrane cell integrity is disrupted during apoptosis, and apoptosis is increased in abnormal conditions such as infection or hyperplasia. These are two challenging conditions for the hysteroscopist to diagnose.

In conclusion, the results of this preliminary study suggest that chromohysteroscopy can increase the diagnostic accuracy of conventional hysteroscopy. Even though the number of cases was small, it opens a new avenue worth pursuing. Testing the procedure with other vital dyes and for other indications like implantation failure in ART cycles in randomized controlled studies is warranted.

References


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Fallopian tube cancer associated with paraneoplastic dermatomyositis - asymptomatic multivisceral exacerbated dermatomyositis mimicking recurrent widespread malignant disease: case report

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Summary

Objective: To report an uncommon case of a recurrent episode of primarily paraneoplastic dermatomyositis which was completely disconnected from the initially triggering malignancy and manifested as a silent pure multivisceral exacerbation.

Case: A 70-year-old woman presented with a pure multivisceral episode of dermatomyositis without characteristic musculo-cutaneous symptoms one year after successful treatment of fallopian tube carcinoma with complete resolvement of a concomittant paraneoplastic dermatomyositis. The uncommon manifestation of recurrent dermatomyositis involving the lungs, spleen and liver, both adrenal glands and abdominal lymph nodes, mimicked a highly disseminated recurrence of the fallopian tube cancer. Physicians participating in the interdisciplinary tumor board were misled to opt for reinductive chemotherapy. Only histologic diagnosis obtained from multiple biopsies uncovered the inflammatory nature of the disease and spared the patient unneeded chemotherapy.

Conclusion: Asymptomatic multivisceral dermatomyositis may mimic metastatic spread of the initially underlying malignancy and may misdirect therapeutic strategies towards inadequate antineoplastic treatment.

Key words: Carcinoma of the fallopian tube; Dermatomyositis; Paraneoplastic disease; Metastatic disease.

Introduction

Primary carcinoma of the fallopian tube accounts for less than 1% of all malignant neoplasms of the female reproductive tract. However, incidence is probably underestimated as many advanced cases are mistaken for ovarian cancer [1, 2]. In rare cases, three have been published in the literature so far [3-5], fallopian tube cancer is complicated by symptoms of paraneoplastic dermatomyositis (DM), which may account for early diagnosis of the underlying silent malignancy.

DM is an infrequent disorder with a prevalence rate estimated at less than one per 100,000 and is presumed to be of autoimmune pathogenesis. The disease is characterized by a symmetric proximal, extensor, inflammatory myopathy and typical cutaneous eruptions. The most important diagnostic feature is poikiloderma of the skin characterized by a violaceous color, features of hyper- and hypopigmentation, telangiectasia and epidermal atrophy. A striking attribute of poikiloderma in DM is photodistribution. Pulmonary disease occurs in approximately 15%-30% of patients with DM and generally presents as a diffuse interstitial fibrosis, which is a feature of patients with anti-transfer-RNA synthetase syndrome with Jo-1 antibodies [6]. Patients may develop adult respiratory distress syndrome, which accounts for a significant proportion of morbidity and mortality because of resistance to therapeutic agents including corticosteroids and therefore follows a course independent from that of the muscle disease.

The autoimmune origin of DM is supported by its association with other autoimmune disorders, autoantibodies and histocompatibility genes. The primary antigen target in DM is the endothelium of the endomysial capillaries [7, 8]. Initiation of the autoimmune-mediated processes is triggered by outside factors (e.g. malignancy, drugs or infections) in genetically predisposed individuals.

The reported frequency of DM as a paraneoplastic disorder varies from less than 10% to over 50% in adults [9]. The most commonly observed cancer types in women with DM are ovarian cancer, followed by breast and other gynecological and gastrointestinal cancers. Malignant disease may occur before the onset of DM, concurrently or afterward. Currently proposed hypotheses to explain the paraneoplastic nature of DM are 1) a common environmental trigger for both cancer and myositis in genetically susceptible hosts, 2) tumor products causing muscle and skin inflammation, and 3) cross-reactivity between tumor and muscle or skin antigens in the context of a tumor-induced dysregulation of the immune system [9].
Fallopian tube cancer associated with paraneoplastic dermatomyositis - asymptomatic multivisceral exacerbated dermatomyositis etc.

Case

A 70-year-old woman applied to the Department of Dermatology in January 2004 because of an itchy exanthema on her face and arms without recovery on conservative therapy with local corticosteroids. The patient exhibited typical features of DM: a characteristic violaceous poikiloderma with photodistribution and nail fold changes (Figure 1). The characteristic clinical picture of DM was supported by laboratory findings: increased CK (707 U/l; normal range: 26-140), LDH (408 U/l; normal range: 130-223) and aldolase (13.5 U/l; normal range: 3.9-9.5). Particular antinuclear antibodies (ANA) were found at a titer of 1:640. Jo-1 antibodies however, were negative. Due to the clinical picture of DM, an extensive search for a malignant condition was initiated. The computed tomography (CT) scan revealed a 6-cm mass in the left iliac fossa that was initially thought to be an ovarian tumor. The pelvic mass was confirmed by transvaginal ultrasound and described as predominantly cystic but partially solid. Serum CA-125 was elevated to 144 U/ml (normal range: 0-35 U/ml).

Systemic therapy with methylprednisolone (80 mg daily) was started, and the 6-cm multicystic tumor adherent to the sigmoid and originating from the left tube was removed during laparotomy. Debulking surgical procedures consisted of bilateral salpingo-oophorectomy, hysterectomy, partial resection of the sigmoid with end-to-end anastomosis, omentectomy and pelvic lymphnodectomy and led to a complete clearance of the macroscopic visible tumor. Paraortal lymphadenectomy was omitted because of major respiratory complications during general anesthesia.

Histopathological examination revealed a poorly differentiated carcinoma of the tube involving the resected colon and the peritoneum of the lower pelvis. Metastases were diagnosed in three out of 32 resected lymph nodes. According to FIGO (International Federation of Gynecology and Obstetrics) classification, disease was staged IIIc.

The patient had an unremarkable postoperative recovery, and the symptoms of the dermatomyositis improved promptly. Treatment was completed by adjuvant chemotherapy with carboplatin AUC-5 and paclitaxel 175 mg/m² given at three-week intervals for six cycles. The corticosteroid dose was reduced to 20 mg daily during and to 10 mg daily after chemotherapy. As all symptoms of dermatomyositis had resolved, the corticosteroid dose was reduced stepwise and consolidation treatment with azathioprine 3 x 50 mg daily was started.

One year after primary diagnosis, in January 2005 a CT scan performed in accordance to the guidelines of our aftercare program, showed multiple lesions in the lung (Figure 2), liver, spleen and in both adrenal glands that were highly suspicious for metastatic disease of the fallopian tube carcinoma. PET-CT scan confirmed these results and caused multiple metastases to be suspected in the lymph nodes of the left lower abdomen. However, serum CA-125 had further decreased to 6 U/ml. The patient was completely asymptomatic, without cough or dyspnea, cutaneous or muscular symptoms. At this time treatment consisted of 2 mg of methylprednisolone and 3 x 50 mg of azathioprine daily.

Based on diagnostic imaging the interdisciplinary tumor-board opted for reinduction chemotherapy with platinum and taxanes. However, before chemotherapy was started a decision was made to confirm the clinical diagnosis of widespread metastatic recurrent fallopian tube cancer by multiple CT scan and ultrasound-guided biopsies from the lesions of the lungs and the liver. Histopathological examination revealed a bronchiolitis obliterans organizing pneumonia with a surrounding lymphocytic interstitial pneumonia and chronic hepatitis without evidence of malignancy. The patient received 500 mg of clarithromycin twice a day for three weeks, and the corticosteroid dose was concomittantly increased to 20 mg daily. Four weeks later a significant regression of all previously described lesions was shown by CT scan.

In June 2005 another CT scan revealed that the liver and lung lesions had further regressed and all other lesions (adrenal glands, spleen, lymph nodes) had completely disappeared. To date, more than two years after the pure visceral episode of DM, the patient is in very good physical condition without any signs of DM and without evidence of recurrence of the fallopian tube carcinoma. Six months ago immunosuppressive medication was discontinued.

Discussion

In the reported case, severe symptoms of DM were decisive in bringing to light an underlying silent carcinoma of the fallopian tube, hence diagnosed at a stage of

Figure 1. — A 70-year-old patient with typical features of DM: characteristic violaceous poikiloderma with photodistribution.

Figure 2. — CT scan, one year after successful treatment of the carcinoma of the fallopian tube, showing multiple lesions in both lungs that were highly suspicious for metastatic disease.

Fig. 1 Fig. 2
relatively confined dissemination, allowing surgical clearance of all macroscopic tumor. The most intriguing aspect of this case, however, was the uncharacteristic purely multivisceral and asymptomatic manifestation of recurrent DM that was furthermore completely disconnected from the initially triggering malignant condition.

In general, a parallel course of both conditions is expected and exacerbation of the symptoms of paraneoplastic DM is commonly observed just before or concomitantly with the diagnosis of recurrent malignant disease [10]. However, our patient was completely free of symptoms when multiple lesions in both lungs and adrenal glands, the liver and lymph nodes of the lower pelvis were diagnosed by CT and PET scan. The lack of characteristic musculo-cutaneous symptoms of DM, the exclusion of interstitial lung disease frequently observed in DM by high-resolution CT scan and the fact that lesions of the liver, spleen and adrenal glands are very uncommon in DM [11] led to the clinical diagnosis of highly hematogenous disseminated recurrent fallopian tube carcinoma. Consequently, the majority of physicians participating in the interdisciplinary tumor-board opted for reinductive platinum-based chemotherapy.

Nonetheless, some of the findings such as the further declining levels of serum CA-125 and the lack of peritoneal involvement or ascites were discrepant with the diagnosis of widespread fallopian tube cancer. Even though hematogenous spread is slightly more frequent in fallopian tube carcinoma than in ovarian cancer, the disease generally remains confined to the abdominal cavity and purely hematogenous tumor dissemination is more than exceptional [12]. Thus, the case was read-dressed and the decision was made to perform CT scan and sonography-guided biopsies of the lesions to obtain a histological diagnosis. Histopathological examination revealed a surprising result since there was no evidence of malignant disease, either in the lung or the liver, but the examined lesions were inflammatory in nature. The DM-related immunologic background of the multivisceral inflammatory disease was finally corroborated by the disappearance of all lesions after increasing the corticosteroid doses.

We conclude from our own experience, that in malignancies complicated by paraneoplastic DM, patients have to be viewed in consideration of each particular disease. Physicians should be aware of a pure multivisceral and asymptomatic manifestation of recurrent DM, which may remain unrelated to the course of the initially underlying malignant tumor, but can convincingly mimic widespread malignant disease. Especially in such cases, it is mandatory to confirm the malignant nature of suspicious lesions by histology in order to spare patients from unneeded chemotherapy.

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Neoadjuvant chemotherapy followed by extended-field concurrent chemoradiotherapy in squamous cell carcinoma of the cervix with positive paraaortic lymph nodes: two cases

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Summary
Purpose: To report the feasibility of neoadjuvant chemotherapy (NAC) followed by extended-field concurrent chemoradiotherapy (EF-CCRT) for squamous cell carcinoma of the cervix (CC) with paraaortic lymph node (PAN) metastasis. Methods: Two patients were diagnosed with CC with positive PAN, and received two courses of cisplatin (120 mg/m²) in a neoadjuvant setting. They then received extended-field, external-beam radiotherapy (50.4 Gy) followed by intracavitary brachytherapy concurrently with cisplatin (20 mg/m² x 5 days) at 21-day intervals. Results: EF-CCRT was interrupted in one patient for five days because of grade 4 neutropenia. No severe late toxicities were observed. The two patients are alive with no evidence of recurrence at present. Conclusions: NAC followed by EF-CCRT is feasible and may improve the survival outcome of patients with CC with positive PAN.

Key words: Cervical cancer; Paraaortic lymph node metastasis; Neoadjuvant chemotherapy; Concurrent chemoradiotherapy.

Introduction
The survival outcome of patients diagnosed as having cervical cancer with paraaortic lymph node (PAN) metastasis is poor. Several retrospective studies have demonstrated a 5-year survival rate of approximately 30% in the patients treated with extended-field (EF) radiation therapy (RT) alone [1, 2]. To improve the survival outcome, cisplatin-based EF concurrent chemoradiation therapy (EF-CCRT) has been used to treat patients with cervical cancer with PAN metastasis. However, the survival rates at three to four years in these trials were reported to still be 30-39% [3, 4]. These trials emphasized that distant metastases were predominant sites of treatment failure. Ayman et al. [5] reported preliminary data showing that concurrent cisplatin-based chemotherapy with EFRT for this subset of patients appeared to improve pelvic and PAN control but not the rate of distant metastasis and survival. All patients in whom the cancer recurred died because of distant metastasis, which suggests that more effective systemic therapy should be explored.

To control distant failure, we treated patients with PAN metastasis using systemic neoadjuvant chemotherapy (NAC) followed by EF-CCRT. Here we present the preliminary report of two cases treated with NAC followed by EF-CCRT.

Materials and Methods
The characteristics of the patients are shown in Table 1. Both patients were diagnosed with International Federation of Gynaecology and Obstetrics (FIGO) Stage IIIb squamous cell carcinoma of the cervix with PAN metastasis (20 x 18 mm and 15 x 12 mm in size, respectively) evaluated by computed tomography (CT). Pelvic lymph node enlargement was also detected by CT (at least 10 mm in diameter). The patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 and adequate hematologic, hepatic, and renal (creatinine clearance: ≥ 60 ml/min) functions. Written informed consent was obtained prior to treatment. Initially, two courses of 120 mg/m² of cisplatin (CDDP) was administered intravenously at 21-day intervals. Appropriate hydration and antiemetics were given before and after CDDP administration. We chose a dose of 120 mg/m² of CDDP for NAC because several studies have demonstrated that nephrotoxicity and peripheral neuropathy in response to this dose is acceptable [6]. After the completion of NAC, PAN shrinkage was observed. A combination of external-beam radiotherapy (EBRT) for five days per week, and high-dose-rate intracavitary brachytherapy (HDR-ICRT) using Ir-192 were delivered. Pelvic and paraaortic areas (EF) were treated as a continuous area, with a superior field border at the space between Th12 and L1. EF irradiation was delivered at a total dose of 45 Gy in 25 fractions, after which whole pelvic irradiation was delivered (5.4 Gy in 3 fractions). A midline block (4 cm width at the midline) was inserted into the center of the pelvic field after 39.6 Gy had been delivered. Boost EBRT was delivered to the enlarged pelvic nodes and infiltrated parametrium. A total dose of 6 Gy in three fractions was delivered. Three fractions of HDR-ICRT with a single dose of 6 Gy was delivered at point A once a week. Cisplatin (20 mg/m² for 5 days) was administered concomitantly with RT every 21 days [7]. Acute toxicity was graded according to NCI-CTC version 3.0. Late complications, such as...
In case 1, NAC reduced PAN size by 60% and reduced the size of the local tumor by 90%. In case 2, PAN swelling disappeared and the cervical tumor shrank to 91% in size. A complete pathologic and clinical response was achieved in both patients at the time of completion of EF-CCRT. At 15 and 22 months of follow-up, respectively, the two patients were alive with no evidence of recurrence. The most severe toxicity experienced by the two patients is shown in Table 2. There were no treatment-related deaths and both patients experienced acute hematologic. RT was interrupted in one patient for five days because of grade 4 neutropenia. No severe late complication associated with RT was observed. Case 1 experienced grade 2 peripheral neuropathy associated with chemotherapy.

### Discussion

The incidence of positive PAN has been reported to be 6%, 16%, and 25% in patients with FIGO Stage I, II, and III disease, respectively [8]. Berman et al. [8] reported that the median survival of 98 patients with Stage IIB and IIIB cervical cancer (PAN metastases) treated with EFRT was 15.2 months and the 3-year survival was 25%. Grigsby et al. [3] reported that the 3-year and 5-year overall survival rates of 43 patients treated with EFRT were 37% and 32%, respectively. Forty percent (n = 17) of the patients developed distant metastasis with or without pelvic failure. Because of the poor prognosis of patients treated with EFRT alone, several studies using CCRT have been conducted. The GOG conducted a multicenter trial of CCRT to evaluate the feasibility of EFRT concurrent with 5-fluorouracil and cisplatin. The main grade 3/4 acute toxicities were gastrointestinal (18.6%) and hematologic (15.1%) in nature. Distant metastasis occurred in 41.9%, and pelvic failure was observed in 31.4% of the patients. The 3-year overall survival and progression-free survival were 39% and 34%, respectively [4]. Recently, Saad et al. [5] reported the treatment outcomes for cervical cancer patients with PAN treated with EFRT with or without chemotherapy. The median follow-up period was 26 months. The 3-year pelvic node and PAN control rate was 100% and 42.2%, respectively, (p = 0.03), and the 3-year distant control rate was 81.8% and 46.2% (p = 0.5) with and without chemotherapy, respectively. However, Saad et al. concluded that the addition of concurrent cisplatin-based chemotherapy to EFRT for this subset of patients appeared to improve the pelvic and PAN control rate but not the rate of distant metastasis and survival. All the patients with recurrent disease died as a result of distant metastasis, which suggests that a more effective systemic therapy should be explored.

Several studies have demonstrated the efficacy of NAC followed by CCRT for the treatment of head and neck cancer. These studies concluded that the treatment decreased distant metastasis by 20% and resulted in a better prognosis [9, 10]. In our patients, NAC was used for the control of distant metastasis in two PAN-positive patients with squamous cell carcinoma of the cervix. The adverse effect of NAC was mild, and there was no grade 3 or 4 toxicity. In contrast, the two patients had grade 3 neutropenia during EF-CCRT. However, the acute and late gastrointestinal toxicities of EF-CCRT were mild, and the patients completed their planned treatments. Because of the short follow-up intervals, the efficacy of NAC followed by CCRT is unclear; however, the patients were alive without recurrence for over a year. Due to its feasibility and potential efficacy, there is the possibility that NAC followed by CCRT may improve the prognosis of cervical cancer patients with positive PAN.
Conclusions

NAC followed by EF-CCRT is feasible and may improve the survival outcome of patients with CC with positive PAN.

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Primary ovarian choriocarcinoma mimicking ectopic pregnancy managed with laparoscopy - case report

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Summary

Nongestational ovarian choriocarcinomas are extremely rare and pose diagnostic challenges in reproductive-aged patients because of elevated human chorionic gonadotrophin (hCG). A 23-year-old nulliparous Chinese woman with nongestational ovarian choriocarcinoma escaped diagnostic testing and was initially treated for an ectopic pregnancy. Three months after her first visit, a diagnostic laparoscopy demonstrated a nongestational ovarian choriocarcinoma. Comprehensive surgical staging was performed by laparoscopy. The tumor was confined to the left ovary. The patient was categorized as FIGO Stage IA. She was given four courses of combined chemotherapy after laparoscopic surgery and has been disease-free for 36 months.

Key words: Nongestational ovarian choriocarcinoma; Human chorionic gonadotrophin; Laparoscopy; Chemotherapy.

Introduction

Nongestational ovarian choriocarcinoma is an extremely rare tumor presumably arising from the transformation of a single germ cell. In a recent report by Lai and colleagues, only one choriocarcinoma was identified among 84 ovarian germ cell malignancies (GCMs) [1]. Notwithstanding its sensitivity to chemotherapy, nongestational choriocarcinoma is associated with an unfavorable prognosis especially in advanced stage. Therefore, early diagnosis and timely initiation of therapy is important and present unique challenges in reproductive-aged women. This report describes the clinical features and outcome of a case diagnosed and managed with laparoscopic ipsilateral salpingo-oophorectomy and surgical staging followed by the administration of a multiagent chemotherapeutic regimen.

Case Report

A 23-year-old sexually active woman, gravida 0, was admitted to our hospital on April 9, 2004. She presented with ten days of vaginal spotting after 50 days of amenorrhea. The hCG level increased from 256.0 U/l (normal range below 10 U/l) to 363.1 U/l during a ten-day interval. Considering ultrasound failed to identify an intrauterine pregnancy, an ectopic pregnancy was suspected and the patient was treated with 75 mg methotrexate (MTX). The hCG nadir of 58 IU/l was recorded two weeks after the second medication was administered. The patient underwent laparoscopic ipsilateral salpingo-oophorectomy and surgical staging followed by the administration of a multiagent chemotherapeutic regimen.

ovarian mass measuring 1.5 cm x 2.2 cm x 2.0 cm with a lower resistance index (RI) of 0.43 (Figures 1a and 1b). Recorded hormone assay indices included LH: 0.41 IU/l, FSH: 2.2 IU/l, TTE: 1.4 nmol/l, E2: 499.8 pmol/l, P: 9.7 nmol/l, PRL: 26.2 ng/ml. Tumor markers including CA125, CEA and α-fetoprotein were within the normal range except for hCG. With an indeterminate diagnosis, a diagnostic laparoscopy was performed on July 14, 2004. Intraoperative assessment revealed a normal appearing uterus and right adnexal structures and a small solid mass 2.0 cm in diameter with a smooth surface in the left ovary (Figure 2). Inspection of all other viscera and peritoneal surfaces failed to identify any suspicious lesions. The solid mass was enucleated and submitted for frozen section analysis. Frozen section examination reported a primary ovarian choriocarcinoma. The patient underwent laparoscopic ipsilateral salpingo-oophorectomy and peritoneal multipoint biopsy and pelvic lymph node sampling.

A detailed pathological examination reported a mixed germ cell tumor consisting predominantly of choriocarcinoma with smaller components of dysgerminoma and immature teratoma. Surgical pathological stage was IA. Adjuvant chemotherapy consisted of one course of EMA-EP and three courses of BEP, completed in October 2004 without major complications. The hCG level normalized within 28 days after the operation and the patient has been without clinical or biochemical evidence of disease for 22 months. The pattern of alterations in the hCG levels during the total clinical course is shown in Figure 3.

Discussion

Nongestational choriocarcinoma is an extremely rare malignant tumor of the ovary. While occasionally detected as a homogeneous lesion, other germ cell components are frequently present. Unfortunately, this biologically aggressive tumor is commonly found in young women prior to age 20. Early-stage ovarian choriocarcinoma presents a significant diagnostic challenge in the reproductive-aged patient because of elevated hCG. While the differential diagnosis includes both an ectopic pregnancy and gestational trophoblastic disease, seldom
is nongestational choriocarcinoma a consideration. Irregular menses and vaginal bleeding may be common but with nonspecific complaints and signs that only reflect high hCG levels. Isosexual precocity has been reported to occur in about 50% of patients whose lesions appear before menarche [2]. The hCG may be the most sensitive measurement in diagnosing and monitoring the response to treatment. In the case reported here, the hCG was elevated before the abnormal image finding was detected. Laparoscopy would provide an additional important diagnostic tool in securing histologic definition. While laparoscopic management of benign ovarian tumors has become the treatment of choice, controversy persists regarding the management of malignant ovarian tumors that appear localized. There is justifiable concern about the risk of tumor rupture. Notwithstanding some studies that have demonstrated no adverse sequelae following intraoperative rupture for Stage I cancer, other reports have shown compromised outcomes [3, 4]. Laparoscopic retroperitoneal lymph node dissection has been applied widely to the staging and treatment of different kinds of cancer [5]. Some researchers consider that this minimally invasive procedure can fully duplicate the open technique and adhere to established strict oncologic principles [6]. A Gynecologic Oncology Group (GOG) study showed that laparoscopic staging of gynecologic malignancies can be successfully undertaken in selected patients [7]. In this reported case, with an indeterminate diagnosis, laparoscopic enucleation of the ovarian tumor was performed before pathological diagnosis was made. We think it is reasonable to complete the surgical staging procedure by laparoscopy when a lesion is confined to the ovary.

Only a limited number of reports exist evaluating the efficacy of the use of chemotherapy for nongestational choriocarcinoma. However, complete responses have been reported with the EMA/CO regimen (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) for pure nongestational choriocarcinoma [8]. The BEP regimen (bleomycin, etoposide, cisplatin) may be preferred as an alternative chemotherapy protocol [9]. An overall 5-year relative survival for ovarian germ-cell

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**Table 1.** — Plasma lipid profile of control subjects & patients with gynecologic cancers (mean ± SD).

<table>
<thead>
<tr>
<th></th>
<th>Triglycerides</th>
<th>Cholesterol</th>
<th>LDL-cholesterol</th>
<th>HDL-cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control subjects</td>
<td>158.29 ± 6.31</td>
<td>176.35 ± 7.62</td>
<td>76.87 ± 5.05</td>
<td>54.42 ± 4.73</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>186.44** ± 5.61</td>
<td>214.13** ± 6.23</td>
<td>109.99** ± 4.12</td>
<td>38.22** ± 3.31</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>109.13 ± 8.45*</td>
<td>127.77 ± 8.09*</td>
<td>68.55* ± 8.01</td>
<td>33.33 ± 7.54**</td>
</tr>
<tr>
<td>Other gynecologic cancer</td>
<td>118.23 ± 7.19*</td>
<td>138.97 ± 5.81*</td>
<td>66.12* ± 6.41</td>
<td>40.00 ± 3.03**</td>
</tr>
</tbody>
</table>

* p < 0.01 as compared to control group; ** p < 0.05 as compared to control group.
tumors of 73% has been reported [10]. In this report, two courses of single-dose MTX were not effective although the pretreatment hCG level was low. The lack of response suggests that a single dose of MTX is not an appropriate choice for nongestational ovarian choriocarcinoma even though our case was in early stage with very low volume.

In conclusion, diagnostic laparoscopy is invaluable in the differential diagnosis between early stages of primary ovarian choriocarcinoma and other diseases with elevated hCG in reproductive-aged women. If the tumor is confined to the ovary, continuing the staging procedure by laparoscopy followed by an adjuvant BEP chemotherapy regimen is feasible when evidence-based therapeutic options are limited or non-existent.

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Unusual histologic finding in tissue obtained from voluntary pregnancy termination: a case report

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Summary

Background: An unusual histologic finding in tissue obtained from voluntary pregnancy termination (VPT) is reported to demonstrate the utility of pathologic examination of this specimen. Methods: A 30-year-old woman with a history of depression was referred to the gynecology clinic for VPT in the eighth week of gestation. Material obtained from uterine cavity curettage was macroscopically and histologically examined. Based on the histological findings, a molecular study by polymerase chain reaction amplification (PCR) was performed to evaluate the presence of human papilloma virus (HPV) DNA. For DNA extraction, 4-μm-thick histological sections were stained with hematoxylin and examined under a stereomicroscope. The PCR amplification was performed with the L1 consensus primers Gp5+/Gp6+, giving an expected PCR product size of 150 bp: these primers have been developed to allow the detection of a broad spectrum of mucosotropic HPV genotypes. Results: Histological examination of tissue obtained from the VPT showed immature villi with post-abortion hydropic degeneration and the presence of a small fragment of cervical mucosa with a squamous intraepithelial lesion characterized by mild to moderate nuclear atypia (SIL). PCR revealed that this lesion was related to HPV. Subsequently, the pap smear and cervical biopsy revealed a high-risk squamous intraepithelial lesion due to high-risk HPV. Conclusions: This report demonstrates that tissue obtained from VPT cannot be considered normal “a priori” and that a histological study can be useful to provide new information regarding a woman’s gynecological health.

Key words: bcl-2; Voluntary pregnancy termination (VPT); Histological examination; Polymerase chain reaction amplification (PCR).

Introduction

In 1977, the World Health Organization (WHO) defined abortion as “the expulsion or extraction from its mother of a fetus or embryo weighing 500 g or less” [1]. Currently, abortion is defined as the spontaneous termination of pregnancy prior to viability of the fetus [1]. Induced abortion is a legalized voluntary abortion, which allows the interruption of an unwanted pregnancy, mainly on the basis of the woman’s physical or psychological condition [2, 3].

Currently, there is no general agreement about the value of histologic examination of tissue obtained from spontaneous or voluntary pregnancy termination (VPT) [4].

An unusual histologic finding in tissue obtained from VPT is reported in order to demonstrate the utility of pathologic examination of this specimen thus providing new information regarding a woman’s gynecological health.

Case Report

A 30-year-old woman with a history of a depression was referred to the gynecology clinic for VPT in the eighth week of gestation.

Material obtained from uterine cavity curettage was macroscopically and histologically examined. On macroscopic examination, the material contained clots and fragments of placental tissue.

Histological examination revealed immature villi with post-abortion hydropic degeneration and the presence of a small fragment of cervical mucosa with a squamous intraepithelial lesion characterized by mild to moderate nuclear atypia (SIL) (Figures 1a and 1b).

Polymerase chain reaction amplification (PCR) was performed to evaluate the presence of human papilloma virus (HPV) DNA in the neoplastic epithelium of the cervical mucosa. For DNA extraction, 4-μm-thick histological sections were stained with hematoxylin and examined under a stereomicroscope. PCR amplification was performed with the L1 consensus primers Gp5+/Gp6+ [5], giving an expected PCR product size of 150 bp: these primers have been developed to allow the detection of a broad spectrum of mucosotropic HPV genotypes (6, 11, 13, 16, 18, 30-35, 39, 40, 42, 45, 51-53, 56, 58, 61, 66). Most of these genotypes are correlated with lesions of high oncogenic risk (16, 18, 45, 56 and 58).

Molecular study by PCR amplification of different dilutions of tumor DNA revealed a positive signal for HPV DNA in the cervical lesion (Figure 1c).

After one month, a cervical smear was performed and was consistent with a high-risk squamous intraepithelial lesion (HSIL).

Subsequently, two small biopsies of the cervical tissue confirmed the diagnosis of HSIL (Figure 1d), with over-expression of the p16 protein on immunohistochemical analysis.

Six months postoperatively, on colposcopic examination and pap smear study, the cervix was healing well.

Conclusions

SIL of the cervix is characterized by abnormal cellular proliferation, maturation and cytologic atypia of the cervical epithelium. The spectrum of epithelial alterations...
which constitute SIL are quantitatively classified into three categories: CIN grade 1, neoplastic cells occupying the lower third of the epithelium; CIN grade 2, neoplasm occupying two-thirds of the epithelium; and CIN grade 3, neoplastic cells occupying two-thirds to full thickness of the epithelium.

Clinically, both LSIL and HSIL are asymptomatic conditions and the diagnosis can be made by cytological or histological studies after colposcopic examination.

In the present case the presence of HPV DNA on PCR study and overexpression of the p16 protein on immunohistochemical analysis revealed that the HSIL was related to high-risk HPV, which could cause the progression of the lesion to invasive cervical cancer [6].

Moreover, this report demonstrates that tissue obtained from VPT cannot be considered normal “a priori” and that a pathological study can be useful to provide new information regarding a woman’s gynecological health.

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Metastatic breast carcinoma initially presenting as acute cholecystitis: a case report and review of the literature

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Summary

Introduction: The gallbladder is an infrequent site of metastatic malignant disease. Although malignant melanoma, renal cell and cervical carcinoma have been documented, breast carcinoma has rarely been reported to metastasize in the gallbladder. Case Report: We describe such a case that manifested as acute cholecystitis and was incidentally recognized after cholecystectomy, in an otherwise disease-free 46-year-old female who had undergone mastectomy for breast cancer two years before. The patient was subjected to adjuvant chemotherapy, but unfortunately died just a year after diagnosis because of generalized peritoneal seeding of the tumor. Discussion: Metastatic gallbladder involvement is rare, especially in cases of primary breast carcinoma, usually leading to symptoms of abdominal pain, mimicking acute or chronic cholecystitis. Thus, abdominal pain in a patient with a previous history of breast carcinoma should raise suspicion of gallbladder metastasis.

Key words: Metastatic breast cancer; Acute cholecystitis; Ductal breast carcinoma; Gallbladder metastasis.

Introduction

Breast cancer mostly metastasizes to the liver, bones and lungs. Less frequently, metastatic sites of breast carcinoma include the central nervous system, the skin, endocrine organs (ovary, adrenal, pituitary), the pericardium and the peritoneum [1]. Generally, no site is immune to the spread of the tumor, either at the time of presentation or later in the course of the disease.

The occurrence of metastases to the gallbladder is rare and has only been reported in the literature exceptionally. Malignant melanoma is the tumor that is most likely to metastasize to the gallbladder [2]. In a series of 7,910 cholecystectomy specimens, 36 cases of metastatic carcinoma were found, all deriving from biliary or gastrointestinal primaries [3]. Metastatic breast cancer to the gallbladder is even less frequent with only four cases having been reported [1, 4, 5].

We report a case of metastatic breast cancer that was discovered incidentally in the specimen of a laparoscopic cholecystectomy in a patient undergoing surgery for acute cholecystitis.

Case Report

A 46-year-old female was admitted to our department complaining of right upper quadrant colic pain. She had experienced similar episodes twice during the preceding six months. According to her medical history, the patient had undergone a right modified radical mastectomy because of an infiltrating ductal breast carcinoma, measuring 2.5 x 3 cm two years before. Pathology had revealed two axillary nodes to be infiltrated. The work-up (chest X-ray, abdominal CT scan) that had been conducted showed no signs of metastatic breast disease.

On admission, the patient was suffering from tenderness on palpation of the right upper quadrant. Examination revealed no signs of metastatic breast disease. Abdominal ultrasound imaging showed thickening of the wall of the gallbladder, indicating cholecystitis, multiple cholelithiasis of the cyst and no common bile duct dilatation. Based on the imaging control and the clinical and laboratory examination, the diagnosis of acute cholecystitis was established. Laparoscopic cholecystectomy was decided and successfully conducted within the first 48 hours after the onset of the symptoms. The gallbladder was found to be hydropic, while no evidence of other intraabdominal pathology was viewed during laparoscopy. Multiple small gallstones were found in the specimen. The patient had an uneventful postoperative course.

Histological examination confirmed the diagnosis of cholecystitis, showing features of chronic cholecystitis with fibrosis of the gallbladder wall and a chronic inflammatory infiltrate, but also revealed glandular poorly differentiated metastasis of a breast carcinoma invading the muscularis and serosa. Hematoxylin and eosin stain showed moderately differentiated adenocarcinoma (Figures 1 and 2). Characteristically scattered signet-ring cells were viewed in the infiltrated mucosa of the gallbladder. The cells of the tumor were immunohistochemically proven to be positive for lactalbumin (Figure 3) as well as, cytokeratin 7-positive and cytokeratin 20-negative. Estrogen and progesterone receptors were negative. Not even a clue of a primary carcinoma or mucosal dysplasia was found, in spite of sectioning the entire gallbladder. Searching for a primary in the biliary tree, stomach and ovaries yielded no evidence. Histological sections of the mammary specimen, from the previous mastectomy, were obtained anew and re-evaluated. It was proven that both carcinomas examined were of the same histologic nature.

The patient was subjected to additional laboratory tests as well as imaging tests afterwards. Carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), and thyroid transcription factor 1 (TTF1) were negative. Blood tumor markers showed CA125, CA19-9, alpha-fetoprotein (AFP), and CEA to be normal, and only CA 15-3 was increased (1784 IU/ml). Mammography of the other breast was normal. Computed tomography (CT) of the brain, chest, abdomen, and pelvis was performed without any pathological findings. Bone Tc-99 scintigraphy was normal.

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The patient was set on a scheme of adjuvant chemotherapy consisting of doxorubicin, cyclophosphamide and 5-FU. Our patient did not receive any hormonal therapy due to her unfavorable hormonal receptor status. A year later she died because of generalized peritoneal seeding of the tumor.

Discussion

Gallbladder cancer is an incidental finding in 1-2% of all open cholecystectomies, while in to laparoscopic cholecystectomies it is less than 1%. In case of acute cholecystitis an incidence up to even 8.8% has been reported, also including metastatic gallbladder carcinoma [6]. The gallbladder wall rarely comprises a metastatic site in the course of malignant disease, with a reporting incidence of only 5.8% in a large series of autopsies [7, 8]. Primary tumors can metastasize to the gallbladder either by direct extension, such as hepatocellular and pancreatic carcinoma, or by hematogenous spread. The tumor most likely to metastasize via the latter way is malignant melanoma. Breast carcinoma metastasizes to the gallbladder extremely rarely, with scattered cases being reported worldwide and mostly diagnosed incidentally from the specimen after cholecystectomy [1, 4, 9]. In autopsy series, however, breast carcinoma metastasizing to the gallbladder arises in 4-7% of cases [4, 5, 10]. In contrast, breast carcinoma, except for lymphomatous spread, frequently metastasizes to the bones, lungs and gastrointestinal system, especially to the liver and extrahepatic biliary system [1, 4, 6].

Metastatic breast carcinoma first detected in the gallbladder appears to be even more infrequent, with only four cases documented in the literature [1, 4, 5]. Autopsy findings have shown that secondary hematogenous metastases from primary organs to the gallbladder initially generate small flat nodules below the mucosal layer, which then grow as a pedunculated tumor, rarely reaching greater than several millimeters in size. This explains why most gallbladder metastases do not cause any symptoms, and are rarely detected during the person’s lifetime [10]. The most frequent symptomatic presentation is acute cholecystitis [11]. Obstructive jaundice, hemobilia, even bile peritonitis due to perforation are rarely described [5, 12-17].

Among the reported cases of gallbladder metastasis manifestation as the first finding of breast cancer recurrence, the first was discovered three years after mastectomy [1] whereas the others were detected after a routine cholecystectomy [9, 18]. The case reported here is unusual due to the long time that had elapsed since mastectomy, as well as being an incidental finding due to coexisting cholecystitis.

The differential diagnosis between primary carcinoma of the gallbladder and metastatic breast carcinoma to the gallbladder is of great significance [14]. Thus, immunohistochemical evaluation is necessary. The most reliable markers are gross cystic disease fluid protein-15 (GCDEP-15), cytokeratin 7, cytokeratin 20, and estrogen and progesterone receptors. Metastatic breast carcinomas are usually positive for GCDEP-15, positive for cytokeratin 7, and negative for cytokeratin 20, and they are often positive for estrogen receptor and/or progesterone receptor [19]. Likewise, the distinction between metastatic breast carcinoma to the gallbladder and diffuse carcinoma of the liver is also essential, because patients suffering from the latter present with a poorer prognosis [14]. Detecting the primary tumor site is based on pathology as well as specific immunohistochemical stains, such as casein and lactalbumin [20]. Moreover, metastases often do not form glands or tubular structures, but do infiltrate as small nests and strands of tumor cells, which are usually of the signet-ring type. In addition, the “signet-ring” morphology of lobular carcinoma may mimic other primary tumors, e.g., gastric carcinoma. Referring to the reported case, the tumor cells were proven to be immunohistochemically positive for lactalbumin. Moreover, primary breast carcinoma and metastasis to the gallbladder were similar in pathology. This evidence is in favor of the diagnosis of metastatic breast carcinoma to the gallbladder [21].

For ten years following initial treatment, distant metastases are the most common cause of death in breast cancer patients. Sixty percent of cases developing distant metastases, being present at the time of diagnosis, will be manifested within 24 months of treatment of the primary cancer [22]. Metastases may become evident as late as ten to 20 years after the initial treatment [23]. Adjuvant therapy does not seem to prolong survival significantly, to date. In case of metastatic breast cancer to the gallbladder and according to the literature, resection of the gallbladder leads to a median survival of 2.5 years, while in coexistence with a metastasis to the liver decreases to 15 months [16, 24]. Survival generally ranges from a few months to three years [14]. In the presented case, the histological features of the metastatic carcinoma combined with those of the primary breast cancer were both suggestive of ductal carcinoma. Prognosis of invasive ductal carcinoma has proven to have worse short- and long-term survival than invasive lobular carcinoma [25].

In general, the treatment of metastatic breast carcinoma is usually aggressive, combining surgery, chemotherapy and hormonotherapy [17]. Multiple-chemotherapy includes two or more cytostatic agents, such as doxorubicin and 5-FU, achieving much better disease-free intervals and overall survival than monotherapy. In our patient, the applied scheme of chemotherapy consisted of three cytostatic agents, while no hormonotherapy was provided as no receptors were detected, neither at the primary nor the metastatic tumor. Prognosis of metastatic breast cancer to solid organs is regarded as dismal. Although resection should be considered as palliative treatment in a patient with gallbladder metastasis from breast carcinoma, it is recommended in a case which exhibits symptoms.

In conclusion, metastatic gallbladder involvement is rare, especially in a case of primary breast carcinoma. It usually manifests with abdominal pain, mimicking acute or chronic cholecystitis. Its prognosis is poor [26]. Thus, right hypochondrial pain in a patient with a history of breast carcinoma should raise the suspicion of metastatic gallbladder disease which should be treated aggressively as it portends a poor prognosis.
References


Virchow’s node as a first manifestation of ovarian serous carcinoma: case report

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Summary

Ovarian carcinoma is a malignancy with a poor prognosis especially in patients with advanced disease. The majority of patients with ovarian serous carcinoma are diagnosed in advanced stages. Palpable extraabdominal lymphadenopathy at the time of presentation is distinctly uncommon. This case report addresses a patient with serous ovarian carcinoma presenting as left supraclavicular lymphadenopathy (Virchow’s node) and no other symptoms. Not only thyroid or thoracic malignancies but also ovarian malignancies like serous ovarian carcinoma could present with a supraclavicular lymph node without any other symptoms.

Key words: Supraclavicular lymph node (Virchow’s node); First presentation; Ovarian serous carcinoma.

Introduction

Ovarian carcinoma is a malignancy with a poor prognosis especially in patients with advanced disease. Unfortunately the majority of patients with serous carcinoma of the ovaries are diagnosed in advanced stages, presenting with gastrointestinal symptoms, increased abdominal girth, a sense of bloating, or a combination of these, all of which are related to extensive intraabdominal disease.

Less is known about patients with serous carcinoma involving the extraabdominal lymph nodes. Extraabdominal lymphadenopathy at the time of presentation of serous carcinoma has been documented in the literature, whereas serous carcinoma more frequently involves the pelvic and paraaortic lymph nodes. Palpable extraabdominal lymphadenopathy at the time of presentation is distinctly uncommon [1, 2].

We report the case of a patient with ovarian serous carcinoma presenting with a supraclavicular lymph node and discuss the differential diagnosis.

Case Report

A 64-year-old woman with a mass in her left supraclavicular region was referred by her general practitioner for a surgical opinion. A large mass (about 4 cm in diameter) was felt in her left supraclavicular region. There was no evidence of generalized lymphadenopathy. The patient had no history of thyroid disease or evidence of a thyroid node.

Fine-needle aspiration of the mass was performed in the clinic. The histology report was serous papillary adenocarcinoma, including psammoma bodies (Figure 1). To evaluate the thyroid, ultrasonography was performed. No evidence of thyroid disease or evidence of a thyroid node was found.

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The tumour marker CA125 was raised (650 u/ml) and the patient was referred for a gynecological oncology opinion. She was advised to have a laparotomy. Laparotomy through a midline incision was performed and the finding was of an enlarged left ovary about 7 cm in diameter. The omentum, liver and the abdominal cavity looked normal; 200 ml of ascites were aspirated. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic-paraaortic lymph node dissection and omentectomy were performed. Histology showed serous adenocarcinoma in the left ovary with metastatic disease in the paraaortic node. The final diagnosis was FIGO Stage IV carcinoma of the ovary. Carboplatin and taxol were recommended as adjuvant therapy.

Discussion

Ovarian cancer accounts for 4% of all cancers in women and is the leading cause of death from gynecologic malignancies. Because early-stage ovarian cancer is generally asymptomatic, approximately 75% of women present with advanced disease at diagnosis [3]. Typically, serous carci-
noma arising in the ovary, fallopian tubes and peritoneum is spread by intraperitoneal seeding, local invasion, or both and leads to widespread intraabdominal disease and peritoneal/pleural effusions causing abdominal and gastrointestinal symptoms such as increased abdominal girth, a sense of bloating and mass in the abdomen. Lymphadenopathy, especially in the supradiaphragmatic region, is an unusual presentation of serous carcinoma of the ovary, fallopian tubes and peritoneum.

The subperitoneal lymph vessels are connected with infradiaphragmatic nodes; peritoneal fluid is drained in part via the diaphragmatic lymphatic vessels. This lymphatic route explains supradiaphragmatic metastatic lymph nodes from ovarian cancer [4, 5].

Several autopsy studies have demonstrated that lymph node metastases are a frequent event in women who die of ovarian cancer and have shown that abdominopelvic lymph nodes, as well as supradiaphragmatic and inguinal lymph nodes, may be involved [2]. However, these studies did not state whether the women had lymph node metastases at presentation. Recent studies have demonstrated that more than 50% of women with ovarian or peritoneal carcinoma may have retroperitoneal lymph node involvement at the time of initial staging with the risk of nodal metastases increasing as the stage of disease advances [1, 6].

The supraclavicular lymph node (SCLN) (also known as the sentinel lymph node), in many instances is the first sign of an underlying malignancy in the thoracic cavity, abdominal cavity, or the pelvic region. SCLN presentations may also mimic thyroid cancer as well as mesothelioma. The left SCLN (also called Virchow’s lymph node) has been known to be a common site of distant metastasis in the spread of gastric cancer.

This case report addresses a patient with serous carcinoma presenting as supraclavicular lymphadenopathy. She had no concomitant symptoms related to intraabdominal disease. It should be kept in mind that not only thyroid or thoracic malignancies but also ovarian malignancies like serous ovarian carcinoma could present with a supraclavicular lymph node without any other symptoms.

References

Vaginal paraganglioma presenting as a gynecologic mass: case report

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Summary

Paragangliomas in the vagina are extremely rare. Unwitting surgical excision of a functional paraganglioma may precipitate life-threatening complications. We present a case of a 38-year-old woman with a vaginal mass 3.0 cm in diameter who experienced a hypertensive crisis during an unwitting attempted surgical excision of the vaginal mass. The diagnosis of a vaginal functional paraganglioma was then made based on to her 16-year history of paroxysmal headaches, chest distress, palpitation and elevated levels of urinary vanillylmandelic acid (VMA). Consequently, after thorough presurgical preparation, the patient again underwent excision of the vaginal mass uneventfully. She has been followed-up for three years since surgery without any evidence of recurrence. The clinical features and perioperative management of functional vaginal paraganglioma are described.

Key word: Paraganglioma; Vagina; Perioperative management; Hypertension crisis.

Introduction

Paragangliomas are rare neuroendocrine tumors with a highly variable clinical presentation. They are rarely reported along the genitourinary tract: the uterus, ovary, vagina, and cervix. Paragangliomas of the vagina are extremely rare. Only four cases have been reported in the literature [1-4]. Only one of these four cases was identified as a functional one. It has been well documented that surgical excision of an untreated functional paraganglioma may cause a serious and potentially lethal cardiovascular crisis. This poses great diagnostic and management challenges for gynecologists. We report the second case of a patient with a functional vaginal paraganglioma who experienced a hypertension crisis during surgery.

Case Report

A 38-year-old Chinese woman, gravida 2, para 2, was found to have a mass located in the anterior wall of the vagina during routine gynecologic examinations over a 7-year period. However, the most recent gynecologic examination revealed an increase in size of the mass to 3.0 cm in diameter. The patient had disregarded 16 years of paroxysmal headaches, chest distress, and palpitations.

Vaginal mass excision was performed under epidural anesthesia in an outpatient operating room. Standard monitors showed her baseline blood pressure was 110/58 mmHg and baseline heart rate was 70 beats/min. Precisely when the surgeon intraoperatively touched the tumor, the patient’s arterial blood pressure and heart rate dramatically increased to 200/120 mmHg and 200-220 beats/min, respectively, accompanied by a severe headache, paleness, polypnea, blurred vision, limb anesthesia and nausea. Immediately, she was given 3 mg of midazolam and 20 mg of furosemide intravenously. Five minutes later, the symptoms disappeared and the operation was continued. However a similar episode occurred again when palpating the mass and an electrocardiogram showed ST-segment depressions in certain leads. The operation was then canceled and the patient was hospitalized for further management.

She recalled her 16-year history of paroxysmal strong headaches, palpitations and chest distress lasting for 3-5 min. Such spells were usually unpredictable but occasionally evoked by sexual activity or heavy exercise. Unfortunately, she had never seen a doctor for these symptoms. Laboratory data revealed elevated urinary vanillylmandelic acid (VMA) (15-18.5 mg/24 hours). Transvaginal ultrasound (Figure 1) showed a low echo-level solid tumor on the anterior wall of the vagina measuring 2.3 x 2.3 x 2.0 cm. Her blood pressure was normal between occasional fluctuations (ranging from 77/45 mmHg to 202/118 mmHg). Paraganglioma of the vagina was diagnosed. After being controlled with alpha-blockade, the tumor was extirpated. During the operation there were several hypertensive episodes which were managed by nitroprusside and phentolamine. Immediately after resection of the tumor, the patient had a severe hypotensive episode (65/40 mmHg) managed by norepinephrine. The postoperative period was hemodynamically stable. The pathohistologic diagnosis was vaginal paraganglioma (Figure 2). The patient has been followed-up for three years since surgery without any evidence of recurrence.

Discussion

Paraganglioma is a rare tumor from extra-adrenal chromaffin tissue or derived from parasympathetic tissue. Paraganglioma may occur in any part of the body where extra-adrenal chromaffin tissue or paraganglion tissue is present. Parasympathetic-associated paragangliomas have a predilection for the head and neck region, most of which do not produce catecholamines, whereas catecholamine-producing extra-adrenal paragangliomas are usually found in the abdomen [5]. Paragangliomas of the vagina are extremely rare. Only four cases have been reported in the literature up to now and our reported case

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is the second case of vaginal paraganglioma that produced catecholamines [1-4].

Clinical presentation of functional paraganglioma can vary greatly, commonly presenting with paroxysmal headaches, sweating, and palpitations while some cases are asymptomatic. Sometimes tumors may be functionally dormant before anesthesia and tumor manipulation during surgery. Among the reported four cases of vaginal paragangliomas, only one case presented with episodes of hypertension during the biopsy and the other three cases had only manifestations of a vaginal mass or vaginal bleeding. In our reported case, the woman had a long-time history of paroxysmal headaches, palpitations and chest distress, first stimulated by her primiparity. Symptoms were usually evoked by menstruation, breath-holding to defeate, and occasionally by sexual activity. Manipulation or palpation of the tumor even evoked a hypertensive crisis.

The potential morbidity and mortality associated with surgery in a patient with an undiagnosed functional paraganglioma is high, and adequate preoperative management is very important, as well reviewed by Lenders et al. [6]. Emergency tumor resection without proper preparation results in poor survival. Complications during surgery include hypertensive crises, cardiac arrhythmias, pulmonary edema, cardiac ischemia, and hypotension or even shock, which are all potentially life-threatening. With adequate pretreatment, perioperative mortality has fallen to less than 3%. This emphasises the importance of adequate preoperative management. The major aim of medical pretreatment which often includes the blockade of \(\alpha\)-adrenoceptors is to prevent catecholamine-induced episodes and to reduce potentially life-threatening perioperative situations. Our reported case experienced a hypertensive crisis during the first unwitting surgical attempt but the second thoroughly preoperatively prepared surgery was uneventful. In conclusion, the possibility that a tumor is a paraganglioma should be considered before surgically removing a vaginal mass, and emergency methods for the treatment of catecholamine crises should be handled, so that the risks of operating on these tumors can be lessened.

Most paragangliomas are benign and curable by surgical resection, but some are clinically malignant. The differential diagnosis of malignancy with benign lesions can be difficult even with pathology. Our case had a clinical course of 16 years and no evidence of metastases have been found after a postoperative follow-up of three years. Although none of the previous paragangliomas of the vagina were associated with malignant behavior, close follow-up is recommended.

References


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Two cases of immature teratoma with positive reproductive outcomes

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Summary
The peak incidence of immature teratoma is in the early reproductive period of a woman’s life and fertility preservation is an inevitable topic when discussing treatment options. We present two cases of immature teratoma with positive reproductive outcome. Our experience supports the standpoint that surgery alone is curative in most cases, irrespective of tumor grade. Bearing this in mind, the long-term effect of chemotherapy on ovarian function can be avoided and fertility, an important factor in the overall quality of life, can be preserved.

Key words: Immature teratoma; Fertility.

Introduction
Immature teratoma is the third most common malignant germ cell tumor of the ovary, and represents 15-20% of such tumors [1]. Immature teratoma of the ovary is uncommon and comprises less than 1% of ovarian teratomas, has a specific age incidence, occurs most commonly in the first decades of life and is virtually unheard of after menopause [2]. With respect to the peak incidence of the tumors in the early reproductive period of a woman’s life, fertility preservation is an inevitable topic when discussing treatment options. We present two cases of immature teratoma with positive reproductive outcomes.

Case Reports
During a routine gynecologic examination, a cystic tumor of the right ovary was diagnosed in a 27-year-old nullipara. Ultrasonographic examination confirmed a cystic lesion with a solid component measuring 4 x 3 cm. A subsequent ultrasound scan performed one month later demonstrated the growth pattern of the tumor which measured 10 x 8 cm. The second patient, a 30-year-old woman para 1, palpated a mass in the lower portion of the abdomen. Ultrasound scan showed a large cystic tumor of the right adnexa with a solid component measuring 13 x 11 cm.

In both cases management consisted of a right salpingo-oophorectomy, biopsy of the left ovary and omentum, and sampling of the peritoneal fluid. Histopathologic analysis identified immature teratoma with predominance of immature glial tissue. Both lesions were classified as immature teratomas, staged as FIGO Ia, tumor grade 1. No adjuvant therapy was utilized. At regular follow-ups both patients remained disease-free. Fourteen months after surgery, the first patient became pregnant and delivered a healthy term infant. Three years following the surgery the second patient became pregnant as well.

Discussion
Since most of these tumors occur in adolescence or early adulthood, the preservation of the ovarian endocrine and reproductive functions is an important issue. Fortunately, localized tumors in Stage I are found in 50 to 80% of patients. Therefore, for a premenopausal patient whose lesion appears to be confined to a single ovary, unilateral salpingo-oophorectomy and surgical staging seems to be the appropriate management. Patients with Stage Ia, grade 1 tumors have an excellent prognosis, and no adjuvant therapy is necessary. Adjuvant therapy consists of multi-drug combination chemotherapy which may decrease or deplete primordial follicles. Although the majority of young patients recover well from ovarian damage within several months following chemotherapy [3], in terms of ovarian endocrine function, this approach clearly influences ovarian reproductive function. Ovarian dysfunction is dependent on numerous factors, such as the type and dosage of cytotoxic drugs, duration of chemotherapy and the patient’s age. Still, there is no means of predicting the effect of chemotherapy on ovarian function. In contrast, in view of the low suspicion of malignancy in young patients, incomplete surgical staging is common. It is interesting that this suboptimal approach does not appear to adversely affect outcome [4].

The two cases presented herein well illustrate the above-mentioned postulate. We diagnosed a unilateral ovarian tumor and performed laparotomy with unilateral salpingo-oophorectomy in both cases. Despite the suboptimal surgical staging, both cases were staged as Ia, grade 1 immature teratomas. Close observation following the surgery and histopathologic diagnosis were performed. Today, both patients are disease-free and have offspring.
Two cases of immature teratoma with positive reproductive outcomes

Conclusion

Along with other published papers addressing this issue, our experience supports the standpoint that surgery alone is curative in most cases, irrespective of tumor grade. Bearing this in mind, the long-term effect of chemotherapy on ovarian function can be avoided and fertility, an important factor in the overall quality of life, can be preserved.

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Pathological complete response after primary chemotherapy in a mother and daughter with hereditary breast carcinoma: two case reports

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Summary

The prognosis of patients with BRCA1-related breast carcinomas is inferior to the patients without BRCA1 mutation, but most of these tumors have a so-called triple negative phenotype characterized by increased chemosensitivity. Information regarding the chemosensitivity of BRCA1-related breast carcinomas is limited. We present a case of a mother and daughter with hereditary breast carcinoma treated with primary chemotherapy using the dose-dense combination of doxorubicin and cyclophosphamide and sequential weekly paclitaxel administration. Pathological complete response was observed in both patients. Subsequent genetic analysis revealed the same BRCA1 mutation with exon 5-14 deletion in both women. The present experience as well as other reports indicate increased sensitivity of BRCA1-related breast carcinoma to primary chemotherapy.

Key words: Hereditary breast carcinoma; BRCA1; Pathological complete response.

Introduction

Breast cancer is the most common malignant disease of women in the Western world [1]. The progress accomplished in the treatment of breast cancer over the last decades is reflected in improved survival. In addition to early diagnosis, there is now strong evidence that much of the improvement in the prognosis of women with breast cancer is the result of systemic therapy, including hormonal treatment and chemotherapy [2].

Primary systemic (neoadjuvant or induction) therapy is currently the treatment of choice in locally advanced breast carcinoma, and the neoadjuvant approach is increasingly being used also in patients with operable tumors [3, 4]. Although both hormonal and cytotoxic drugs may be used in primary systemic chemotherapy, chemotherapy with cytotoxic agents is in most cases the preferred modality as the activity of hormonal therapy is restricted to patients with tumors expressing hormone receptors, response onset is more rapid and response magnitude more pronounced with administration of cytotoxic agents. Currently, most regimens of primary systemic chemotherapy comprise anthracycline-based combinations with or without taxanes.

The term pathological complete response denotes complete disappearance of tumor cells in the operative specimen obtained at definitive surgery after primary chemotherapy [5]. Although instances of pathological complete response are relatively rare (for most regimens pathological complete response is achieved only in 10-20% of patients), pathological complete response is important as it represents the most significant prognostic parameter in women undergoing primary chemotherapy [6-9].

Hereditary breast carcinoma represents 5-10% of all cases of breast carcinoma. Most cases of hereditary breast carcinoma are caused by the mutations of BRCA1 or BRCA2 genes. A carrier of BRCA1 mutation carries a lifetime risk of breast carcinoma of about 80% and of epithelial ovarian carcinoma of about 50% [10]. The prognosis in patients with BRCA1-related breast carcinomas is inferior to the patients without BRCA1 mutations [11, 12], but patients with epithelial ovarian carcinoma harboring BRCA1 mutation have significantly better survival [13-15]. Most BRCA1-related breast carcinomas have a so-called triple negative phenotype, and triple negative breast carcinomas are characterized by increased chemosensitivity [16]. However, information on the chemosensitivity of BRCA1-related breast carcinomas is limited [17, 18].

We present two cases of pathological complete response after primary chemotherapy for breast carcinoma in a mother and her daughter, both carriers of BRCA1 mutations.

Case Reports

Case I

A 44-year-old woman presented in September 2003 with a 3-cm lump in the right breast and enlarged axillary lymph nodes. Biopsy confirmed poorly differentiated invasive breast carcinoma. On immunohistochemical examination, the tumor cells did not express estrogen receptors, progesterone receptors or HER-2, but the expression of Ki67 was extremely high (95%), and p53 was expressed in 40% of tumor cells. Because of the
stage (T2N1M0) and phenotype of the tumor, primary chemotherapy with a dose-dense administration of four cycles of a combination of doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) was given every two weeks with filgrastim support, and subsequently 12 cycles of weekly paclitaxel (90 mg/m²) were indicated. The therapy was well tolerated and resulted in almost complete radiologic response. A partial mastectomy with exenteration of the axilla was performed on February 27, 2004. No tumor cells were detectable in the resection specimen, and pathological complete response was determined in the surgical specimen based on the Chevallier classification [5]. The patient was subsequently treated with adjuvant radiotherapy. At the last control in April 2007 the patient was without any signs of disease activity.

Case 2
A 26-year-old woman (daughter of the first case) observed a lump in her right breast during the last month of pregnancy. On September 2, 2004 she delivered a healthy female infant. During breastfeeding the patient observed enlargement of the lump and was referred for a biopsy. Lactation was interrupted. The biopsy revealed moderately differentiated invasive ductal carcinoma with no expression of estrogen or progesterone receptors, high expression of Ki67 (40-50 %), p53 (100%) and HER-2 (3+). At the time of diagnosis, the tumor was 3 cm in size, and there were no clinical or radiological signs of lymph node involvement (T2N0M0). Because of the high risk associated with the patient’s age, the tumor size and phenotype, the patient was submitted to primary chemotherapy using the regimen outlined above. A partial response was detected after the completion of therapy, and a partial mastectomy with exenteration of the axilla was performed on June 22, 2005. A pathological complete response was detected in the surgical specimen with no residual tumor cells. The patient subsequently received adjuvant radiotherapy, and at the last control in April 2007 she was without signs of recurrence.

Molecular genetic analysis revealed the same BRCA1 mutation in both women (exon 5-14 deletion; g.21716_53298del 31583).

Discussion
The present observation of pathological complete response in a mother and daughter harboring the same BRCA1 mutation is in line with earlier reports of increased chemosensitivity of BRCA1-related carcinomas [13-15, 17, 18]. Due to the obvious difficulty associated with prospective assessment of response to chemotherapy in carriers of these relatively rare mutations, the data on this topic are limited to retrospective series. Among 615 women of Ashkenazi Jewish or French Canadian ancestry with known BRCA1/BRCA2 mutation status, Chappuis et al. [17] identified 37 breast carcinoma patients treated with primary chemotherapy, including 11 BRCA1/BRCA2 mutation carriers. Even in this cohort of limited size, the rate of clinical and pathological response was significantly higher in mutation carriers, and complete pathological response was observed in four out of nine (44%) evaluable patients harboring BRCA1/BRCA2 mutations compared to only one control case (4%). A single case of a BRCA1 positive patient with pathological complete response to primary chemotherapy has also been reported by Warner et al. [18]. In a retrospective series, presence of BRCA1 mutations in breast carcinoma patients was associated with inferior survival, but adjuvant chemotherapy significantly improved survival in BRCA1-positive patients [11, 12]. In contrast, the presence of a mutation in epithelial ovarian carcinoma, another BRCA1/BRCA1-related tumor with higher mortality and almost universal use of chemotherapy, is associated with markedly better survival [13-15]. Available experimental data also point out the generally increased chemosensitivity of BRCA1 mutant cells [19]. The BRCA1 protein is one of the molecules responsible for response to DNA damaging agents. BRCA1 protein participates in DNA repair, messenger RNA transcription, cell cycle regulation and protein ubiquitination, and the cells lacking BRCA1 protein are highly sensitive to alkylating agents, platinum derivatives and anthracyclines.

Currently, there is no universally accepted regimen for primary chemotherapy of breast carcinoma [3, 4]. The most important aim of primary chemotherapy, prolongation of patient survival, is identical with the aim of adjuvant chemotherapy. The trials of adjuvant chemotherapy in breast carcinoma have included a substantially higher number of patients than studies of primary chemotherapy, and survival benefit has been demonstrated in the adjuvant setting for the administration of anthracyclines [2], dose-dense approach [20], and the addition of taxanes [21], while the trials of primary chemotherapy usually lacked statistical power to demonstrate a survival advantage. Based on earlier randomized clinical trials, the regimen used in both patients included dose-dense administration of the combination of doxorubicin and cyclophosphamide [20] as well as sequential weekly paclitaxel administration [22]. Among the agents administered to the two patients presented here, BRCA1 mutation has been associated with increased in vitro sensitivity to doxorubicin and alkylating agents, but relative resistance to paclitaxel [19]. Most BRCA1-related breast carcinomas are characterized by lack of estrogen and progesterone receptor expression as well by no increase of HER-2 expression (triplet negative) [16]. In the present two cases, this triple negative phenotype was observed in the older patient (mother), while the younger patient (daughter) had estrogen and progesterone receptor-negative breast carcinoma with HER-2 overexpression. Trastuzumab was not used in this patient because at that time the results of studies demonstrating the survival benefit of this drug in an adjuvant setting were not available, and thus trastuzumab was not indicated.

The information on BRCA1 mutation status has so far had clinical significance restricted to the prevention of second primary tumors (most importantly contralateral breast carcinoma and epithelial ovarian carcinoma) in affected patients and to the genetic counseling of the relatives. The present observation illustrates genetic predisposition for chemosensitivity in BRCA1 mutation carriers and, along with other data, indicates that awareness of BRCA1 mutation status may be even more important for
the choice of therapy, including the decision of whether to administer primary chemotherapy. A marked response to primary chemotherapy allows breast-conserving surgery in patients indicated for mastectomy, and factors predictive of tumor response are of obvious importance in deciding whether to proceed to primary mastectomy or primary chemotherapy with the aim of breast conserving surgery.

Along with prolongation of survival and improvement of surgical options, the other aim of primary chemotherapy is the assessment of tumor response to a particular regimen in vivo, although the possibility of determining tumor response has so far been of little use in clinical practice. On the other hand, more widespread use of primary chemotherapy may lead to identification of patients in whom primary chemotherapy could be of benefit. Presently only retrospective and anecdotal data are available on increased chemosensitivity of BRCA1-related breast carcinomas, and additional information from prospective cohorts is needed.

In conclusion, the present two cases demonstrated increased sensitivity of BRCA1-related breast carcinoma to primary chemotherapy. The growing evidence of exquisite chemosensitivity of breast carcinoma in BRCA1 mutation carriers should affect the decision about primary chemotherapy in these patients.

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References


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Summary

Background: Uterine leiomyosarcoma is a rare female neoplasm with a high recurrent and metastatic rate. However, only a few cases have been reported on metastasis to the breast. The purpose of this work is to stress the role of follow-up and to increase physicians' awareness of such lesion. Case: A 62-year-old female suffered from a breast nodule and multiple metastases six years after resection for uterine leiomyosarcoma. Pathology revealed a rare condition of uterine leiomyosarcoma with breast metastasis. Conclusion: The case highlights the important role of long-term follow-up in uterine leiomyosarcoma and implies the necessity of tissue proof in patients with the disease.

Key words: Uterine leiomyosarcoma; Breast tumor; Metastasis.

Introduction

Excluding the cases from contralateral breast carcinomas, metastatic breast cancers from extra-mammary malignancies are rare, especially from sarcoma [1, 2]. Uterine leiomyosarcoma is a rare female neoplasm which accounts for about 25-36% of uterine sarcomas and 1% of all uterine malignancies [3]. It demonstrates a poor prognosis with a high recurrent and metastatic rate [3, 4]. In a review of the literature, however, only a few cases of uterine leiomyosarcoma have been reported on metastasis to the breast [2, 6, 7]. We report the case of a patient with a breast tumor which metastasized from uterine leiomyosarcoma six years after resection of the uterus. The purpose of this work is to highlight the role of long-term follow-up in uterine leiomyosarcoma cases and to increase physicians' awareness of patients with the disease.

Case Report

A 62-year-old gravida 3, para 2 female with a history of uterine leiomyosarcoma after total hysterectomy and bilateral salpingo-oophorectomy six years before was transferred to our hospital due to a prolonged cough and poor appetite in November 2002. A non-tender, movable, soft-tissue nodule over the upper-middle area of the left breast was found on physical examination. Ultrasonic scan of the breast revealed a solid homogeneous nodule (Figure 1). Mammography showed only a cluster of microcalcifications in the lesion. Other image studies showed multiple lung, liver, and bone metastases. Fine-needle aspiration of the breast was performed but failed to make a clear diagnosis.

Excisional biopsy of the breast nodule was done and the tumor exhibited a well encapsulated mass surrounded by adipose tissue. The pathology report demonstrated a spindle-shape tumor with positive results of smooth muscle actin and desmin staining, which were comparable with the previous uterine leiomyosarcoma. Furthermore, cytology studies of liver and bronchoscopic brushing also supported the metastatic lesions. Under the diagnosis of uterine leiomyosarcoma with multiple metastases, the patient received four courses of chemotherapy with ifosfamide (1 gm/m² for 5 days), etoposide (80 mg/m² for 5 days), and carboplatin (200 mg/m² for 2 days). Stable disease was achieved after chemotherapy, but she was lost to follow-up later. Progression of disease was noted in October 2003. She received hospice care and died in May 2004 due to multiple organ failure.

Discussion

Although breast cancer is one in most common tumors in women, metastatic involvement of the breast from extra-mammary malignancies is rare [1-2]. An accurate diagnosis of metastatic breast cancer from a primary cancer is important for optimum treatment; nonetheless, metastatic lesions are not easily distinguished due to the revised manuscript accepted for publication July 30, 2007

Figure 1. — Ultrasound scan of the breast nodule revealed a homogeneous hypoechoic nodule 2 x 2 cm in size.
wide spectrum of presentations [1]. Therefore, a clear history and a comparable histological picture, like our case, help in the final diagnosis of a metastatic tumor to the breast.

Uterine leiomyosarcoma is a rare female neoplasm with a poor prognosis and a high potential to metastasize [3, 4]. However, the most frequent sites of distant metastasis from uterine leiomyosarcoma are the lung, kidney, and liver. Only a few cases with breast metastasis have been reported. Including this case, a total of four cases with uterine leiomyosarcoma metastasis to the breast have been reported (Table 1) [2, 6, 7]. Most of them revealed a homogeneous nodule with none or microcalcification in the ultrasonic study. The characteristics of these patients are long duration from the initial diagnosis to metastasis (ranging from 18 months to 12 years) and older age (ranging from 40 to 62 years old). These results may be associated with characteristics of uterine leiomyosarcoma which is a rare malignancy with slow progression and strong metastatic potential, even many years after hysterectomy [3-5].

The optimal therapy and the outcome of breast tumor metastasis from uterine leiomyosarcoma are still uncertain due to the limited cases. Nonetheless, the prognosis of uterine leiomyosarcoma is poor without effective treatment in advanced stage [3, 4]. As in our patient, the breast metastasis was one of the presentations of multiple metastases and the advanced disease eventually led to the poor outcome. However, the case highlights the important role of long-term follow-up in uterine leiomyosarcoma cases. It also implies the necessity of good tissue proof from the breast in such patients.

### References


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**Table 1. — Clinical features of cases with breast tumor metastasized from uterine leiomyosarcoma.**

<table>
<thead>
<tr>
<th>References</th>
<th>Age</th>
<th>Location/ Size</th>
<th>Ultrasound findings</th>
<th>Calcification</th>
<th>Other lesions</th>
<th>Time from primary diagnosis</th>
<th>Diagnosis of breast metastasis</th>
<th>Therapy</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref. 2</td>
<td>40</td>
<td>UNK, 4 cm</td>
<td>Ill-defined</td>
<td>UNK</td>
<td>UNK</td>
<td>18 months</td>
<td>Fine needle aspiration biopsy</td>
<td>UNK</td>
<td>UNK</td>
</tr>
<tr>
<td>Ref. 6</td>
<td>44</td>
<td>Bilateral, 0.95 x 0.7 cm</td>
<td>Well-defined, homogeneous, hypoechoic</td>
<td>No</td>
<td>Lung, liver, intestine</td>
<td>12 years</td>
<td>Excisional biopsy</td>
<td>UNK</td>
<td>12 months</td>
</tr>
<tr>
<td>Ref. 7</td>
<td>60</td>
<td>Right, 0.8 cm</td>
<td>Well-circumscribed</td>
<td>No</td>
<td>Subcutaneous</td>
<td>10 years</td>
<td>Fine needle aspiration biopsy</td>
<td>UNK</td>
<td>12 months</td>
</tr>
<tr>
<td>Current case</td>
<td>63</td>
<td>Left, 2 x 2 cm</td>
<td>Well-defined, homogeneous, hypoechoic</td>
<td>Micro</td>
<td>Lung, liver, bone</td>
<td>6 years</td>
<td>Excisional biopsy</td>
<td>UNK</td>
<td>18 months (expired)</td>
</tr>
</tbody>
</table>

UNK: unknown.
A sarcomatous-type peritoneal malign mixed mullerian tumor implant in association with ovarian adenocarcinoma: a case report

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Summary

A rare case of a patient with a histopathological diagnosis of a sarcomatous-type peritoneal malign mixed müllerian tumor implant in association with ovarian adenocarcinoma is reported. A 52-year-old patient was referred to our clinic for an adnexal mass. At pelvic examination, an irregular, fixed, approximately 7-8 cm in size mass was detected in the right adnexal area. At transvaginal ultrasonographic examination, it was observed that there was an 80 x 70 mm sized, irregularly contoured, semisolid mass with hyperechogenous areas inside originating from the ovary in the right adnexal area. At laboratory examination tumor marker CA-125 was 280.4 U/ml (< 35), CA-15-3 was 146.5 U/ml (< 25), whereas other markers were within normal range. The patient was operated on for a right adnexal mass. A staging laparatomy procedure was applied. Postoperative histopathological diagnosis was reported as malignant mixed mullerian tumor of the ovary, with the ovarian component as poorly differentiated adenocarcinoma, and the metastatic foci over serosal surfaces as a sarcomatous component. Postoperatively six courses of adjuvant and consolidation chemotherapy were administered to the patient. Further studies are needed to set a consensus about evaluation of treatment and prognosis for this kind of pathology.

Key words: Ovarian malign mixed mullerian tumor; Peritoneal implant; Treatment.

Introduction

Malign mixed mullerian tumors of ovary are rarely seen [1]. The mean survival in these cases is 7-13 months [2]. For the management of these tumors, similar to malign epithelial ovarian tumors, platinium-based treatment in adjuvant chemotherapy is the accepted treatment modality [3]. Our case of a malign mixed mullerian tumor implant in association with ovarian adenocarcinoma is the first one reported in the literature. There was an aggressive adenocarcinomious component of primary malign mixed mullerian tumor of the ovary, and there was a dominance of the sarcomatous component at the metastatic foci.

Case Report

A 52-year-old patient was referred to our clinic after an adnexal mass was detected in her pelvic ultrasonograph (US) during a routine postmenopausal checkup. At pelvic examination, a 7-8 cm sized, irregularly contoured, fixed mass was detected in the right adnexal area. At transvaginal ultrasonographic (TVS) evaluation, it was observed that there was an 80 x 70 mm sized, irregularly contoured, semisolid mass with hyperechogenous areas inside originating from the right adnexal region. Laboratory results showed tumor marker CA-125 as 280.4 U/ml (< 35) and CA-15-3 as 146.5 U/ml (< 25) while other markers were within normal range. Computerized tomography showed an approximately 10 x 12 x 7 cm sized, lobulated and contoured almost cystic mass with centrally located solid components inside, originating most probably from the right ovary occupying the right middle side of the pelvis. Moreover there were approximately 5 and 3 cm sized solid components located superolaterally to the lesion. There was diffuse dirtiness and thickening on the omental fatty tissue, and omental infiltration (Figure 1). There were no pathological findings at rectosigmoidoscopy and cystoscopy. The patient was operated on with pre-diagnosis of a ‘right adnexal mass’. During operative abdominal exploration, there was an 8 cm sized, fixed, solid, irregularly contoured mass originating from the right ovary, omental infiltration, miliary foci on the serosal surfaces and also diffuse adhesions between the sigmoid colon, omentum, uterus and a lesion located in the right adnexal area. A staging laparotomy procedure, right tumoral oophorectomy, bilateral salpingo-oophorectomy, total abdominal hysterectomy, total omentectomy.

Figure 1. — The mass-like lesion in the ovary - "adenocarcinoma".
tomy, pelvic-paraaortic lymphadenectomy, and appendectomy were performed. Appendectomy is applied to all ovarian cancer patients according to our clinical approach. The postoperative histopathological diagnosis was reported as malign mixed mullerian tumor of ovarian origin, with an ovarian component as a poorly differentiated adenocarcinoma, and metastatic foci on the serosal surfaces as a sarcomatous (muscle, cartilage) component (Figure 2a, Figure 2b). The patient received six courses of adjuvant chemotherapy consisting of a carboplatin and paclitaxel combination after surgery. Following adjuvant chemotherapy, the patient received six courses of consolidation chemotherapy with paclitaxel (175 mg/m²), and the last CA-125 level was detected as 9.4 U/ml. The patient died due to a recurrent ileus one year after the operation.

Discussion

Malign mixed mullerian tumors of ovarian origin are rather rare conditions. Tumor prognosis is poor, and advanced stage at the time of diagnosis is the most important factor affecting prognosis negatively. In 70% of cases diagnosis is at Stage 3 and 4 and after a short period of time cases are lost due to advanced stage poor prognosis [4]. Disease is usually observed in the postmenopausal period, in the 7th decade. The tumor originates from pluripotent mesenchymal cells and differentiates to epithelial and stromal components [5]. Ovarian malignant mixed mullerian tumors (OMMMT) are classified as heterologous and homologous. Homologous tumors may differentiate to natural or foreign cells to the ovary such as ‘spindle cells’, while heterologous tumors may include tissues such as bone and cartilage that are not present in the ovary.

Clinically, they have a progression similar to epithelial tumors and the initial symptoms mainly include abdominal distension, pain, nausea, vomiting and weight loss. Prognosis in homologous OMMMT appears better compared with heterologous tumors. However there is not any concensus on this topic [6, 7].

Malign mixed mullerian tumors of the uterus have lung metastasis frequently, but ovarian malign mixed mullerian tumor have metastasis primarily on peritoneal and serosal surfaces like primary ovarian cancer [8]. In our case also, metastasis occurred in this way. However in the literature, the histopathological diagnosis of OMMMT of the ovary and peritoneal surfaces is similar. In this case, we detected a carcinomatous component in the ovary, whereas the sarcomatous component was detected in the metastatic foci. Thus, although the case seemed similar to primary ovarian carcinoma, after histopathological investigation it was clear that it was a malign mixed mullerian tumor originating from the ovary.

In OMMMT cases after staging laparatomy, usually platinium-based chemotherapy protocols are preferred [9]. Since the number of cases in the literature is limited, there is not any concensus on an optimal chemotherapeutic regimen. Nonetheless the generally accepted treatment protocol for these tumors is platinum-based adjuvant chemotherapy, similar to that for malign epithelial ovarian tumors. We believe that we would have more information about the efficacy of chemotherapeutic agents used in OMMMT with the help of an increased number of cases and series in older women. Our patient received six courses of adjuvant chemotherapy consisting of a combination of carboplatin and paclitaxel after surgery. Following adjuvant chemotherapy, the patient received six courses of consolidation chemotherapy with paclitaxel (175 mg/m²), and the last CA-125 level was detected as 9.4 U/ml.

The co-existence of ovarian adenocarcinoma together with a serosal malign mixed mullerian tumor is a rare entity. Thus, to establish a concensus on the treatment and prognosis of these types of pathologies, further studies are needed.

References

A sarcomatous-type peritoneal malign mixed mullerian tumor implant in association with ovarian adenocarcinoma: a case report


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Secondary involvement of breast with non-Hodgkin’s lymphoma in a patient with HIV infection - case report

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Summary
Secondary lymphoma of the breast is a rare entity in patients with non-Hodgkin’s lymphoma (NHL). HIV infection is associated with an increased risk for developing NHL, however lymphomatous involvement of the breast in AIDS patients has rarely been reported. We present the case of a 33-year-old HIV-infected female patient with diffuse NHL who presented with a unilateral breast mass. Histologic examination of the biopsy specimen revealed a highly-malignant diffuse large B-cell lymphoma.

Key words: Breast lymphoma; HIV; non-Hodgkin’s lymphoma.

Introduction
Breast lymphoma is a rare entity seen in < 5% of patients with non-Hodgkin’s lymphoma (NHL) [1]. Although HIV infection is known to predispose to NHL, lymphomatous involvement of the breast in AIDS has rarely been reported. We report a case of an HIV patient with diffuse NHL and secondary lymphoma of the breast.

Case Report
A 33-year-old African female presented to our Radiology Department and reported a left-sided palpable breast mass which had exhibited slow enlargement over the previous two months. The patient had been HIV-positive for the past five years and suffered from diffuse NHL which had been diagnosed in another hospital eight months earlier. The diagnosis was established via inguinal lymph node biopsy. The patient had undergone chemotherapy and remained in good condition thenceforward.

Physical examination revealed slight enlargement of the left breast. A palpable, well-circumscribed, painless mass was located in the subareolar region. There were no palpable axillary lymph nodes or signs of skin or nipple involvement. Mammography demonstrated a well-defined 7.0 x 8.0 cm mass of uniform high density and smooth contours which was located centrally in the left breast (Figure 1). Examination of the right breast revealed no abnormal findings. The solid nature of the lesion was established by ultrasonography which depicted a heterogeneous, hypoechoic mass with irregular internal vascularity. The above clinical and imaging characteristics were highly suspicious for malignancy and, based on the medical history of the patient, they suggested the diagnosis of lymphomatous involvement of the breast.

Surgical biopsy of the lesion was performed. Histologic examination of the biopsy specimen revealed highly-malignant diffuse large B-cell lymphoma, according to the WHO classification (Figure 2). Immunohistochemical assays showed the

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Figure 1. — Craniocaudal mammograms demonstrate a 7.0x8.0 cm well-circumscribed mass located centrally in the left breast.

Figure 2. — Histology of diffuse large B-cell lymphoma infiltrating the breast parenchyma (HAE, 10x).
tumor cells to be positive for CD20 and negative for UCHL-1. The Ki-67 (clone MIB-1) proliferation index was high (95%). The tumor was histologically identical to the initial inguinal localization of the disease.

Discussion

Lymphoma of the breast is an uncommon disease which represents 2.2% of all extranodal lymphomas [2]. It is seen predominantly in females and nearly all cases are of non-Hodgkin’s type [1,3]. Breast lymphomas are classified as primary and secondary, with the latter being more common [4]. In the primary type, the disease is confined to the breast and the ipsilateral axillary nodes [1]. The secondary type refers to cases in which a prior diagnosis of lymphoma has been established as well as those in which presentation involves the breast but additional staging has demonstrated concurrent disease in sites other than the breast [5]. HIV infection can affect the glandular, mesenchymal and intramammary lymphoid tissue and predispose these patients to various malignancies by means of a decreased immunologic response to tumor cells and an increased susceptibility to oncogenic viral infection [1,6]. Although patients with HIV infection have an increased incidence of NHL, lymphomatous involvement of the breast in AIDS has rarely been reported. Chanan-Khan et al. [1] recently reviewed a tumor registry database of 177 patients with AIDS-associated NHL and observed only three cases of breast involvement.

Breast lymphoma usually presents as a painless breast mass most frequently located in the outer quadrants. Skin retraction, erythema, peau d’orange appearance and nipple discharge are uncommon [3]. The imaging findings of breast lymphoma are nonspecific [3]. Mammography usually demonstrates a circumscribed, sharply margined uncalcified mass, however a variety of rarer appearances such as irregular or spiculated contour, multiple densities, diffuse increased parenchymal density with skin thickening as well as miliary pattern have also been reported [4]. Ultrasonography exhibits a well-defined to poorly-defined hyper- or hypoechocic mass with variable attenuation [7]. Magnetic resonance imaging findings are not pathognomonic either [8].

This case not only highlights the multifocal nature of NHL but additionally indicates that lymphoma of the breast should be considered in every HIV patient with NHL who presents with breast symptoms. Since imaging features are nonspecific, the diagnosis is based solely on histologic criteria.

References

Tamoxifen and giant endometrial polyp

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Summary

We present the case of a woman with a giant endometrial polyp of uncommon dimension who was receiving adjuvant tamoxifen for breast cancer. In her gynecologic examination, she had a mass measuring 3 x 4 x 4 cm protruding from the cervical os. The mass was extirpated under general anesthesia. The mass originated from the endometrial cavity. The endometrial polyp measured 10 x 6 x 3 cm macroscopically and was found to be benign under microscopic examination. We conclude that physicians should be aware of the confounding effects of tamoxifen on the histological and ultrasonographic appearance of the endometrium.

Key words: Tamoxifen; Endometrial polyp; Breast cancer.

Introduction

Tamoxifen (TAM) is a synthetic non-steroid anti-estrogen that has been used effectively for several years in the adjuvant treatment of breast cancer. Although its therapeutic effect is due to its anti-estrogenic properties, the drug also shows modest type B estrogen-receptor agonist activity during the menopausal period in which estrogens are at a low level. Owing to the fall in estrogen levels in menopause, tamoxifen provokes an up-regulation of both estrogen and progesterone receptors in endometrial tissue. This causes an inappropriate response of basal layer proliferation of the endometrium and constitutes the basis of hyperplasia and polyps in the tissue [1]. TAM has been reported to be associated with various endometrial pathologies, including endometrial carcinoma [2, 3]. However, endometrial polyps have been described as the most common endometrial pathology in association with postmenopausal tamoxifen treatment [1, 4]. Malignant changes were observed in 3-10.7% of endometrial polyps recovered in postmenopausal breast cancer TAM-treated patients [5-7].

Various risk factors have been identified for endometrial polyps in these patients, such as older age at menopause, longer duration of breast disease, long-term TAM therapy (48 consecutive months), heavier body weight, and thicker endometrium measured by transvaginal ultrasonography (TVS) [7-9]. We present the case of a woman with a giant endometrial polyp of uncommon dimension who was receiving adjuvant TAM for previous breast cancer.

Case Report

A 55-year-old, gravida 7, parity 6, was referred to the Department of Obstetrics and Gynecology, Faculty of Medicine, University of Süleyman Demirel for postmenopausal bleeding in March 2007. She had been treated by a modified radical mastectomy for an estrogen receptor-positive and progesterone receptor-negative T2/N1/M0 grade 2-3 invasive ductal right breast cancer in 2002 and she had been receiving 20 mg of adjuvant tamoxifen daily for five years. In her previous gynecologic history, she had had a D&C in 2005 which was reported to be an endometrial polyp and a biopsy of the present mass in February 2007 was reported as a suspected cervical adenocarcinoma.

In her gynecologic examination, she had a mass measuring 3 x 4 x 4 cm protruding from the cervical os. TVU revealed an enlarged uterus with a markedly increased endometrial thickness of 3 to 4 cm, with a multicystic appearing mass. She had extirpation of the mass under general anesthesia. The mass originated from the endometrial cavity and measured 10 x 6 x 3 cm (Figure 1). Microscopically cystically dilated glands lined with flattened epithelium surrounded by dense, condensed stroma were found (diagnosis was benign endometrial polyp). The patient was discharged on the same day without any complications.

Discussion

This was a case of a large, benign endometrial polyp in a postmenopausal patient after five years of TAM treatment. Since TAM is widely used in breast cancer treatment, an increased incidence of endometrial hyperplasia, polyps, and a two- to three-fold increased risk of endometrial adenocarcinoma and endometrial sarcoma have been described [10, 11]. Endometrial polyps represent the most common endometrial pathology with postmenopausal TAM exposure, with an incidence of 8-36% [1, 4]. Various risk factors have been identified for endometrial polyps recovered from postmenopausal breast cancer TAM-treated patients [7-9]. Age at menopause was significantly older, duration of breast disease was significantly longer, body weight was significantly heavier, and endometrial thickness measured by TVS was significantly thicker among postmenopausal breast cancer TAM-treated patients with endometrial polyps than in similar patients without any endometrial pathology [9]. A significant increase in secondary endometrial thickening, measured ultrasonographically, in postmenopausal TAM-treated patients was found to be associated with a high rate of endometrial pathologies, including polyps [4].
TVU is a noninvasive method of screening for endometrial cancer; however, in postmenopausal tamoxifen-treated women, TVU can give confounding ultrasound images [12]. In as many as 90% of postmenopausal tamoxifen users, TVU shows an increased irregular endometrial thickness suggestive of endometrial pathology [12, 13]. TAM-treated patients should be instructed and encouraged to report abnormal vaginal bleeding. Those who present with symptoms should have a hysteroscopy with endometrial sampling to exclude endometrial cancer or sarcoma, irrespective of the ultrasound findings.

Physicians should be aware of the confounding effects of TAM on the histological and ultrasonographic appearance of the endometrium. A multicystic endometrium or benign polyps, such as found in our patient, are typical for chronic TAM users, and may confuse the unaware.

References

Figure 1. — A giant endometrial polyp which developed after prolonged tamoxifen treatment.

Figure 2. — Extirpated mega-polyp measuring 10x6x3 cm.