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EUROPEAN JOURNAL OF GYNAECOLOGICAL ONCOLOGY (ISSN 0392-2936) publishes original peer reviewed works in the fields of female genital cancers and related subjects and also proceedings of gynecologic oncology society meetings all over the world. The Journal is covered by CURRENT CONTENTS, SCISEARCH, RESEARCH ALERT, INDEX MEDICUS, MEDLINE, EMBASE/Excerpta Medica, CURRENT ADVANCES IN CANCER RESEARCH, BIOSIS.
Sentinel node biopsy for ipsilateral breast cancer recurrence: a review
G. Palit, Y. Jacquemyn, W. Tjalma - Edegem, BELGIUM
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H. Oksefjell, B. Sandstad, C. Tropé - Oslo, NORWAY
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C.R. Nogueira de Carvalho, I.D.C. Guerreiro da Silva, J.S. Pereira, N.C. Nogueira de Souza, G. Rubino de Azevedo Focchi, J.C.L. Ribalta - São Paulo, BRAZIL
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I. Rzepka-Górskia, R. Bedner, A. Cymbaluk-Płoska, A. Chudecka-Głąz - Szczecin, POLAND
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M.L. Meggiorini, L. Labi, A.R. Vestri, L.M. Porfiri, S. Savelli, C. De Felice - Rome, ITALY
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P. Tsikouras, V. Liberis, G. Galazios, C. Panagiotidou, A. Savidis, A. Chatzimachail, G. Maroulis - Alexandroupolis, GREECE

Evaluation and treatment of ovarian tumors in teenagers.

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Carboplatin concurrent with radiation is well-tolerated in older, diabetic and hypertensive cervical cancer patients, however its efficacy remains to be proven.

Preoperative transforming growth factor-beta 1 (TGF-beta 1) plasma levels in operable breast cancer patients

J. Chod, E. Zavadova, M.J. Halaska, P. Strnad, T. Fucikova, L. Rob - Prague, CZECHOSLOVAKIA

The level of TGF-beta 1 in operable breast cancer patients with positive SLNs was higher as compared with a group with negative SLNs.

The effect of combined therapy on activity of cathepsin D and alpha-1-antitrypsin in the blood serum of women with cervical cancer


The determination of lysosomal enzymes may help in estimating the management efficacy but not in monitoring the treatment process.

Tragic results of suboptimal gynecologic cancer operations

U. Kuyumcuoglu, A. Kale - Diyarbakir, TURKEY

Suboptimal surgeries in gynecologic cancer patients were analyzed. These results may highlight the importance of postgraduate fellowship programs for general gynecologists and patient education.

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Data gathered from 2003 to 2006 on cervical cancer patients who regularly attended a gynecologist were analyzed, thereby allowing further training of all involved in the work process and improvement of their work efficiency.

Uterine sarcoma diagnosed during colon surgery - a complete precise diagnosis

M. Gojnic, V. Dugalic, M. Brankovic, M. Pervulov, M. Cvetkovic, M. Antic - Belgrade, SERBIA

Gynecological examination should always include diagnostic procedures, even invasive ones, after a primary diagnosis of a colon tumor.

Malignant germ cell tumors of the ovary: a review of 41 cases and risk factors for recurrence

S. Topuz, A. Cem Iyibozkurt, S. Engin Akhan, N. Keskin, E. Yavuz, Y. Salihoglu, E. Bengisu, S. Berkman - Istanbul, TURKEY

Outcome of the treatment and risk factors for recurrence of patients with malignant ovarian germ cell tumors were reviewed.

Fascin can be an auxiliary immunomarker of ovarian granulosa cell tumors: comparison with calretinin and inhibin-α

E. Kostopoulou, S. Angelidou, A. Daponte, C. Galani, I. Chiotoglou, A. Terzis, G. Koukoulis - Larissa, GREECE

Intense fascin immunostaining may assist in the histopathologic diagnosis of ovarian granulosa cell tumors in cases with ambiguous calretinin or inhibin-α staining.

Abdominal pillow for the sparing of small bowel in four-field conventional pelvic radiotherapy

M. Saynak, S. Kucucuk, I. Aslay - Istanbul, GREECE

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Ovarian malignant immature teratoma associated with pregnancy - a case report

O. Pujade, E. Pujade-Lauraine, M. Levardon, D. Luton - Paris, FRANCE

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CASE REPORTS
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J.P. Kesterson, S. South, S. Lele - Buffalo, NY (USA)

A case of squamous cell carcinoma of the vulva developing in a Crohn’s disease-associated fistula in a young woman is reported.

Ectopic breast cancer in the anterior chest wall: a case report and literature review

B.B. da Silva, A.R. dos Santos, C.G. Pires, M.A. Rosal, L.G. dos Santos, P.V. Lopes-Costa - Piauí, BRAZIL

Ectopic breast cancer in the chest region is rare and should be treated early in view of the aggressivity.

Primary endometrial B-cell lymphoma: case report

S. Lemos, E. Magalhães, V. Sousa, M. Dias, C. de Oliveira - Coimbra, PORTUGAL


Sclerosing stromal tumor of the ovary: a case report

M.H. Ergeneli, S. Bulut - Ankara, TURKEY

The case of an 11-year-old girl with a sclerosing stromal tumor of the ovary treated by laparoscopic excision is described.

Conservative management of a patient with endometrial carcinoma desiring fertility: how to inform?

S. Topuz, I. Kaleliog˘lu, C. Iyibozkurt, B. Ergun - Istanbul, TURKEY

A 36-year-old women with early-stage endometrial carcinoma who desired fertility was treated with megestrol acetate and she became pregnant spontaneously.

Life-saving hysterectomy in choriocarcinoma: presentation of two cases

S. Topuz, C. Iyibozkurt, Ö. Mete, S. Akhan, Y. Salıhoğlu, E. Bengisu, S. Berkman - Istanbul, TURKEY

Life-saving hysterectomy was performed in two patients with choriocarcinoma who had profuse vaginal bleeding.

Metastasis from breast carcinoma to endometrial polyp

O. Aydin, P. Bagci, E.U. Akyildiz, M. Ozgueroğlu, S. İlvan - Istanbul, TURKEY

The case of a 60-year-old woman with an endometrial polyp containing foci of breast carcinoma metastasis is presented.
Sentinel node biopsy for ipsilateral breast cancer recurrence:
a review

G. Palit, M.D.; Y. Jacquemyn, M.D., Ph.D.; W. Tjalma, M.D., Ph.D.

Department of Obstetrics and Gynecology, Antwerp University Hospital UZA, Edegem (Belgium)

Summary

The aim of this study was to review published reports on the feasibility, results, and reliability of sentinel node biopsy in cases of ipsilateral recurrent breast cancer. A Medline search on publications from January 1999 to December 2007 and cross-references in published articles were looked for. We identified 16 reports on sentinel node biopsy in recurrent breast cancer, including a total of 287 patients. In 210/287 (73.2%) a sentinel node was identified, 77/210 (37.7%) had had previous axillary lymph node dissection and 131 (62.3%) a previous sentinel node procedure. Aberrant lymphatic drainage, other than the ipsilateral axilla was noted in 68/210 (32.4%). Of these 16/68 (23.6%) were located in the contralateral axilla. Of the removed contralateral axillary sentinel nodes 8/17 (47.1%) were invaded by cancer. We conclude that sentinel node biopsy in cases of recurrent ipsilateral breast cancer is feasible. In about one out of three cases drainage to the contralateral axilla with invasion in almost half the cases takes place. The therapeutic consequences of these findings need further study.

Key words: Sentinel node; Breast cancer; Recurrent; Lymphatic drainage.

Introduction

Sentinel lymph node biopsy (SLNB) is accepted as the standard procedure for axillary staging in patients with primary operable breast cancer and clinically uninvolved axillary lymph nodes, mainly because of the lower resultant morbidity as compared to complete axillary lymph node dissection (ALND). In most patients this is combined with breast conserving therapy (BCT) and radiotherapy. About 10-15% of these patients will develop locally recurrent disease within ten years [1] and chestwall recurrence after mastectomy is reported to be between 5-10%. If a complete axillary lymph node dissection was previously performed, salvage mastectomy without further lymph node dissection is considered the standard of care. But what after SLNB?

The procedure of SLNB requires an intact lymphatic flow from the tumor site, which can be interrupted or modified by previous surgery and/or radiotherapy. Most breast tumors drain through a few common afferent lymphatic vessels to the common axillary lymph nodes irrespective of tumor location or number of tumor foci [2]. After previous therapy one or more lymphatic channels can be definitely or temporarily interrupted and alternative paths to the sentinel lymph node may occur for migration both of the radio-isotope and tumor cells. The time of restoration of lymphatic drainage after previous surgery or radiotherapy is unknown.

Originally previous breast surgery was considered a contraindication for SLNB, but Luini et al. [3] have demonstrated the accuracy of SLNB after previous surgery with results comparable with those obtained in other SLNB validation studies. As SLNB is being performed more and more, patients with local recurrence after breast conserving surgery or after mastectomy (without ALND) will be seen. Also in women with ductal carcinoma in situ (DCIS) who have been treated by wide local excision, most often followed by radiation therapy, or by mammectomy without ALND, 10% to 30% will develop local recurrence, be it DCIS or invasive carcinoma [4].

In the present review we try to evaluate whether SLNB in locally recurrent breast cancer after previous SLNB or ALND is feasible, adds any new information, and might possibly change treatment and/or prognosis.

Materials and Methods

We performed a Medline search including studies published between January 1999 and December 2007 with the search terms “sentinel” and “recurrent breast carcinoma” or “recurrent breast cancer”. Studies were selected on title and abstract (if available). Of all relevant articles the full text was obtained and the reference list checked for other possible relevant publications.

Results

The original Medline search yielded 17 publications which all seemed relevant. From these 17 publications, two were only comments on other publications [5, 6] and two studies partially reported on the same series of patients, both giving an update with more patients included at a later period in time [7-10], leaving 13 original studies. Reviewing the reference lists revealed three more studies, resulting in a total of 16. An overview of the publications is given in Table 1.

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Different methods were used in the studies published to perform SLNB, some including lymphoscintigraphy and blue dye injection, but all also used 99m-technetium sulfur colloid and gamma probe localization. Identification of sentinel nodes was with dye, 99m-technetium or both. A longer time, necessitating delayed images, for lymphoscintographic identification in a repeat procedure has been reported [16].

Discussion

As a consequence of the frequent application of SLNB a new group of breast cancer patients is emerging without ALND. In case of local recurrence in these patients it seems that clinically involved axillary lymph nodes are a clear indication to perform ALND (although data are lacking whether this significantly improves prognosis). It is unknown what the benefit of adjuvant chemotherapy versus expected management after locoregional resection in these cases is, however a National Surgical Adjuvant Breast and Bowel Project is performing a trial on this. The potential value of SLNB in these cases is to facilitate the identification of nodes that might harbor microscopic metastases that could be prognostically valuable, but this has not yet been proven.

In the very first report on repeat SLNB [11] Chung et al. argued their second SLNB was falsely negative. Actually SLNB was performed and the node removed was negative for metastatic disease but ten months later the patient presented with an axillary recurrence, which of course did not prove that there was (microscopic) axillary disease present at the time of SLNB; only a simultaneously performed ALND (which was not done) could have proven this. The only data available are from Port et al. [10] in their series on 23 patients where additional (other than sentinel node) lymph nodes were removed concurrently; in two of seven (9%) the SLNB was falsely negative.

Aberrant lymphatic drainage has been published at different sites: contralateral axillary, intramammary, internal mammary, epigastric and contralateral supracervical.

The number (16/68 = 23.6%) of aberrant lymph nodes invaded with cancer in the contralateral axilla was remarkable, and without SLNB all of these cases would have been overlooked. In all studies reported, one out of three (32.4%) of SLNB is at an aberrant location. This may change our idea about the way recurrent breast cancer spreads but it is not yet clear whether this has any therapeutical implications. The number of positive SLNB in recurrent breast cancer was low, around 14.6% in our review. From those publications where it is mentioned, of 17 reported contralateral axillary lymph nodes, eight were positive (47.1%). Boughey et al. [16] have concluded that if more than ten axillary lymph nodes are removed at the original operation, or when radiation is part of the previous treatment, the incidence of alternative lymphatic drainage is increased. Port et al. [10] concluded that success of reoperative SLNB was inversely related to number of nodes removed previously, and was more likely to be successful after a previous SLNB than ALND (74% vs 38%, p = 0.0002).

The studies reported have clearly demonstrated the feasibility of SLNB both after previous SLNB and after previous ALND. It has become clear that aberrant breast lymphatic drainage is more common in cases of local recurrence both after SLNB and ALND.

Table 1. — Overview of published studies on SLNB and recurrent breast cancer.

<table>
<thead>
<tr>
<th>Study (author, year, reference)</th>
<th>No. patients</th>
<th>SLNB identification</th>
<th>Aberrant lymphatic drainage</th>
<th>Metastatic SLNB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>287</td>
<td>210/287 (73.2%)</td>
<td>77/210 (36.7%)</td>
<td>131/210 (62.3%)</td>
</tr>
<tr>
<td>Previous ALND</td>
<td>131/210 (62.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous SLNB</td>
<td>68/210 (32.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location (C)</td>
<td>31/210 (14.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aberrant SLNB</td>
<td>115 (36.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

s: supraclavicular; i: internal mammary ipsilateral; p: interpectoral; c: contralateral axillary; m: intramammary ipsilateral; e: epigastric; sc: supracervical contralateral.
A: One patient had a mastectomy for ductal carcinoma in situ, but whether an axillary dissection was performed is not mentioned.
B: One patient had undergone previous axillary node dissection for malignant melanoma on the same side as the breast cancer.
C: In the discussion four more patients are mentioned with successful repeat SLNB but no further details are given.
D: Two patients had no previous axillary surgery at all.
Publication bias can influence the reported incidence of aberrant lymphatic drainage as it is reasonable to expect cases with “normal” drainage not to be published. This aberrant drainage can result both from surgical scarring or radiotherapy-induced fibrosis. It is not known whether a patient that had a previous SLNB and then demonstrates a local recurrence should also undergo ALND as a means of documenting false-negative repeat SLNB? Probably the surgical morbidity of ALND outweighs the risk of understaging with a false-negative result, but there are no real data to corroborate this statement [6]. If a positive sentinel node is identified in a contralateral axilla it has not been documented if there is any advantage in performing complete ALND of the contralateral axilla. Not performing SLNB could lead to not diagnosing metastasis to aberrant lymph nodes, but it is not yet clear how this might influence treatment (surgically but also considering contralateral radiotherapy and adjuvant chemotherapy) and prognosis.

There is some discussion on how patients with positive contralateral axillary lymph nodes should be staged, as M or as N1; some have proposed that this should be considered a direct drainage pathway (N1) and not a distant metastasis (M) [22].

**Conclusion**

In conclusion repeat SLNB can demonstrate aberrant lymphatic drainage and metastasis that could otherwise have been overlooked, however the clinical significance of this is quite unclear. The risk of false-negatives has been poorly studied. Perhaps the best way at this time is to perform SLNB for aberrant lymphatics and concurrent ipsilateral ALND in case this was not performed at the original surgery.

**References**


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A phase 2 trial of oral imatinib in patients with epithelial ovarian, fallopian tube, or peritoneal carcinoma in second or greater remission

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Summary

Purpose of investigation: To determine the effect of imatinib on progression-free survival in patients with epithelial ovarian cancer in second or greater complete clinical remission (CCR). Methods: 35 patients were enrolled between 10/2002 and 1/2005. Eligible patients received imatinib at 400 mg daily orally. Results: One patient withdrew consent, and two patients received protocol therapy in first remission and were excluded. Five patients were removed for possibly related toxicity. No associations were seen between PDGF-R staining and PFS. Conclusions: Treatment with imatinib for patients with ovarian cancer in second CCR or greater did not prolong the PFS beyond the historical estimate.

Key words: Imatinib; Ovarian cancer; Peritoneal; Remission.

Original Articles

Introduction

Aggressive optimal surgical debulking and platinum with taxane therapy improved the median overall survival for patients with advanced ovarian cancer to in excess of five years in 2006, with the use of intraperitoneal treatment, but the long-term cure rate remains in the 20-30% range [1, 2]. Approximately 50% of patients will enter a pathologic first complete clinical remission, yet 90% of suboptimally debulked patients and 70% of optimally debulked patients relapse in 18-24 months. Subsequent and repeated chemotherapy responses are often seen with shortening intervals of disease control until broad chemotherapy resistance develops [3]. Opportunities to improve the outcome for patients exist by making primary therapy more effective, or by applying “consolidation” or “maintenance” approaches to patients in a complete primary or subsequent remission.

Numerous targets have been proposed for consolidation strategies. One such target, platelet-derived growth factor (PDGF), is produced by many cell types and mediates an autocrine transformation in responsive cells. It may also function in a paracrine fashion by stimulating angiogenesis, connective tissue and stromal development, and suppression of natural killer (NK) cells [4]. Normal human ovarian surface epithelial cells (HOSE) demonstrate a dose-dependent increase in [3H] thymidine incorporation when stimulated with PDGF in culture, and immunohistochemical analysis reveals that both PDGF-R-α and PDGF-R-β receptors are expressed [5]. There is also evidence that PDGF and PDGF-like molecules produced by ovarian cancer cells may be involved in paracrine stimulation of surrounding stroma. Cultured media with secreted PDGF-like molecules from malignant epithelial cell lines significantly stimulate the mitogenic activity of 3T3 fibroblasts [6].

PDGF is present by immunohistochemistry in 73-100% of human ovarian cell lines where no expression is noted in normal epithelial cells [7, 8]. PDGF-R is expressed in 36-81% of ovarian cancer tissues based on prior reports [5, 7, 9]. In this phase II study, we sought to determine whether inhibition of the PDGF-PDGF-R system could result in a decrease or delay in tumor recurrence among women in second or greater clinical remission. Our hypothesis was that remission prolongation might be achieved with imatinib by altering the autocrine transformation of ovarian epithelial cells, inhibiting the growth of residual malignant cells, and/or inhibiting stromal remodeling via the paracrine function.

Materials and Methods

Patient population, inclusions and exclusions

Eligible patients had 1) histologic confirmation of epithelial ovarian, primary peritoneal, or fallopian tube cancer at diagnosis; 2) initial surgical cytoreduction and chemotherapy with at least one platinum containing regimen; 3) failure of the primary regimen manifested by recurrent disease; and 4) were in a second or greater complete clinical remission following additional chemotherapy or surgery. Patients must have enrolled within 4.6 months of completing chemotherapy for recurrent disease. Complete clinical remission was defined as CA-125 < 35 U/ml, negative physical examination, and no definite evidence of disease by computed tomography (CT) imaging. Lymph nodes and/or soft tissue abnormalities < 1.0 cm are often

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present and were not considered definite evidence of disease. Patients must have had Karnofsky performance status (KPS) ≥ 60 and adequate organ function defined as absolute neutrophil count (ANC) ≥ 1,500/μl, platelet count ≥ 100,000/μl, total bilirubin and serum creatinine ≤ 1.5 times institutional upper limit of normal, and SGOT and alkaline phosphatase ≤ 2.5 times institutional upper limit of normal. Patients were excluded from the study if they had received any investigational drug or radiation therapy during the four weeks before study entry. Patients were also excluded if they had any uncontrolled cardiac, pulmonary, metabolic, renal, gastrointestinal or infectious diseases, the inability to take oral medications, or a history that placed the patient at an unacceptable risk for participation in the study. Therapeutic warfarin was not permitted.

The pretreatment evaluation included history and physical examination, assessment of KPS, complete blood cell count, hepatic function profile, serum creatinine, serum CA-125 level, ECG, and CT. During treatment, patients were evaluated monthly with physical examinations, and all laboratory studies were repeated. CT imaging was repeated every 12 weeks, or sooner at the discretion of the investigator if progression was suspected.

Treatment plan

Patients received imatinib orally daily continuously by taking four 100 mg tablets with food and a large glass of water. No dose interruptions or modifications were performed for grade 1 or 2 hematological toxicity. For grade 3 or 4 hematological toxicity defined as ANC < 1 X 10^9/l, or platelet count < 50 X 10^9/l, imatinib was held until toxicity resolved to ≤ grade 2, but no longer than two weeks or the patient was removed from the study. If grade 3 or 4 toxicity recurred after an interruption, the patient was removed from the study. Patients were also removed from the study for any other unacceptable ≥ grade 2 toxicity.

Immunohistochemistry studies

Representative slides of the primary malignancy were processed at our institution or by referring institutions (formalin-fixed paraffin-embedded), and were stained at Memorial Sloan-Kettering Cancer Center (MSKCC) via immunohistochemistry (IHC) for PDGF-R (commercial polyclonal assay, Santa Cruz, CA). PDGF-R α antibody (#SC-338) from Santa Cruz Biotechnology is a commercial rabbit polyclonal antibody raised against a peptide corresponding to amino acids 1065-1084 mapping within the carboxy terminal domain of PDGF-R. The antibody reacts with PDGF-R of mouse, rat, and human cell origin by Western blotting, immunoprecipitation and immunohistochemistry (data on file, Santa Cruz, Biotechnology). Standard immunoperoxidase techniques were used by the immunohistochemistry core facility at MSK as outlined in the laboratory procedures manual (revision 1995). Slides were reviewed by the investigating pathologists (RS and KP). Specimens were graded as 0-4 using a qualitative scale.

Study endpoints

The primary endpoint of the study was to determine the effect of imatinib therapy on progression-free survival (PFS). Treatment failure was defined based on the data from Rustin et al. [10] and was characterized by 1) physical examination evidence of tumor recurrence, 2) preferably radiographic evidence of disease recurrence using RECIST criteria, or 3) CA-125 elevation to twice the upper limits of normal (i.e., 70 U/ml), confirmed by a second sample, also > 70 U/ml. Patients were removed from the study at the time of treatment failure.

All patients provided written informed consent. The protocol was approved by the institutional review board and was reviewed annually.

Statistical considerations

The objective of this study was to estimate the median PFS among women in second or greater remission treated with oral imatinib as remission consolidation. PFS (protocol) was defined as the time from the protocol start date to progression, or last follow-up for the patients who did not progress; PFS intervals are reported in months. The first PFS (pre-protocol intervention) was measured as the time interval from the start of primary therapy to the date of first relapse (PFS1). The second PFS was measured as the interval from the start of secondary therapy to the date of the second relapse (PFS2). The third PFS was measured as the interval from the start of tertiary therapy to the date of the third relapse (PFS3).

In the second or greater complete clinical remission group of patients, historically the median PFS2 is nine months. We planned to accrue 35 patients, at an accrual rate of three patients per month, with follow-up after accrual for an additional two years. A minimum follow-up of 18 months was required to enable us to estimate the median time to recurrence with a 95% confidence interval (CI) given by ± 4.5 months. This CI was computed under an exponential survival model. We would study the treatment further if we observed a median of more than 13.5 months.

Results

Patient characteristics

Thirty-five patients were enrolled in the study from October 2002 to January 2005. After initial enrollment, one patient withdrew consent prior to starting treatment.

Table 1. — Patient characteristics (n = 32).

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Number</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>30</td>
<td>94</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>III</td>
<td>25</td>
<td>78</td>
</tr>
<tr>
<td>IV</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Unstaged</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Histologic Type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>22</td>
<td>69</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>Clear cell</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>78</td>
</tr>
<tr>
<td>Size of residual at primary debulking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal (≤ 1 cm)</td>
<td>22</td>
<td>69</td>
</tr>
<tr>
<td>Suboptimal (&gt; 1 cm)</td>
<td>9</td>
<td>28</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>2nd Remission</td>
<td>26</td>
<td>81</td>
</tr>
<tr>
<td>3rd Remission</td>
<td>6</td>
<td>19</td>
</tr>
</tbody>
</table>

KPS, Karnofsky performance status.
Two additional patients (6%) received imatinib in first clinical remission and were excluded from the analysis, leaving a total of 32 evaluable patients. Patient characteristics are detailed in Table 1. The median age was 53 years (range, 25-72 yrs) with median KPS of 90% (range, 80-100%). The majority of patients were Stage III (78%) or IV (9%) at diagnosis. Most patients (69%) were optimally debulked (≤1 cm residual disease) and the majority had papillary serous (69%) or endometrioid (28%) histology. All patients received taxane and platinum-based primary therapy. Thirteen (41%) patients underwent second-look assessment, and 21 (66%) received additional consolidation therapy after primary treatment. Eighteen (56%) of patients underwent a surgical procedure at the time of a recurrence. The majority of patients were enrolled on protocol in second complete remission (81%), with six patients (19%) receiving imatinib in the third remission. The median number of cycles of protocol therapy was three (range, 1-11). The median interval between the date of last chemotherapy and the start of protocol therapy was 1.7 months, ranging from 0.59-4.6 months.

**Treatment toxicities**

Two (5.9%) of 34 patients were removed from treatment owing to related toxicity (G2 petechiae and G3 diarrhea), while 29 patients (85.3%) were removed for progression of disease. An additional three patients (8.8%) were removed from the study secondary to possibly related toxicity: pulmonary embolism (n=1), elevated creatinine (n=1), and ureteral calculi (n=1). All five patients taken off the study for possible or definite related toxicity, were included in the analysis. Toxicities ≥grade 3 not requiring removal from study were neutropenia (n=3), thrombocytopenia (n=1), and hyperglycemia (n=1). The most frequent toxicities were grade 1 and 2 (Table 2).

**Table 2. Treatment toxicities (n = 32).**

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>12 (38%)</td>
<td>9 (28%)</td>
<td>3 (9%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (50%)</td>
<td>8 (25%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10 (31%)</td>
<td>8 (25%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (9%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>9 (28%)</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3 (9%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry Eyes</td>
<td>2 (6%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (9%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (34%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (31%)</td>
<td>2 (6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (9%)</td>
<td>2 (6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>7 (22%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12 (38%)</td>
<td>2 (6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash (cellulitis)</td>
<td>4 (12%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Petechia</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other (ureteral calculi)</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Primary treatment endpoint: progression-free survival**

The PFS (PFS2) for patients receiving protocol therapy in second remission (n = 26) was 12.1 mos (95% CI, 9.1-15.1 mos) as seen in Table 3. The PFS (PFS3) for patients receiving protocol therapy in third remission (n = 6) was 15.9 mos (95% CI, 9.5-23.4 mos). The PFS from the start of protocol therapy or PFS (protocol) was 3.7 mos (95% CI, 2.7-5.8 mos).

The PFS (PFS1) for all evaluable patients on protocol (pre-study intervention) was 20.4 mos (95% CI, 17.6-24.1 mos). The median time on treatment prior to initiation of imatinib therapy (i.e., time to return to complete clinical remission) for second remission patients was 4.8 mos (range, 0-32.8 mos). However, the median time on treatment for those patients receiving imatinib therapy in a third remission was 14.5 mos (range, 3.6-40.6 mos).

**Table 3. Treatment outcome: duration of progression-free survival.**

<table>
<thead>
<tr>
<th>Patients treated in PFS 2 or 3 (n = 32)</th>
<th>PFS 1 (pre-protocol therapy)</th>
<th>PFS 2</th>
<th>PFS 3 (n = 9)</th>
<th>PFS 2 (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS 1</td>
<td>20.4 mos (95% CI, 17.6-24.1 mos)</td>
<td>12.1 mos (95% CI, 9.4-15.5 mos)</td>
<td>10.2 mos (95% CI, 9.5-23.4 mos)</td>
<td>12.3 mos (95% CI, 10.2-15.1 mos)</td>
</tr>
<tr>
<td>PFS 2</td>
<td>10.2 mos (95% CI, 9.5-23.4 mos)</td>
<td>12.3 mos (95% CI, 10.2-15.1 mos)</td>
<td>12.3 mos (95% CI, 10.2-15.1 mos)</td>
<td>12.3 mos (95% CI, 10.2-15.1 mos)</td>
</tr>
</tbody>
</table>

**Table 4. Exploratory outcome: patients with PFS 2 > PFS 1 treated in PFS 2 (n = 26).**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>PFS 1</th>
<th>PFS 2</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>26.5 mos</td>
<td>31.7 mos</td>
<td>5.2 mos</td>
</tr>
<tr>
<td>8</td>
<td>19.9 mos</td>
<td>20.6 mos</td>
<td>0.7 mos</td>
</tr>
<tr>
<td>14</td>
<td>7.96 mos</td>
<td>8.65 mos</td>
<td>0.66 mos</td>
</tr>
<tr>
<td>21</td>
<td>17.7 mos</td>
<td>26.8 mos</td>
<td>9.1 mos</td>
</tr>
<tr>
<td>28</td>
<td>10.9 mos</td>
<td>12.5 mos</td>
<td>1.6 mos</td>
</tr>
</tbody>
</table>

PFS, progression-free survival.
Abl [12]. demonstrates activity against PDGF-R, c-Kit, and Bcr-9, 11]. Imatinib is an oral tyrosine kinase inhibitor that may inhibit their activity and thereby prevent tumor growth [4, 5, 9, 11]. PDGF-R and Bcr-kit and PDGFR may have a role in ovarian pathogenesis, which is consistent with our findings. Preclinical studies have shown that c-Kit and PDGFR may have a role in ovarian pathogenesis, and that their inhibition may prevent tumor growth [4, 5, 9, 11]. Imatinib is an oral tyrosine kinase inhibitor that demonstrates activity against PDGF-R, c-Kit, and Bcr-Abl [12].

### Discussion

There is much interest in investigating targeted consolidation or maintenance strategies for patients having ovarian cancer in both primary and secondary complete clinical remission. Preclinical studies have shown that c-kit and PDGFR may have a role in ovarian pathogenesis, and that their inhibition may prevent tumor growth [4, 5, 9, 11]. Imatinib is an oral tyrosine kinase inhibitor that demonstrates activity against PDGF-R, c-Kit, and Bcr-Abl [12].

This single-institution, open-label, phase II study examined PFS of patients with epithelial ovarian, fallopian tube, and primary peritoneal cancer in second or greater complete clinical remission who were treated with imatinib as consolidation therapy. In this study, the median PFS (PFS 2 or PFS 3) was 12.1 months. Progression-free survival (protocol) was relatively short (3.7 mos). The predetermined target of 13.5 months needed to reach the approach worthy of further study was not reached. Furthermore, over the range of PFS reported and recognizing the small sample size, there were no associations between PDGF expression and PFS.

During the reporting of our clinical trial, two other studies evaluating imatinib as treatment for measurable disease were reported and neither showed objective partial or complete responses. Coleman et al. [13] reported no objective clinical responses to imatinib in a phase II study of single-agent imatinib (600 mg daily) in 16 patients with recurrent platinum- and taxane-resistant epithelial ovarian and primary peritoneal carcinomas whose tumors expressed PDGF by immunohistochemistry. Stable disease was seen in four patients, including three patients with lack of disease progression greater than six months. More recently, Alberts et al. [14] reported the Southwest Oncology Group Experience with 19 evaluable patients (2 positive for c-kit expression by IHC and 17 positive for PDGF-R expression by IHC) again showing no objective responses. Taken together, these two recently reported studies of imatinib in patients with measurable disease and our study for patients in remission demonstrate that meaningful activity of imatinib in patients with ovarian cancer is absent.

The target PFS from complete second clinical remission we selected as our endpoint is rarely separately reported in the literature in trials of recurrent disease. There is generally mention of the small subset of complete responders in each study, but little information about their specific characteristics and duration of remission. Therefore, making comparisons with historical data as we investigate more agents for consolidation is difficult if we rely on a PFS endpoint. Heterogeneous populations also provide possible confounding variables, including the number of chemotherapy or hormonal agents required to achieve remission, the duration of therapy, as well as treatment alterations based on changes including the number of chemotherapy or hormonal agents required to achieve remission, the duration of therapy, as well as treatment alterations based on changes in CA-125 or radiographic findings not meeting strictly defined RECIST definitions for progression of disease. The issue of a variable number of chemotherapy regimens required to return to remission (i.e., preprotocol therapy) is well illustrated in our study. The median duration of therapy was 4.8 months for second remission and 14.5 months for the six patients in third remission. It will clearly be important to limit the number of treatment regimens and cycles required to achieve remission in the design of future consolidation trials. This is particularly required if our endpoint is to prolong the standard definition of PFS 2 or 3, which is defined from the start of second- or third-line therapy to disease progression. Moreover, recent data have suggested that a simple deter-

### Table 5 — Exploratory outcome: PFS2 rate at given time intervals.

<table>
<thead>
<tr>
<th>Time point (months)</th>
<th>PFS 1 (n = 32)</th>
<th>PFS 2 (n = 32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>6</td>
<td>100%</td>
<td>96%</td>
</tr>
<tr>
<td>9</td>
<td>90%</td>
<td>75%</td>
</tr>
<tr>
<td>12</td>
<td>81%</td>
<td>53%</td>
</tr>
<tr>
<td>15</td>
<td>71%</td>
<td>37%</td>
</tr>
<tr>
<td>18</td>
<td>59%</td>
<td>28%</td>
</tr>
<tr>
<td>21</td>
<td>46%</td>
<td>15%</td>
</tr>
<tr>
<td>24</td>
<td>34%</td>
<td>12%</td>
</tr>
</tbody>
</table>

PFS, progression-free survival.

### Table 6 — PDGF-R immunohistochemistry (n = 25).

<table>
<thead>
<tr>
<th>PDGF-R Score</th>
<th>Number of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
<td>56%</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>20%</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>12%</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>12%</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>

PDGF, platelet-derived growth factor.
mination of the median PFS may not be the most suitable endpoint by which to investigate consolidation approaches. Other suggested endpoints have included the proportion of patients having a second remission longer than the first [3] or patients continuously in remission at given time points [15].

In considering alternate endpoints, six of 26 (23%) of second complete remission patients in our study had a second remission longer than the first (23%) with four of them (11%) having potentially clinically meaningful differences (arbitrarily defined as > 1 month). This initially appears in contrast to the reported range of 3-8% in the literature [3]. However, five of six of these patients in our study had secondary complete surgical debulking at the time of their recurrence followed by chemotherapy. Secondary surgical cytoreduction in appropriate patients may prolong PFS, and thus the frequent use of secondary surgical cytoreduction for management of relapse may represent a confounding factor to exploring duration of second complete clinical remission as an endpoint for our patient group [16-18]. In future studies using PFS2 versus PFS1 duration endpoints, it will be important to define clinically significant differences in duration of PFS, as well as control for other variables such as secondary surgery. This endpoint, however, is still worthy of consideration as larger data sets of patients in remission are examined, and potential confounding factors can be understood.

Finally, based on the understanding that binary endpoints at fixed time points may avoid some inherent reporting biases [15], we reported the number of patients remaining in remission at a given time point. As large data sets of patients in remission are accumulated and analyzed, the goal of improving the percent of patients still in remission at a predetermined time point may be a useful outcome measure.

Conclusions

In summary, our study showed that imatinib given as consolidation treatment to women in second or greater complete remission did not prolong the expected median PFS, and is consistent with other trials showing no objective responses in patients with measurable disease. Future studies of consolidation in patients in remission could explore alternate endpoints including the use of the number of patients remaining in complete clinical remission at a given time point.

Acknowledgment

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References


Weekly paclitaxel/5-fluorouracil followed by platinum retreatment for patients with recurrent ovarian cancer: a single institution experience

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Summary

Purpose: Since the prognosis of recurrent ovarian cancer patients is still poor, we need to establish a useful treatment strategy to achieve their long-term survival. We treated recurrent ovarian cancer patients with weekly paclitaxel (PTX)/5-fluorouracil (5-FU) followed by platinum retreatment to investigate its clinical efficacy in a preliminary manner. Methods: Sixteen patients with recurrent ovarian cancer, pretreated with taxane and platinum, were treated with weekly paclitaxel (PTX)/5-fluorouracil (FU). PTX (80 mg/m²) on day 1, 8, and 15 was combined with a bolus injection of 5-FU (500 mg/m²) on day 2, 9, and 16. Chemotherapy was given every four weeks. Patients with stable disease or progressive disease were subsequently retreated with a platinum-containing regimen. Response was evaluated by RECIST criteria or CA125 criteria. Toxicities were evaluated according to the National Cancer Institute-common toxicity criteria (NCI-CTC) version 3. Results: Among five patients with sensitive disease, one of four patients with measurable tumor and one without measurable tumor responded to weekly PTX/5-FU. Among 11 patients with resistant disease, none of five patients with measurable tumor and three of six patients without measurable tumor responded to weekly PTX/5-FU. Overall objective response rate by platinum retreatment after weekly PTX/5-FU was 31.3% (5/16). Among 16 patients, 13 patients who showed no response or progressive disease (three with sensitive disease, ten with resistant disease) received platinum retreatment after weekly PTX/5FU. All three patients with sensitive disease and three of ten patients with resistant disease revealed response to platinum retreatment. Overall objective response rate by platinum retreatment after weekly PTX/5-FU was 46.2% (6/13). Conclusions: Weekly PTX/5FU followed by platinum retreatment could be a useful treatment strategy for recurrent ovarian cancer patients. We need to establish the standard treatment strategy for recurrent ovarian cancer patients with a poor prognosis.

Key words: Paclitaxel; 5-fluorouracil; Recurrent disease; Platinum-free interval; Ovarian cancer.

Introduction

With advances in treatment, the median 5-year survival rate among ovarian cancer patients has improved to approximately 50% in women diagnosed in the mid-1990s, compared with approximately 40% in those diagnosed a decade earlier [1, 2]. In the setting of long-term management for advanced-stage disease, patients may experience a number of relapses, each of which represents a particular challenge. With the availability of newer agents, combinations, and alternative dosing schedules, it has become increasingly apparent that the choice of sequential treatments may have an important impact on future treatment options based on tolerability, cumulative toxicity, and patterns of drug resistance.

Although only a minority of patients with advanced-stage disease can be “cured”, extended survival (often measured in years) is observed in a substantial percentage of women with recurrence. Unfortunately, there are currently very few phase III trials with long-term outcomes to help clinicians select an optimal regimen, or sequence of regimens, for management of persistent or recurrent disease. Furthermore, for a patient whose cancer has stabilized or responded, the optimal duration of therapy is unknown. In this setting, the concern is for the potential toxicity and impact on quality of life associated with prolonged therapy versus the theoretical benefits of sustained suppression of tumor growth, including delayed onset of symptoms and enhanced opportunity for extended survival.

As paclitaxel (PTX) is known to be a cell-cycle-specific agent, a number of alternative schedules have been explored to enhance efficacy and minimize toxicity. In particular, Markman et al. [3] and the Gynecologic Oncology Group [4] reported that weekly PTX (80 mg/m²) is generally well tolerated with activity against measurable platinum-resistant ovarian cancer, including patients with early relapse after front-line platinum/PTX delivered on a conventional 3-week schedule. Since platinum sensitivity is related to the time between completion of platinum-based therapy and relapse, it has been hypothesized that prolongation of the platinum-free interval with the use of other drugs might improve responses to subsequent platinum therapy [5-7]. Weekly PTX could be utilized as a component of sequential chemotherapy to extend the platinum-free interval. The optimal use of sequential or combined therapy in the management of platinum-resistant recurrence has not been defined. However, two randomized trials have suggested that multiagent therapy might be superior in the setting of platinum-sensitive recurrence [8, 9].

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Murad et al. reported that a combination of PTX and 5-fluorouracil (5-FU) was effective for advanced gastric cancer with a response rate of 65.5% in a phase II trial [10]. Loesch et al. also reported that weekly PTX/5-FU with leucovorin was active as first-line therapy for metastatic breast cancer with a response rate of 48% in a phase II study [11]. As far as we know, no report on weekly PTX/5-FU for ovarian cancer has been published in the literature yet. We, therefore, explored the toxicity and efficacy of weekly PTX/5-FU for patients with recurrent ovarian cancer pretreated with PTX or docetaxel (DTX)/carboplatin (CBDCA). Patients showing stable disease or progressive disease after treatment by weekly PTX/5-FU were subsequently retreated with platinum-containing regimen such as irinotecan (CPT-11)/cisplatin (CDDP), which has been reported to be an active regimen for refractory or recurrent ovarian cancer [12]. We, then, evaluated the clinical efficacy of our treatment strategy, consisting of weekly PTX/5-FU followed by platinum retreatment, for recurrent ovarian cancer.

Patients and Methods

Patients (Table 1)

All patients were treated with surgery including extended total hysterectomy, bilateral salpingo-oophorectomy, pelvic and paraaortic lymphadenectomy, omentectomy, and appendectomy except two cases, and systemic chemotherapy (PTX: 175 mg/m² or DTX: 70 mg/m² + CBDCA: AUC 5) on an every-3-week schedule at Hokkaido University Hospital and had clinical diagnoses of relapsed ovarian cancer. All patients had pathological diagnosis of serous papillary adenocarcinoma. Fourteen patients had Stage IIIc, one Stage IIC and one Stage IIb disease. A median of nine cycles of initial platinum treatment was given. All patients provided their informed consent to participate in the study.

Enrollment criteria for this study were as follows: a definitive tissue diagnosis, age between 20 and 75 years, performance status of 0-2 (according to Eastern Cooperative Oncology Group (ECOG) criteria), neutrophil count > 1500/mm³, hemoglobin > 9.5 g/dl, platelet count > 100,000/mm³, serum bilirubin < 1.5 mg/dl, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) less than 1.5 times the institutional reference values, serum creatinine < 1.5 mg/dl; and predicted survival of at least three months. The exclusion criteria were as follows: borderline malignancy, active infection, psychiatric disorders, poorly controlled hypertension or diabetes, a history of drug hypersensitivity, and a history of interstitial pneumonia.

Treatment regimen weekly PTX/5FU

PTX (80 mg/m²) was administered intravenously on day 1, 8, 15. After 24 hours of starting time of PTX administration, 5-FU (500 mg/m²) was administered by bolus injection on day 2, 9, 16.

CPT-11/CDDP

CPT-11 (60 mg/m²) and CDDP (60 mg/m²) were administered intravenously on day 1 and CPT-11 (60 mg/m²) alone was administered on day 8, 15.

DTX/CBDCA (CDDP)

DTX (70 mg/m²) and CBDCA (AUC 5) was administered intravenously on day 1 and repeated with 3-week intervals.

DTX (30 mg/body) and CDDP (30 mg/body) was administered intravenously on day 1, 8, 15. This regimen was employed when CPT-11/CDDP was not used after weekly PTX/5FU.

For all above-mentioned treatment regimens, an anti-emetic agent (5-HT antagonist) was administered prophylactically from day 1 to 2, from day 8 to 9, and day 15 to 16 to reduce the gastrointestinal toxicity. Granulocyte colony stimulating factor (G-CSF) was administered subcutaneously when the WBC count was < 2000.

Definition of toxicity

Toxicities were evaluated according to the National Cancer Institute-common toxicity criteria (NCI-CTC) version 3.

Criteria for response

For the cases with measurable tumors, evaluation of radiographic findings was based on the response evaluation criteria in solid tumors (RECIST) guidelines [13]. For the cases without measurable tumors, 50% response definition was employed to evaluate the response by CA-125 [14]. Briefly, sample 1 = x and ≤ 40 U/ml; sample 2 = y; sample 3 ≤ 50% of both x and y; and sample 4 ≤ 110% sample 3 and ± 28 days after sample 3. If samples 3 and 4 are less than the upper limit of normal, intervening samples between 2 and 3, or 3 and 4, that are within the normal range must be ≤ 150% of sample 2 or 3, respectively. Intervening samples between 2 and 3, or between 3 and 4, that are outside the normal range must be ≤ 110% of sample 2 or 3, respectively, and ≤ 110% of the preceding sample. For progressive disease, the serum CA-125 level must have been at least 70 U/ml and have doubled from the previous value. This had to be repeated 28 days later and met the same criteria. The date of progression was the date of the level confirming the doubling of the CA-125 value and at least 70 U/ml.

Results

From January 2003 to February 2005, a total of 16 patients with a median age of 58 years (range; 40-71) were treated by weekly PTX/5FU. The chemotherapy-free interval ranged from one to ten months. Five patients showed sensitive disease and 11 revealed resistant disease. A median of time to recurrence/progression after initial platinum treatment was three months (range; 0-16 months) (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first surgery (years); median (range)</td>
<td>58.0 (40-71)</td>
<td>100</td>
</tr>
<tr>
<td>Stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIC</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>IIb</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>IIIc</td>
<td>14</td>
<td>87.4</td>
</tr>
<tr>
<td>Response to initial platinum treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sensitive</td>
<td>5</td>
<td>31.3</td>
</tr>
<tr>
<td>resistant/refractory</td>
<td>11</td>
<td>68.7</td>
</tr>
<tr>
<td>Time to recurrence or progression after last platinum treatment; median (range)</td>
<td>3 months (0-16)</td>
<td>100</td>
</tr>
<tr>
<td>Cycles of platinum treatment before weekly PTX/5-FU; median (range)</td>
<td>8.8 months (3-12)</td>
<td>100</td>
</tr>
</tbody>
</table>
Toxicity of weekly PTX/5-FU (Table 2)

All patients were fully evaluable for toxicity of weekly PTX/5-FU. Table 2 summarizes the incidence of certain toxic effects. Leukopenia was the most frequent form with this combination regimen. Although seven patients revealed grade 3 toxicity on leukopenia, G-CSF administration was effective for all patients.

Non-hematological toxicity was modest. One patient complained of febrile neutropenia (grade 3). Elevation of total bilirubin grade 3 was observed in one patient with a maximum value of 4.7 mg/dl and grade 2 for one patient with a maximum value of 2.4 mg/dl. Nine patients experienced nausea/vomiting grade 1 and one grade 2. One patient experienced arthralgia/myalgia grade 1. Peripheral neuropathy grade 1 was observed in two patients. One patient experienced nail disorder grade 1.

Table 2.—Hematological and non-hematological toxicity of weekly PTX/5-FU.

<table>
<thead>
<tr>
<th>Toxic effect</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td></td>
</tr>
<tr>
<td>leukemia</td>
<td>0 7 9 0 0</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>1 0 0 0 0</td>
</tr>
<tr>
<td>anemia</td>
<td>4 8 2 0 0</td>
</tr>
<tr>
<td>Non-hematological</td>
<td></td>
</tr>
<tr>
<td>arthralgia/myalgia</td>
<td>2 0 0 0 0</td>
</tr>
<tr>
<td>nausea/vomiting</td>
<td>15 1 0 0 0</td>
</tr>
<tr>
<td>fever</td>
<td>0 0 1 0 0</td>
</tr>
<tr>
<td>allergy</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>total bilirubin</td>
<td>0 1 1 1 0</td>
</tr>
<tr>
<td>peripheral neuropathy</td>
<td>0 0 0 0 0</td>
</tr>
<tr>
<td>nail disorder</td>
<td>0 0 0 0 0</td>
</tr>
</tbody>
</table>

Efficacy of weekly PTX/5-FU (Table 3)

All patients were assessable for response of weekly PTX/5-FU. Five patients with sensitive disease and 11 with resistant disease received weekly PTX/5-FU. Median of platinum-free interval prior to weekly PTX/5-FU was ten months for sensitive disease and three months for resistant disease. Among five patients with sensitive disease, one of four patients with measurable tumor and one without measurable tumor responded to weekly PTX/5-FU. Among 11 patients with resistant disease, none of five patients with measurable tumor and three of six patients without measurable tumor responded to weekly PTX/5-FU. Notably, six patients (75.0%) with measurable disease revealed stable disease without remission of measurable tumor and appearance of a new lesion. Overall objective response rate by weekly PTX/5-FU was 31.3% (5/16).

Platinum retreatment after weekly PTX/5-FU (Table 3)

Among 16 patients, 13 patients who showed stable disease or progressive disease (three with sensitive disease, ten with resistant disease) received platinum retreatment including CPT-11/CDDP (10 cases), DTX/CDDP or CBDCA (3 cases) after weekly PTX/5-FU. Among three patients who were not retreated with platinum, one was treated with cytoreductive surgery followed by radiotherapy, one received non-platinum treatment (liposomal doxorubicin), one continued weekly PTX/5-FU. A median of platinum-free interval after weekly PTX/5-FU was 19 months for sensitive disease, five months for resistant disease. All three patients with sensitive disease and three of ten patients with resistant disease revealed response to platinum retreatment. Overall objective response rate by platinum retreatment after weekly PTX/5-FU was 46.2% (6/13).

Discussion

As far as we know, this is the first report on the toxicity and efficacy of weekly PTX/5-FU for ovarian cancer. In this preliminary report, we confirmed that PTX/5-FU in a weekly cycle is largely tolerable for patients with recurrent ovarian cancer and even for heavily pretreated patients.

In an effort to improve response rates of chemotherapy, taxanes have been combined with other cytotoxic agents such as antimetabolites including 5-FU. Combination of PTX and 5-FU has been reported to be effective in gastric cancer and breast cancer. If 5-FU is administered prior to PTX, it can induce a G-S block in cell lines, potentially limiting the efficacy of subsequent taxane exposure. Indeed, Kano et al. investigated various schedules of paclitaxel and 5-FU in vitro in four human cancer cell lines, evaluating dose-response effects with isobolograms. They found that sequential exposure to 5-FU for 24 hours followed by PTX for 24 hours showed an antagonistic interaction, while reversal of the sequence revealed an additive effect [15]. Therefore, to optimize antitumor effects, it would appear that 5-FU should be administered after PTX treatment for 24 hours, which can block the cell cycle at the G2-M phase. In previous reports on PTX/5-FU, 5-FU was continuously administered for 24 hours. In this study, we administered 5-FU by bolus injection. Although the optimal duration of 5-FU infusion following PTX is unknown, preclinical models suggest similar toxicity from 5-FU irrespective of

<table>
<thead>
<tr>
<th>Platinum-sensitive</th>
<th>Platinum-resistant</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received PTX/5-FU</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td>Median platinum-free interval (months, prior to PTX/5-FU)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Response (measurable)</td>
<td>1/4</td>
<td>0/5</td>
</tr>
<tr>
<td>Response (CA 125)</td>
<td>1/1</td>
<td>3/6</td>
</tr>
<tr>
<td>Response (overall)</td>
<td>2/5</td>
<td>3/11</td>
</tr>
<tr>
<td>Platinum retreatment after PTX/5-FU</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Median platinum-free interval (months, prior to PTX/5-FU)</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Response (measurable)</td>
<td>3/3</td>
<td>1/4</td>
</tr>
<tr>
<td>Response (CA 125)</td>
<td>0</td>
<td>2/6</td>
</tr>
<tr>
<td>Response (overall)</td>
<td>3/3</td>
<td>3/10</td>
</tr>
</tbody>
</table>
duration. We treated two human ovarian cancer cell lines (OVCAR-3 and PA-1) with the combination of PTX/5-FU and found that sequential exposure to PTX for 24 hours followed by 5-FU for one hour with higher dose has a similar synergistic cytotoxic effect as 24-hour treatment by 5-FU with lower dose (unpublished observation).

Concerning the quality of life of patients with recurrent ovarian cancer, bolus injection is superior to a 24-hour continuous infusion, because we can administer this combination chemotherapy in the outpatient clinic without the need for ambulatory infusion pumps. Four studies investigating paclitaxel and 5-FU in weekly cycle noticed tolerable side-effects of mainly leukocytopenia and mild neurotoxicity [10, 16, 17]. Indeed, we found that hematological side-effects were easily manageable with G-CSF as previously reported [17].

In this preliminary report, we obtained an objective response rate of 31.3% by weekly PTX/5-FU for patients with recurrent ovarian cancer. It is unclear if 5-FU showed synergistic effect with weekly PTX in this study, because the response rate of weekly PTX has been reported to be 20-25% for patients with resistant disease [3, 4]. However, we might expect a better response rate for ovarian cancer if we employed this regimen as the first-line treatment or for patients with sensitive disease since 11 patients showed resistant disease to PTX or DTX + CBDDA in our cohort.

It is notable that we found only two cases of rapid disease progression (2/16 = 12.5%) during weekly PTX/5-FU in this study. The clinical value of prolonged stable disease in ovarian cancer has been established [18]. Survival among patients who achieved stable disease was statistically comparable with those who experienced a partial response to topotecan. Thus, stable disease may offer equal clinical benefits compared with partial tumor responses in patients with relapsed ovarian cancer. In the context of maintaining stable disease, weekly PTX/5-FU must be considered as the second-line chemotherapy for recurrent ovarian cancer since this regimen is less toxic and effective to keep at least stable disease for the third-line chemotherapy.

We obtained an objective response rate of 46.2% by platinum treatment after weekly PTX/5-FU for patients with recurrent ovarian cancer. According to current dogma in ovarian cancer treatment, the potential for patient sensitivity to platinum might be the most important factor in planning subsequent treatment. Tumor response rates are directly related to the platinum-free interval among all the novel agents currently used in second-line therapy [5-7, 19]. An important goal of treatment, therefore, is to extend the platinum-free interval for all patients, regardless of platinum sensitivity. The use of a non-platinum agent at first relapse, for instance, can lower the probability that tumors will become increasingly resistant to the platinum treatment. In terms of platinum-free interval, we can use weekly PTX/5-FU as the second line regimen for prolongation of platinum-free interval. Indeed, the median platinum-free interval was six months after weekly PTX/5-FU in this study. Possible third line chemotherapy after weekly PTX/5-FU should be the regimen containing platinum such as CPT-11/CDDP for patients with recurrent disease.

In summary, weekly PTX/5-FU is a useful treatment as the second-line regimen at least to maintain stable disease and to prolong the platinum-free interval, which might result in better response to platinum retreatment as the third-line chemotherapy, and in improvement of survival of patients with recurrent ovarian cancer with poor prognoses.

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References

Weekly paclitaxel/5-fluorouracil followed by platinum retreatment for patients with recurrent ovarian cancer: a single institution etc.


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Audit of suspected chronic intestinal pseudo-obstruction in patients with gynecologic cancer


1Department of Obstetrics and Gynecology; 2Division of Gastroenterology and Hepatology; 3Division of Radiation Oncology; 4Department of Radiology, Mayo Clinic, Rochester, MN (USA)

Summary

Purpose: To describe chronic intestinal pseudo-obstruction (IPO) syndromes that occur after radiotherapy or chemotherapy (or both) for gynecologic cancer. Methods: All 48 patients in the study population had a history of gynecologic cancer, treatment with radiotherapy or chemotherapy (or both), and suspected chronic IPO. The final diagnosis was based on clinical symptoms, radiographic imaging, motility studies, and surgical findings. Treatment was expectant for 27 patients and surgical for 21. Results: In six of the 21 surgical patients, the final diagnosis was mechanical obstruction. In the other 15, it was IPO syndrome: six had an idiopathic dysfunction (ID) and nine had a thick fibrinous coating (FC) on the serosal surface. Intestines of these 15 patients had patent lumens but decreased motility. The ID and FC groups differed in mean age, chemotherapy administration, and mean time from radiotherapy to surgery. Symptoms improved in 67% of FC patients compared with 17% of ID patients. Among patients treated expectantly, symptoms improved in 50% of the ID patients and in 38% of the FC patients. Motility studies were useful for distinguishing ID from FC or mechanical obstruction. Conclusion: Clinical history and motility studies may assist in diagnosing IPO syndrome in gynecologic cancer patients treated with radiotherapy or chemotherapy (or both) and in identifying patients who might benefit from surgical intervention.

Key words: Chemotherapy; Gastrointestinal motility; Gynecologic cancer; Intestinal pseudo-obstruction; Radiotherapy.

Introduction

Intestinal pseudo-obstruction (IPO) is a clinical entity for which the signs and symptoms of intestinal obstruction are present but no intrinsic or extrinsic luminal occlusive process exists. Usually, this entity is caused by functional damage of the myenteric plexus or by a pathologic infiltrative process that involves the intestinal wall and impairs intestinal motility, leading to pseudo-obstruction [1, 2]. Radiotherapy and chemotherapy have been hypothesized to alter the myenteric plexus, causing functional intestinal obstruction [3-5].

Mechanical intestinal obstruction is a well known complication for patients with gynecologic cancer who have had surgical therapy or radiotherapy, or both. Preoperative evaluation of patients with intestinal obstruction may show obvious radiographic or clinical (i.e., recurrence of disease) signs of mechanical obstruction. However, one cannot always identify a clear point of intestinal stricture or kinking in patients who have an obstructive syndrome, and, on the basis of clinical and radiographic findings, the preoperative diagnosis may be intestinal obstruction of uncertain etiology.

Surgical treatment may not be necessary if no point of mechanical obstruction is identified. Moreover, surgical treatment may be accompanied by high morbidity in patients who have gynecologic cancer that was previously managed with radiotherapy [6, 7]. Therefore, one should identify women who have gynecologic cancer and functional obstruction of the intestine who will not benefit from surgical management [8]. Results of preoperative motility studies may potentially help distinguish mechanical from functional intestinal obstruction [9].

In our clinical experience, we observed patients with ovarian cancer who had whole abdominal radiotherapy, with or without chemotherapy, and who presented with intestinal pseudo-obstruction and did not benefit from surgical intervention. For this reason, we hypothesized that whole abdominal and pelvic radiotherapy, sometimes combined with cytotoxic chemotherapy, may cause chronic IPO in patients who have gynecologic malignancy. Our aim was to select and describe a case series of patients who had gynecologic cancer, a previous history of radiotherapy or chemotherapy (or both), and IPO. We attempted to identify clinical characteristics that might aid in selecting patients who may not benefit from surgical exploration.

Materials and Methods

Our selection criteria were based on the presence of gynecologic cancer, IPO, and radiotherapy or chemotherapy (or both). Medical records were reviewed for 86 patients who had gynecologic cancer and a history of IPO, Ogilvie syndrome, or intestinal motility dysfunction and for 105 patients who had ovarian cancer and were treated with whole abdominal radiotherapy at Mayo Clinic between 1976 and 1997. Patients presenting with symptoms of intestinal obstruction or pseudo-obstruction (e.g., abdominal distension, abdominal pain, bloating, constipation,
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Diarrhea, nausea, vomiting, and anorexia without unequivocal clinical, radiographic, or endoscopic findings of mechanical obstruction (i.e., a massive recurrence of tumor or an area of stricture or obstruction) were suspected of having IPO syndrome. Of the 191 patients, 57 had received a diagnosis of IPO, but nine of the 57 were suspected of having IPO before they received treatment for gynecologic cancer (because of underlying disease, such as scleroderma) and were excluded from the study. Therefore, 48 patients were in the study population (34 had ovarian cancer, 10 had endometrial cancer, and 4 had other types of cancer). All had received radiotherapy (n = 17), platinum-based chemotherapy (n = 4), or both (n = 27). Radiotherapy was limited to the pelvis in six patients, and it included the whole abdomen in the remaining 38. Of the 48 patients with IPO, 21 were managed surgically and 27 expectantly (i.e., with restrictive diet or home total parenteral nutrition).

Clinical studies to distinguish mechanical obstruction from IPO included radiographic, histologic, and motility studies. Reports of radiographic findings were usually available in the medical records. The actual radiologic films were readily available for 17 patients. The films were reviewed to verify the presence of nonspecific findings and the lack of unequivocal evidence of mechanical obstruction. Hematoxylin-eosin–stained histologic specimens (available for 15 of the 21 surgical patients) were reviewed to compare histologic findings with clinical and surgical findings. For seven patients, available tissues were also stained with the antibody c-kit for interstitial cells of Cajal (ICC), and stained tissues were interpreted (Figure 1).

Motility studies were performed in a standard fashion [10] in accordance with previously published criteria for distinguishing mechanical obstruction from functional obstruction [9]. Motility tracings were reviewed blindly to distinguish IPO from mechanical obstruction. The results of the studies were available for 11 patients (Figure 2).

A diagnosis of IPO was assigned surgically when dilated bowel was present without a clear point of obstruction. IPO due to functional damage was distinguished from IPO with a fibrous coating surrounding the intestine; intestinal lumens were patent in both types of IPO. The final clinical diagnosis for patients treated expectantly was mechanical obstruction if mechanical obstruction or progressive disease became evident. However, patients who did not subsequently demonstrate any clear sign of mechanical obstruction were categorized as having a chronic IPO syndrome. When the diagnosis remained uncertain, owing to the presence of inadequate follow-up information, the clinical entity was defined generically as late radiation enteropathy.

Three months postoperatively (for surgical patients) and six months after nutritional therapy began (for patients treated expectantly), the outcome was defined as the persistence or resolution of IPO, depending on whether the patient was able to reestablish oral nutrition. Surgical complications were defined as those occurring within one month postoperatively. The following were evaluated as indications of surgical morbidity: the preoperative American Society of Anesthesiologists physical status score (11), operative time, estimated blood loss, febrile morbidity (defined as having a temperature > 38°C at 2 different times, at least 6 hours apart, after the first 24 hours postoperatively), perioperative transfusions, and duration of hospital stay.

Descriptive statistics were used for the clinical and pathologic characteristics of patients. Fisher exact test, χ² test, and Student t-test were used when appropriate. Differences between groups were considered statistically significant at p < .05. SAS System 6.10 statistical software (SAS Institute, Inc, Cary, NC) was used for the analysis.

Results

For the 21 patients who were managed surgically, surgical morbidity was as follows: nine patients (43%) needed perioperative transfusions, median operative time was 179 minutes (range, 95-469 minutes), median esti-
Estimated blood loss was 500 ml (range, 50-3,000 ml), and median duration of hospital stay was 19.5 days (range, 12-50 days). The following postoperative complications occurred: thromboembolic episode in one patient, dehiscence of the stoma and subsequent reoperation in one patient, and death in one patient.

Of these 21 patients, six (29%) had a final surgical diagnosis of mechanical obstruction. No point of obstruction was identified in 15 patients (71%): six demonstrated IPO reflecting probable idiopathic dysfunction and nine had a thick fibrinous coating on the serosal surface (Figure 3). Intestines of these 15 patients had patent lumens but markedly decreased motility. All 21 patients had received prior radiotherapy. Significant differences in age, mean time from cancer diagnosis to development of IPO syndrome, and mean time between radiotherapy and surgical diagnosis were observed between patients with IPO resulting from fibrinous coating and those with IPO from idiopathic dysfunction (Table 1). No differences existed between patients with fibrinous coating and idiopathic dysfunction for mean operative time, estimated volume of blood loss, duration of hospital stay, dose of radiotherapy, duration of preoperative symptoms, preoperative American Society of Anesthesiologists score, need for perioperative transfusions, or febrile morbidity.

Symptoms improved for six of the nine patients (67%) with fibrinous coating three months postoperatively, compared with one of the six patients (17%) with ID. The patient with idiopathic dysfunction whose symptoms mildly improved postoperatively needed endoscopic decompression of the intestine. The other five patients needed to be treated subsequently with long-term home total parenteral nutrition. Seven of the nine patients (78%) with fibrinous coating were receiving fluids and nutrition orally at latest follow-up, compared with three of the six patients (50%) with idiopathic dysfunction.

Among the 27 patients who were managed expectantly, mechanical obstruction became evident in six, whereas five patients were classified as having late enteropathy, owing to the scarcity of data and follow-up. Therefore, 16 patients with a final clinical diagnosis of IPO were treated expectantly. On the basis of direct intraoperative assessment and subsequent outcomes analyses in surgical patients, we identified time from completion of radiotherapy to IPO symptoms as an important clinical characteristic that could assist in the classification of the IPO syndrome (Table 1). Therefore, on the basis of time from completion of radiotherapy (radiotherapy had been administered to 14 of the 16 patients) to suspected IPO, we identified patients in whom symptoms developed within two years after treatment (clinical history consistent with fibrinous coating) and patients in whom symptoms developed after two years (clinical history consistent with idiopathic dysfunction). The clinical history was consistent with idiopathic dysfunction in six patients and with fibrinous coating in eight patients. Six of the eight patients with suspected fibrinous coating but none of the six with suspected idiopathic dysfunction had received chemotherapy before radiotherapy (Table 2). Outcomes of expectant therapy were evaluated six months after diagnosis of IPO. Improvement of symptoms was

Table 1. — IPO characteristics associated with surgically determined FC and ID.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FC</th>
<th>ID</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, yrs.</td>
<td>53</td>
<td>65</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Chemotherapy, no. of patients (%)</td>
<td>8 (89)</td>
<td>2 (33)</td>
<td>.08</td>
</tr>
<tr>
<td>Mean time from Ca Dx to IPO, mos.</td>
<td>22</td>
<td>93</td>
<td>.02</td>
</tr>
<tr>
<td>Mean time from RT to surg, mos.</td>
<td>11</td>
<td>85</td>
<td>.02</td>
</tr>
</tbody>
</table>

CA Dx, cancer diagnosis; FC, fibrinous coating; ID, idiopathic dysfunction; IPO, intestinal pseudo-obstruction; RT, radiotherapy; surg, surgical diagnosis.

Table 2. — IPO characteristics associated with clinically suspected FC and ID managed expectantly.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FC</th>
<th>ID</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time from RT to IPO Dx, mos.</td>
<td>9 (4-16)</td>
<td>104 (32-208)</td>
<td>.002</td>
</tr>
<tr>
<td>Chemotherapy, no. of patients (%)</td>
<td>6 (75)</td>
<td>0 (0)</td>
<td>.009</td>
</tr>
<tr>
<td>Mean age, yrs.</td>
<td>55</td>
<td>58</td>
<td>.73</td>
</tr>
</tbody>
</table>

FC, fibrinous coating; ID, idiopathic dysfunction; IPO Dx, intestinal pseudo-obstruction diagnosis; RT, radiotherapy.
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described in three of the six patients (50%) with idiopathic dysfunction and in three of the eight patients (38%) with fibrous coating.

Motility studies were available for 11 patients with IPO syndrome; five were managed surgically and six expectantly. Studies demonstrating IPO (n = 4) were all associated with idiopathic dysfunction, whereas studies suggestive of both mechanical obstruction and IPO (n = 3) were associated with fibrous coating. Of the three patients for whom motility study findings suggested mechanical obstruction, surgical exploration confirmed mechanical obstruction in one and fibrous coating in another; the third patient was treated expectantly, and the final clinical diagnosis was uncertain (late radiation enteropathy) (Table 3).

Table 3. — Comparison of diagnoses from motility studies and definitive diagnoses for 11 patients with intestinal pseudo-obstruction.

<table>
<thead>
<tr>
<th>Motility study diagnosis</th>
<th>Definitive diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical treatment</td>
<td></td>
</tr>
<tr>
<td>MO</td>
<td>MO</td>
</tr>
<tr>
<td>MO</td>
<td>PO (FC)</td>
</tr>
<tr>
<td>MO and PO</td>
<td>PO (FC)</td>
</tr>
<tr>
<td>MO and PO</td>
<td>PO (FC)</td>
</tr>
<tr>
<td>PO</td>
<td>PO (ID)</td>
</tr>
<tr>
<td>Expectant treatment</td>
<td></td>
</tr>
<tr>
<td>MO</td>
<td>PO*</td>
</tr>
<tr>
<td>MO and PO</td>
<td>PO (FC)</td>
</tr>
<tr>
<td>Equivocal</td>
<td>PO (FC)</td>
</tr>
<tr>
<td>PO</td>
<td>PO (ID)</td>
</tr>
<tr>
<td>PO</td>
<td>PO (ID)</td>
</tr>
</tbody>
</table>

FC, fibrinous coating; ID, idiopathic dysfunction; MO, mechanical obstruction; PO, pseudo-obstruction. *Late radiation enteropathy.

As expected by use of the selection criteria, radiographic findings were equivocal and did not help in distinguishing mechanical obstruction from functional obstruction. These equivocal findings had been confirmed by the review of a sample of films from 17 patients.

Histologic and immunohistochemical assessments showed mild to moderate damage of the myenteric plexus in six of the seven patients analyzed but did not correlate with surgical diagnosis or postoperative outcomes (Table 4). Likewise, serosal adhesions were associated with obstruction from either mechanical causes or fibrous coating.

Table 4. — Comparison of damage of the ICC network with clinical findings in seven patients*.

<table>
<thead>
<tr>
<th>ICC (MY/CM)†</th>
<th>Surgical diagnosis</th>
<th>Postoperative outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>++/+</td>
<td>MO</td>
<td>No change</td>
</tr>
<tr>
<td>++/+</td>
<td>MO</td>
<td>Improved</td>
</tr>
<tr>
<td>+++/++++</td>
<td>PO (FC)</td>
<td>No change</td>
</tr>
<tr>
<td>++/ns</td>
<td>PO (FC)</td>
<td>Improved</td>
</tr>
<tr>
<td>++/++</td>
<td>PO (FC)</td>
<td>No change</td>
</tr>
<tr>
<td>+/+</td>
<td>PO (FC)</td>
<td>No change</td>
</tr>
</tbody>
</table>

CM, circular muscle; FC, fibrinous coating; ICC, interstitial cells of Cajal; MO, mechanical obstruction; MY, myenteric plexus; ns, no staining; PO, pseudo-obstruction. *All tissue samples were from the small bowel. †The number of plus signs indicates the intensity of staining. Normal ICC network is indicated by “+++.” No staining, “+,” and “++” indicate damage.

Discussion

Radiotherapy may damage the myenteric plexus, thus leading to a functional intestinal obstruction [3, 4]. Reports of only a few patients with gynecologic malignancy and IPO have been published. Most of the patients experienced acute colonic pseudo-obstruction [12-15] rather than chronic IPO [3, 16, 17]. This is probably because IPO is an underrecognized clinical entity for patients who have intestinal obstructive symptoms after radiotherapy or chemotherapy. Alternatively, this under-reporting might be due to the relatively infrequent use of whole abdominal radiotherapy for the treatment of ovarian cancer. In fact, most of the patients in our series had ovarian cancer that had been managed with postoperative whole abdominal radiotherapy.

For our analysis, we excluded patients who had IPO unrelated to radiotherapy or chemotherapy and selected only women for whom previous treatment for cancer was the only identifiable possible cause of IPO. For patients who had surgical therapy, a definitive diagnosis of mechanical obstruction or IPO was made, and patients with IPO due to fibrous coating were correctly distinguished from those with idiopathic dysfunction. Diagnoses for patients treated expectantly are questionable, however, and they were made on the basis of clinical findings (i.e., time between radiotherapy and onset of symptoms of IPO) (Table 2).

As expected by use of the selection criteria, radiographic findings were not helpful in distinguishing between mechanical obstruction and functional obstruction. On the contrary, motility tracings were often predictive of surgical findings (Table 3). In fact, motility tracings helped to correctly predict mechanical obstruction and IPO due to idiopathic dysfunction. IPO due to fibrous coating was often interpreted as being a mechanical obstruction or as having a mixed cause. Whether or not the function of the myenteric plexus in patients with fibrous coating was altered (Table 4), the fibrous coating was a mechanical obstacle for motility. Two-thirds of patients with fibrous coating improved after surgery (compared with only one-third when treated expectantly), and motility studies assisted in distinguishing patients who might benefit from surgical treatment. As described in the study, surgical morbidity may be high in these patients and must be avoided whenever possible.

Histologic findings did not usually add useful information to the surgical findings, as previously reported [18]. For this reason, we looked for possible damage to the ICC, which had been previously reported from findings in patients with intestinal pseudo-obstruction [19]. Unfortunately, staining for ICC has been limited to seven patients with available tissue and has not been performed for any patient with demonstrable idiopathic dysfunction. The analysis of the ICC demonstrated mild to moderate damage of the ICC network in six of seven patients who had previous radiotherapy with or without chemotherapy (Table 4). The status of the ICC did not correlate with the surgical diagnosis or with the clinical outcome postoper-
atively. These findings suggest that there was damage to the ICC (due to radiotherapy or chemotherapy, or both) that was not always clinically evident. In fact, ICC are responsible for normal, coordinated gastrointestinal tract motility, and radiotherapy-induced damage to ICC may possibly contribute to the development of IPO or may simply make a mechanical obstruction more evident. Other authors previously described abnormalities in the ICC causing IPO [20].

With the selection criteria in our study, we cannot draw conclusions about the frequency of IPO syndrome in gynecologic cancer patients treated with external radiation with or without chemotherapy. However, this case series does permit recognition of the existence of IPO after radiotherapy in gynecologic cancer patients presenting with symptoms of intestinal obstruction but equivocal radiologic findings.

Conclusions

Our sample size was too small to draw definitive conclusions but, as demonstrated in Table 1, patients with the following may have idiopathic IPO that is extremely unlikely to benefit from surgery: gynecologic cancer, symptoms of chronic intestinal obstruction, unclear radiologic findings, history of previous radiotherapy, and time from initial radiotherapy to symptoms of IPO longer than two years. In those patients an operation should be avoided (or at least preceded by a trial of conservative nonsurgical therapy), and as many as 50% of them may benefit from expectant management. By contrast, patients with a mechanical obstruction or clinical characteristics consistent with an IPO due to fibrinous coating (Table 1) may benefit from surgical intervention. In fact, although surgical intervention did not always lead to a good outcome (probably some cases of obstruction had mixed causes), surgical treatment may have been more efficacious than expectant treatment in patients with fibrinous coating. Among patients with a history of gynecologic cancer, previous radiotherapy or chemotherapy, or symptoms consistent with chronic intestinal obstruction or partial obstruction but equivocal radiologic findings, the clinical history and motility studies may assist in making the correct diagnosis preoperatively, thereby guiding subsequent management decisions.

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References


Is the watch and wait approach adequate after comprehensive surgical staging in invasive Stage I epithelial ovarian cancer? The Norwegian Radium Hospital Experience

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Summary

Objectives: The aim of this study on stage I epithelial ovarian cancer (EOC) was to see if our different treatment policies after 1995, when lymph node staging and paclitaxel were introduced, have affected the survival, try to define risk groups for relapse and who should get adjuvant chemotherapy (AC). Methods: A retrospective study based on record information from all patients with invasive EOC stage I operated at the Norwegian Radium Hospital (NRH) 1984-2001, in total 252 patients. Results: Total 5-year survival was 83 and 82%, respectively, in both time periods. We found age and histology to be significant prognostic factors for overall survival (OS) (p < 0.01). From 1995 survival was significantly better for those who had been properly staged than for the others (p = 0.08), with a 5-year survival rate of 87 vs 64%. Those who did not get chemotherapy but were staged, had a significantly better overall survival than those who were not (p = 0.02), with a 5-year survival of 93 vs 77%. In the period 1995-2001 the patients who received no adjuvant treatment lived longer than those who underwent chemotherapy and/or radiotherapy (p = 0.03). In the first period 17% had no adjuvant treatment vs 58% in the last. Patients in a high-risk group getting AC had a tendency toward better survival than those who did not (p = 0.08). Conclusions: Patients with Stage I low and medium risk EOC do not need AC if properly staged. For the high-risk group the optimal AC has not yet been established.

Key words: early stage ovarian cancer.

Introduction

In Scandinavia the age-adjusted incidence of epithelial ovarian cancer (EOC) is among the highest in the world. In Norway the incidence has been reasonably stable over the past 20 years, approximately 14 per 100,000 women [1]. Worldwide EOC is the most common cause of death in gynaecological cancer. One of the main reasons for this is that more than 70% of cases are diagnosed after the tumour has already spread beyond the ovaries. Only about one-third of patients with EOC have localised disease confined to the ovaries or pelvis. The prognosis for these women is much better. In Norway the population-based overall relative 5-year survival rate improved between 1976 and 2000 from 80% to 91% for FIGO (Federation International of Obstetrics and Gynaecology) Stage I with tumour growth limited to the ovaries [1]. Still approximately 30-50% of women with early stage (FIGO Stage I-II) disease eventually relapse and succumb to their disease [2].

These suboptimal survival results have led to major efforts to identify prognostic factors, improve surgical staging, and develop adjuvant therapies that could improve patient outcome.

The retrospective study of Vergote et al., from seven hospitals in six countries between 1980 and 1994, identified degree of differentiation as the most powerful prognostic indicator of disease-free survival, followed by rupture before surgery, rupture during surgery, FIGO 1973 sub-stage and age [3]. Other studies have reported DNA ploidy by image- or flow-cytometry as an independent prognostic factor for survival [4, 5]. A new study from 2007 pointed out the pretreatment value of CA-125 ≤ 30 U/ml as the strongest predictive factor to identify a subgroup of Stage I with extremely good survival [6]. Several molecular biologic parameters have been tested and some like p53 have shown promising prognostic importance, but will have to be further investigated [7, 8]. Patients with Stage I EOC who suffer a relapse after surgery do so because of sub-clinical metastases at time of surgery, most commonly in the peritoneal cavity but occasionally in extraperitoneal locations such as the lymph nodes. Therefore an accurate surgical staging is crucial in the assessment of prognosis of Stage I EOC. With a second laparotomy with lymph node staging of improperly staged patients, presumed to be early-stage EOC, and with a high-risk profile for relapse, approximately 28% were found to have positive nodes and had to be upstaged to Stage III C in our experience [9] which is similar to Trimbos et al. [10], Young et al. [11], and Zanetta et al. [12].

Patients with a statistically significant risk for having persistent disease should be treated with adjuvant chemotherapy (AC). However, only a fraction of the patient population treated has micro metastatic disease and can potentially benefit from the treatment. Therefore the role of AC in patients with Stage I EOC remains controversial [13].

A review of 22 prospective randomised studies has discussed adjuvant treatment for early-stage EOC [13].

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The two prospective trials, the International Collaborative Ovarian Neoplasm I (ICON I) and Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION), and the combined analysis of the two trials from 2003, add important information on AC but leave some critical issues unsolved [10, 14, 15]. It was concluded that platinum-based AC, six cycles, improved overall- and recurrence-free survival at five years in the combined group of patients with early-stage ovarian cancer defined by the inclusion criteria of the ICON1 and ACTION trials. The inclusion criteria were however different, and no data presented in the ICON I trial suggested that the low-risk subset of patients with well-differentiated histology and sub-Stages IA and IB benefit from AC. In a long-time follow up of women in the ICON 1 study presented at ASCO 2007, there was clear evidence that AC reduces the risk of recurrence/death or death alone in high-risk patients but not in the medium and low-risk group. The high-risk group was defined as FIGO Stage I A grade 3, I B or IC grade 2 or 3, and clear cell tumours [16].

The sub analysis of the ACTION trial suggested that accurate surgical staging identifies patients who do not require AC [10]. The study has been criticised because only one-third of the patients were properly staged.

At present the combination of paclitaxel and carboplatin (PC) is generally accepted as the standard chemotherapy for EOC and carboplatin has been shown to be as good as cisplatin with fewer side-effects [16-19]. A randomised phase III trial GOG 157 on 457 early-stage EOC, where about 70% of the patients had complete surgery, concluded that three cycles compared to six cycles of PC do not significantly alter the recurrence rate in high-risk early-stage EOC but are associated with less toxicity [20]. Therefore three cycles of PC is today in most parts of the world considered as the standard AC in high-risk Stage I EOC [13].

The Norwegian Radium hospital (NRH) is one of four cancer centres sharing the main responsibility for cancer treatment in Norway and the hospital mainly serves as a referring hospital for the south-eastern parts of the country including about 60% of the Norwegian population. Most patients with Stage I EOC are operated on at local hospitals except for patients considered as complicated cases, e.g., high-risk patients who are referred to NRH for primary surgery. If the surgery was not radical enough at the local hospital or they had to be evaluated for intraabdominal P32 [21], or inclusion in the NSGO (Nordic Society of Gynecologic Oncology) prospective randomised study in Stage I EOC [5], they were referred and reoperated on immediately at NRH.

The aim of our study was to evaluate the treatment of patients with Stage I EOC during the two time periods, 1984-1994 and 1995-2001, to see if our different surgical and chemotherapy treatment policies during the periods have affected survival. From this we would try to define risk groups for relapse and which patients who would benefit from AC or not.

Materials and Methods

All patients with histological verified invasive Stage I EOC operated on at NRH between 1984 and 2001 were included in this retrospective study, a total of 252 patients. This is about half the patients with Stage I EOC referred to NRH in that period. The second half had their primary surgery at local hospitals and were referred to NRH for further planning and chemotherapy. All patients with borderline tumours were excluded from the beginning. Data were collected from patient records found via the hospital code registry for diagnosis and operation. No patients were lost in follow-up.

Registered parameters included age at start of treatment, period of diagnosis, histological subgroups, and degree of differentiation. Types of chemotherapy were subdivided in four groups: 1 = single platinum, 2 = platinum in combination with non-paclitaxel chemotherapy, 3 = all regimens with paclitaxel single or in combination and 4 = others (antracyclins, cyclophosphamide, thiotepa and fluorouracil). Before 1995 mostly single platinum was used as AC. Paclitaxel was introduced around the mid-nineties and followed by the combination platinum/paclitaxel. Staging of the patients was performed according to the system developed by FIGO in 1988. Before that staging was done retrospectively from the records. Histological classification was done according to criteria defined by the World Health Organisation (WHO). Clear cell tumours were not graded. All histological sections were reviewed by the specialised pathologists at NRH. We registered if the patient was reoperated on or primarily operated on at NRH and if lymph node staging was done. Number of nodes removed was registered. In the eighties, patients were randomised to cisplatin or radioactive phosphorus or whole abdominal irradiation as adjuvant treatment [21]. From 1992 to 1997 patients with a high-risk profile of Stage I EOC were randomized to six courses of adjuvant carboplatin or no adjuvant treatment at all [5]. NRH’s surgical staging procedures in EOC have been followed from the mid-nineties [13]. From about the same period in inadequately Staged I EOC we chose a high-risk group for re-laparotomy to be all grade 3 and undifferentiated tumours, all aneuploid tumours, all clear cell adenocarcinomas and patients with elevated CA-125 values for a second laparotomy within three weeks for a complete restaging procedure. Gynaecologists at the referring hospitals do not do lymph node dissection. The ICON 1 classification for low-, medium- and high-risk Stage I epithelial ovarian cancer was used for grouping our patients. Low-risk (Stage I A grade 1, non-clear cell), medium-risk (Stage I A grade 2 and Stage I B or IC grade 1, non-clear cell), and high-risk (Stage I A grade 3, Stage I B or IC grade 2 or grade 3 and all clear cell) [16]. Time of final status (alive, dead or emigrated) was registered as January 2007.

Statistical analysis

Overall survival was estimated using the Kaplan-Meier method and groups were compared with log-rank tests. The five-year survival was estimated. Some of the most important suggested factors were far from proportional hazards, making them unsuitable for inclusion in the Cox proportional hazards regression model. We therefore decided to present results of univariate survival analysis only; p values ≤ 0.05 were regarded as statistically significant. Data analysis was performed using SPSS 15.0.
Is the watch and wait approach adequate after comprehensive surgical staging in invasive Stage I epithelial ovarian cancer? etc.

**Results**

Patient characteristics are shown in Table 1. The 252 patients with invasive cancer had a 5-year survival rate of 83%. Most patients were between 50 and 70 years in both periods. The last period contained proportionately fewer patients below 39 years and more between 50 and 70 years. The best overall and 5-year survival rates were found for the group below 39 years, and the worst for the oldest group over 70 (Table 1, Figure 1). The difference was significant (p < 0.001).

There was a nearly equal distribution of patients between the main histological subgroups, and univariate analysis showed a significant difference (p < 0.01) overall (OS) between the groups (Figure 2). The OS and 5-year survival rates were best for the endometrioid and mucinous group and worst for the clear cell and non-classified group. The serous group did not do so well either. The last period contained relatively more patients with clear cell cancers than the first period relatively (Table 1).

Table 1 shows no difference in 5-year survival in the well, moderate, and poorly differentiated tumours, and the difference in OS was not significant in univariate analysis.

As for the sub-stages no significant differences were found in OS and 5-year survival. Most patients with Stage IC were found in the last time period and most with Stage IA in the first period.

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**Table 1. — Characteristics of patients with invasive Stage I EOC (n) and five-year total survival (%) for different treatment periods.**

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**Table 2. — Characteristics of patients with Stage I EOC, with and without lymph node staging, 1984-2001.**

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**Table 3. — Treatment frequencies (n) and 5-year OS (%) for EOC Stage I with and without lymph node staging or AC.**

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<tr>
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Figure 1. — Stage I EOC. OS for different ages (p < 0.01).
Figure 2. — Stage I EOC. OS for different histological groups (p < 0.01).
Figure 3. — Stage I EOC. OS with adjuvant treatment or not (p = 0.03).
Figure 4. — Stage I EOC. OS with lymph node staging or not (p = 0.02).
Figure 5. — Stage I EOC. OS combining lymph node staging and adjuvant chemotherapy (p = 0.05).
Figure 6. — Stage I EOC. OS for different treatment periods (p = 0.68).
No significant difference in survival was found between the chemotherapy groups or between those who got AC and those who did not (Table 1). For the last period however, there was a tendency towards better OS for those who did not get AC compared to those who did get it (p = 0.06). In the first period the 5-year survival was best for those who received AC.

Intraperitoneal radioactive phosphorus was in use in the first period and a few patients received external abdominal and pelvic irradiation adjuvant to surgery in both periods. A few patients even received combined chemo- and radiotherapy as shown in Table 1. For the whole cohort no significant difference in survival was observed in the groups who received either radiotherapy or chemotherapy, or no adjuvant treatment at all. However from 1995 we found a significantly better OS for those who received no adjuvant treatment compared to those who had cytostatica and/or radiotherapy (p = 0.03) (Figure 3) with a 5-year survival of 91% (Table 1).

Only 17% of the patients had no adjuvant treatment in the first time period compared to as much as 58% in the last period.

Lymph node staging was mostly performed after 1995 and in 85% of the cases. We found a tendency towards better OS for all patients that had been properly staged compared to those who had not (p = 0.08). After 1995 the OS difference was significant (p = 0.02) (Figure 4). Table 2 shows the characteristics of the patients with and without lymph node sampling. There were more patients with clear cell, poorly differentiated and Stage IC tumours among those who had lymph node staging, and 63% vs 16% had no adjuvant treatment at all. Thirty-six percent versus 4% however received paclitaxel in combination.

There was no significant difference in survival for those who received or did not receive AC. By combining AC and lymph node staging however, we found a significantly better survival for those who did not have AC but had lymph node staging than for those who had not been staged (p = 0.02). Comparing the four combined groups (Figure 5), also shows a difference which is significant (p = 0.05).

Table 3 shows the 5-year survival rates for the AC and lymph node staging groups, and the same condition is demonstrated with a 5-year survival rate of 93% for those who did not undergo AC but were staged and 77% for those who were not staged.

The OS was not significantly better when 15 or more lymph nodes were removed compared to less than 15. When comparing the two treatment periods 1984-1994 and 1995-2001, no significant difference in OS was demonstrated between the periods (p = 0.68) (Figure 6).

When defining three different risk groups as in the ICON I study, we found no significant difference in OS in the high-risk group between those who received AC and those who did not (p = 0.6). The same nonsignificant difference was demonstrated for the medium- and low-risk groups. Table 4 shows more characteristics for the different risk groups.

**Table 4. — Characteristics and number of patients in the different risk groups of invasive EOC Stage I.**

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Low risk: Stage I A, diff grade 1, non-clear cell. Medium risk: Stage I A, grade 2 and Stage I B or c, grade 1, non-clear cell. High risk: Stage I A, grade 3, I B or c grade 2 or 3 and all clear cell.

**Discussion**

The results of this retrospective study taking place between 1984 and 2001 are influenced by the two randomised studies described that the department took part in during that time [5, 21]. In the last period more patients were reoperated on for proper staging and more were also referred for primary surgery at NRH because they were considered preoperatively as high-risk patients. The 5-year survival rate for the whole cohort of 83% is almost the same as reported from Norway for the same period [1]. Age and the histological types as prognostic factors for overall survival are also comparable with Vergote et al. [3]. The distribution between the histological groups and survival showed the same tendencies and is in accordance with others that found nodal disease more frequent in serous and clear cell tumours than in mucinous and endometrioid types and best survival for mucinous and endometrioid types [3, 10, 22, 23]. For the degree of differentiation and sub-stages we did not find significant differences in univariate analysis opposed to Vergote et al. [3], but we saw the same tendencies.

Two prospective observational studies have been published, Trimbos et al. [24] and Monga et al. [25] in which patients did not receive AC after surgery. These studies demonstrated the natural course for patients with Stage I EOC and emphasised the importance of proper staging of EOC [13]. On the basis of these findings we started systematic lymph node staging from about 1995, and from that time we found a significant better survival for the patients who had lymph node sampling than those who did not in accordance with the optimally staged patients in the observation arm of the ACTION study [10] (Figure 4). The group that was properly staged also consisted of
more patients with a poor prognosis and more who did not receive any adjuvant therapy. Comparing the survival with or without AC alone we found no significance in contrast to the conclusion of the ICON 1 and the combination of ICON 1 and ACTION study [14, 15]. By combining AC and lymph node staging we found the significantly best survival for the patients who did not receive AC but had been properly staged compared to those who were not. This is in accordance with the conclusion of the ACTION study which says that the benefit of AC appears to be limited to patients with non-optimal staging. The poor survival of the improperly staged patients with no AC can be explained by the fact that many of them could be Stage III C as we have shown earlier [9].

By using the risk groups of the long-time follow-up of ICON 1 study in our work, we got nearly the same results as them, showing that AC reduces the risk of death in the high-risk group of patients but not in the medium- or low-risk groups [16]. However, none of the ICON I patients were properly staged. For selected patients who were staged incompletely at the time of initial surgery, completion of the staging procedure with either laparoscopy or laparotomy is another reasonable approach before a final decision can be made regarding the need for AC.

No significant difference in survival was found between the chemotherapy groups, but the numbers in some of the groups are small.

After 1995 we found the best significant survival for “the no-adjuvant-treatment-at-all-group”.

We could not demonstrate better OS for the last period, but there were relatively less young patients, more patients with serous and clear cell and poorly differentiated tumours and patients with Stage IC EOC after 1995. This result makes the effect of AC in adequately staged high-risk patients more doubtful given that no statistically significant effect of AC was shown in this group in the ACTION trial [10]. We believe many world leading gynaecologic oncologists may consider AC even in properly staged high-risk patients Stage I as over-treatment [11, 26, 27]. Tropé et al. [5] and Bolis et al. [28] have shown that salvage treatment was more effective in the optimally staged observation arm. They suggested that salvage treatment should be postponed until the time of recurrence. In a small select group of very high-risk patients we consider the use of three cycles of adjuvant PC [13, 20].

In a Norwegian study [29] including 70 (54%) Stage I patients, 22% had chronic fatigue. Five-year survivors of Stage I EOC had more somatic and mental morbidity, more fatigue, poorer quality of life, and used more medication and health services than controls (compared with an age representative sample of the general female population). The relative risk for developing secondary malignancies is increased from 3.3 to 6.5 after platinum therapy depending on dose [30]. This supports our belief that the use of AC should be reduced for patients who are likely to be long-term survivors [13].

We have demonstrated however that a lot of patients avoided stressing AC and probably got a better quality of life the last time period compared to the first time period and even with better survival.

All this should indicate that there are two groups of patients with low- and medium-risk Stage I invasive EOC that do not need AC treatment, and according to what we have found it is important that these patients undergo a proper staging operation and do not belong to the high-risk group defined above. We also mean that it is better to centralise the patients to get the primary surgery done by a gynaecological oncologist to avoid a second restaging laparotomy.

Acknowledgments

We thank the scientific secretary, Mrs. Gry Seppola for technical and organizational help, and the financial support from Inger and John Fredriksen’s Foundation for Ovarian Cancer Research. We also thank Anne Birgitte Jacobsen at the Clinical Trials Unit, The Norwegian Radium Hospital for supporting the construction of the electronic database, and we thank our specialized pathologists for reviewing all the histological sections.

References


Is the watch and wait approach adequate after comprehensive surgical staging in invasive Stage I epithelial ovarian cancer? etc.


[16] Swart A.C. on behalf of ICON collaborators: “Long-term follow-up of women in a randomized trial of adjuvant chemotherapy for early stage ovarian cancer (ICON 1)”. ASCO 2007; abstract nr 5509 (oral presentation).


[27] Colombo N., Pecorelli S.: “What have we learned from ICON1 and ACTION?”. *Int. J. Gynecol. Cancer*, 2003, 13 (suppl. 2), 140.


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Polymorphisms of p53, GSTM1 and GSTT1, and HPV in uterine cervix adenocarcinoma

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Summary

Objective: To analyze the participation of glutathione-S-transferase (GST) M1 and T1 polymorphisms associated or not with protein p53 polymorphism at codon 72 and in the presence of HPV in the carcinogenesis of uterine cervix adenocarcinoma. Methods: Forty-three samples of uterine cervix adenocarcinoma were studied and 86 samples of endocervical cells of women without tumors formed the control group. The presence of HPV was determined in order to genotype the isoforms of p53 at codon 72, GSTM1, GSTM1*0, GSTT1 and GSTT1*0 which were evaluated by the PCR method. Results: HPV was present in 97.67% of the adenocarcinoma cases and in 31.40% of the control group. Statistical analysis showed differences (p = 0.001) and an OR of 113.3 (CI 95%: 13.67-947.14). GSTT1 and GSTT1*0 analysis showed a significant difference between the groups (p = 0.001) with an OR of 4.58 (CI 95%: 2.041-10.28) (p < 0.001) for the presence of GSTT1*0. When it was associated with HPV OR was 6.6 (CI 95%: 0.04-0.50). Analyses of p53 and GSTM1 and GSTM1*0 either alone or associated with HPV were not significant. Conclusion: The presence of GSTT1*0 increased the risk for uterine cervix adenocarcinoma development while the allele GSTT1 had a protective action. The other isoforms did not appear to participate in the carcinogenesis of uterine cervix adenocarcinoma.

Key words: p53; GSTM1; GSTT1; HPV; Adenocarcinoma.

Introduction

Polymorphisms are structural DNA modifications of a certain gene, inherited and transmitted to a part of the population. Repetitions of microsatellites, insertion, inversion and deletion of small segments may occur. The simple exchange of a nucleotide for another, called single nucleotide polymorphism (SNP) is the most frequent occurrence [1]. Variations of p53 and of the metabolizing glutathione-S-transferase M1 and T1 (GSTM1 and GSTT1) are examples of polymorphisms [2, 3]. Protein p53 is a phosphoprotein whose function is related to blockade of cell cycle progression and to the start of the apoptosis chain. In humans polymorphism at codon 72 occurs with substitution of the amino acid proline (PRO) for arginine (ARG). Both alleles may be functionally homozygous or heterozygous [4, 5]. Women with ARG homozygosis when infected by human papillomavirus of high oncogenic risk have a seven-fold higher risk of developing squamous cell carcinoma of the uterine cervix than the others [2].

Glutathione-S-transferases (GST) are part of a phase II superfamily of metabolizing enzymes [6]. Their fundamental role is due to the detoxification of endogenous and exogenous compounds, forming non-toxic and more soluble derivatives ready to be excreted or transported and stocked by phase III metabolism transporters. In humans there are seven cytosol GST superfamilies. Among them the GSTM and GSTT superfamilies should be pointed out [7, 8].

The GST-M family has five isoforms or subfamilies GSTM1 to GSTM5. The GSTM1 gene, localized in 1p13.3, has three alleles, GSTM1*A, GSTM1*B and GSTM1*0. The first two differ regarding substitution of the guanine for cytosine in nucleotide 534 of exon 7, so that, in position 172 of the enzyme there is substitution of one lysine (GSTM1*A) for asparagine (GSTM1*B). The third allele (GSTM1*0) is the result of an unequal exchange between GSTM1 and GSTM2 loci which are physically near and share 99% of the nucleotide sequence, with the occurrence of a 15 kb deletion which contains the whole GSTM1 gene [9].

The GST-T family, instead, has two isoforms or subfamilies, GSTT1 and SGTT2, separated by 50 kb. The GST1 gene is localized in 22q11-2, and presents three alleles, GSTT1*A, GSTT1*B and GSTT1*0 or null allele. The two first differ regarding substitution of the arginine for cytosine in nucleotide 310 of exon 3, which exchanges the threonine (GSTT1*A) of residue 104 for proline (GSTT1*B). GSTT1 is located in a region of extensive homology and is flanked by two 18 kb regions called HA3 and HA5 which each have in their central region 403 bp with 100% identity. Recombination of 403 bp to the right with those to the left results in a 54 kb deletion containing the whole GSTT1 gene; as a result allele GSTT1*0 or null allele emerges [9].

Several authors demonstrate or refute the association of the null alleles with higher susceptibility to develop intraepithelial neoplasias and squamous cell carcinoma of the uterine cervix associated or not with p53 polymorphisms [10-15].
Epidemiologic studies confirmed that HPV is the causal factor of uterine cervix cancer associated with several cofactors, being found in 95% of adenocarcinomas of the uterine cervix.

Uterine cervix adenocarcinomas are little known tumors when compared to the squamous cell variety. They have a worse prognosis and are more resistant to the immunologic reaction of the host body when compared to the cell variety [20-23].

The present aim was to analyze an eventual association of polymorphisms present in the p53 gene, as well as the metabolizing enzymes GST1/GSTM1*0 and GSTT1/GSTT1*0 with the emergence of cervical adenocarcinoma.

Materials and Methods

The study group consisted of tumor fragments obtained from 44 women with uterine cervix adenocarcinoma at any clinical stage, proven by histopathologic examination and still without treatment. The fragments were processed histologically with a final diagnosis of adenocarcinoma.

The control group consisted of 100 samples of endocervical scrapings obtained with a brush. Smears were made on a slide for the cytopathologic examination and the remainder dispersed in a cytosolic Tris EDTA solution. Absence of any intraepithelial and inferior genital tract invading neoplasia was proven by cytopathologic and colposcopic examination.

Biomolecular analyses were performed in the Laboratory of Molecular Gynecology of the Department of Gynecology, UNIFESP-EPM. After paraffin removal from the histopathologic sections of both the study and control groups, DNA was extracted [25], presence of HPV was searched [26], polymorphism at codon 72 of the TP53 gene was analyzed [27] and alleles of GSTM1 and GSTT1 families was studied [28] using polymerase chain reaction (PCR).

Statistical analysis was performed using the following tests: Student’s t-test to compare age between groups; chi-square test to compare presence of HPV in the study and control groups to verify the participation of the polymorphic varieties of GSTM1 and GST1 families in the two groups; Fisher’s exact test for the analysis of p53 isoforms in the study and control groups; analysis of the association of HPV with p53 protein isoforms and with GMST1 and GSTT1 enzyme alleles in the genesis of uterine cervix adenocarcinoma, as well as analysis of the association of p53 isoforms with alleles of the GSTM1 and GSTT1 families; and statistical analysis of the GSTM1 and GSTT1 families’ association with the T1 enzyme family in the carcinogenesis of uterine cervix. In all performed and applicable tests rejection of the null hypothesis was equal to or less than 5% (0.05).

Results

Of the 44 selected specimens for the study group one case was excluded because of non-amplification of DNA, so that 43 samples remained. In the control group 14 cases were excluded for the same reason so that this group consisted of 86 DNA samples of endocervical cells. A mean of 52.48 years and median of 45 years. The analysis of the groups using the Student’s t-test showed that they were homogeneous (p = 0.1402) (CI 95%).

Presence of HPV in the study and control groups is shown in Table 1. The statistical analysis by the chi-square test showed a significant difference between the two groups (p = 0.001). Analysis of maximum likelihood estimation, odds ratio (OR) with 95% confidence interval (CI) showed a 113.79-fold risk (CI 95%: 13.67 - 947.14) for adenocarcinoma development in the presence of HPV. The p53 polymorphism at codon 72 in the two groups was evaluated by Fisher’s exact test and there was no statistical difference (p = 0.397) (CI 95%). Association between the presence of virus and the different p53 isoforms also did not show any statistical difference (p = 0.01; CI 95%).

Similarly the distribution of GSTM1 and GSTT1*0 alleles did not show a statistically significant difference by the chi-square test (p = 0.374; CI 95%). The presence of HPV associated with the GSTM1 family, verified by Fisher’s exact test, did not show any significant difference (p = 0.256; CI 95%). Association of the p53 isoforms with the family of the GSTM1 enzymes, analyzed by Fisher’s exact test also did not show significant differences (p = 1.000; CI 95%).

Evaluation of enzyme GSTT1 with alleles GSTT1 and GSTT1*0 (Table 2) evidenced a difference between the study and control groups by the chi-square test (p = 0.001; CI 95%). Analysis of maximum likelihood estima-
tion, OR with 95% CI showed a 4.58-fold risk (CI 95%: 2.041-10.28) (p = 0.001) for acquiring uterine cervix adenocarcinoma with GSTT1*0. Analysis of HPV-associated enzymes GSTT1 and GSTT1*0 (Table 3) revealed a significant difference between the two groups (p = 0.001; CI 95%) using Fisher’s exact test. Analysis of maximum likelihood estimation, OR with CI 95% showed a 6.6-fold risk (CI 95%: 1.99-22.17; p < 0.001) of the association HPV with GSTT1*0 and 0.15 times (CI 95%: 0.04-0.50; p = 0.0021) for the association HPV with GSTT1. The association of the protein p53 isoforms with the GSTT1 enzyme family did not show significance by Fisher’s exact test (p = 0.56; CI 95%).

Evaluation of the association between GSTM1 and GSTT1 families was performed using a logistic regression model. This fact allowed us to conclude that the GSTM family is not a prognostic factor for uterine cervix cancer either alone or associated with the GSTT1 family.

**Discussion**

In this study, the mean age of patients with adenocarcinoma was 52.48 years, superior to the reports by Pirog et al. [17] and Bulk et al. [29], but was similar to those by Lea et al. [30] and Baalbergen et al. [31].

The significant difference of HPV presence (p = 0.001) in the study and control groups and the 113.8-fold risk (p < 0.001) of developing adenocarcinoma agree with Pirog et al. [17] and Castellsagué et al. [19].

The lack of statistical significance between the study and control groups suggests the lack of participation of p53 polymorphism at codon 72 in the generation of uterine cervix adenocarcinoma in the presence of HPV in the studied population. These findings agree with the results obtained by Hildesheim et al. [32] and Gustafsson et al. [33] and are at variance with those obtained by other authors [34, 35].

In the studied population, phase II metabolizing enzymes GSTM1 and their null allele GSTM1*0 did not participate in adenocarcinoma genesis. Analyses of the association of these enzymes with HPV and with p53 isoforms were also not significant.

In contrast the risk of a woman with the GSTT1*0 genotype of developing uterine cervix adenocarcinoma was 4.6 times higher compared to those with GSTT1. The risk of women with HPV infection associated with genotype GSTT1*0 of developing adenocarcinoma was 6.6 higher than for women with the GSTT1 isoform. In the face of a HPV infection the presence of the metabolizing enzyme GSTT1 would exert a protecting function according to what the applied statistical tests revealed.

The trend toward participation of the p53 Arg/Arg isoform associated with the alleles GSTT1 and GSTT1*0 in the genesis of adenocarcinomas was noted in this study, however confirming trials are needed. It seems that only the GSTT1 family would have a prognostic value for adenocarcinomas.

Our results are similar to those described by Ueda et al. [27] although the histological type analyzed by those authors was squamous type.

Association studies between complex genic traits and common diseases, although popular, are marked by lack of reproducibility. The possible causes would include a false-positive association which corrected, would not be replicated; true association which would fail on replication in a low statistical power study, constituting a false-negative study; true association in a certain population would not occur in another due to genetic heterogeneity or environmental variables [36].

In our research it was not possible to establish real comparisons regarding reproducibility. Although focusing on uterine cervix carcinoma, the comparisons of the associations were performed with the squamous variety in spite of the fact that up to now the correct identification of the differences or similarities between both varieties of the cervical neoplasia is lacking.

This study is the first to analyze the association between HPV and the isoforms of the metabolizing enzymes GSTM1 and GSTT1 in uterine cervix adenocarcinoma. Other studies should be performed to confirm or refute the data reported in this research.

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**References**


Polymorphisms of p53, GSTM1 and GSTT1, and HPV in uterine cervix adenocarcinoma

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Serum adiponectin in relation to endometrial cancer and endometrial hyperplasia with atypia in obese women

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Summary

Objectives: The aim of this work was to compare concentrations of adiponectin in the serum of obese women with endometrial cancer, endometrial hyperplasia with atypia, and normal endometrium. Methods: We enrolled 105 obese women treated at the Department of Gynecological Surgery and Oncology of Adults and Adolescents. The patients were allocated to groups depending on the histological diagnosis (R - endometrial cancer, P - polyps, K - normal endometrium). We subdivided group R depending on the stage and grade of cancer. Results: Significantly lower concentrations of adiponectin were found in patients with endometrial cancer (mean 15.28 μg/ml) as compared with polyps (29.94 μg/ml, p < 0.001) or normal endometrium (22.7 μg/ml, p < 0.05). Stage of cancer had no significant effect on the adiponectin level. When cancer grade was compared, lower levels of adiponectin were observed in patients with G3 (12.86 μg/ml) than G1 (19.04 μg/ml, p < 0.05). Conclusion: Reduced levels of adiponectin may represent an independent risk factor for endometrial cancer.

Key words: Endometrial cancer; Endometrial hyperplasia; Adiponectine; Obesity.

Introduction

It is presently known that adipose tissue, besides storing energy, actively modulates metabolic processes and participates in energy metabolism of such vital organs as the brain, muscles (heart), and liver. To play its metabolic role, adipose tissue is the source of several substances possessing unquestionable physiologic significance [1]. Some of them, including leptin, adiponectin, angiotensinogen, resistin, and estrogens, have endocrine properties. Other substances, like tumor necrosis factor-α (TNF-α) and insulin-like growth factor (IGF-1), exert paracrine action.

Adiponectin is produced exclusively in adipose tissue. Interest in this adipocytokine has grown after it was shown that hypoadiponectinemia is associated with metabolic syndrome, overweight, obesity, type 2 diabetes, insulin resistance, hyperlipoproteinemia, and some neoplasms [2-8]. A five-year study by Chow et al. [9] has demonstrated that reduced adiponectin levels in blood are associated with arterial hypertension. As hypoadiponectinemia precedes progression to hyperglycemia, this cytokine has been termed by some as a biomarker of metabolic disease [9]. On the other hand, high concentrations of adiponectin appear to exert a protective effect on the cardiovascular system [10-12]. Hyperadiponectinemia seems to be of benefit for energy homeostasis of the organism in cases of anorexia nervosa [13].

Endometrial cancer is a hormone-associated and estrogen-dependent neoplasm usually diagnosed in women continuously exposed to estrogens not followed by gestagenic action. In postmenopausal women, estrogens are produced during steroidogenesis in the reticular layer of the adrenals. Androstendione is the substrate for estrone, the chief postmenopausal female hormone. The same metabolic process of aromatization serves to produce estradiol from testosterone. Obesity, hypertension, diabetes, and androgenic syndromes in women, particularly polycystic ovary syndrome, are the main risk factors of endometrial cancer.

This work was undertaken: (1) to determine serum concentrations of adiponectin in obese women with endometrial cancer, endometrial hyperplasia with atypia, endometrial polyps, and normal controls; (2) to determine serum concentrations of adiponectin in obese women with endometrial cancer depending on the presence of other risk factors – arterial hypertension or type 2 diabetes (three risk factors); and (3) to determine serum concentrations of adiponectin depending on the stage and grade of endometrial cancer.

Material and Methods

We studied 105 obese women admitted to our department for hysterectomy for different reasons. The patients were divided in three basic groups: R - with endometrial cancer and endometrial hyperplasia with atypia, P - with endometrial polyps, and K - with normal endometrium.

Three other subgroups were created depending on risk factors of endometrial cancer: B1 - obesity + hypertension + diabetes (n = 21), B2 - obesity + hypertension (n = 46), and B3 - obesity only (n = 27). Staging and grading of the endometrial cancer was done postoperatively in all cases of the tumor (n = 34). The control group (K) consisted of obese women with normal endometrium. All participants provided their written informed consent to participate in the study. The study protocol was approved by the local bioethics committee.

Adiponectin concentrations were determined at the laboratory of the Department of Endocrinology, Arterial Hypertension...
and Metabolic Diseases, Pomeranian Medical University, using radioimmunoassay kits from R&D. Sensitivity was 1 ng/ml and inter-series repeatability was 1.8-6.2%.

Results

Mean concentrations of adiponectin in the serum of patients with endometrial cancer and hyperplasia with atypia (n = 37) was 15.28 μg/ml (3.7-26.5 μg/ml) as compared with 22.7 μg/ml (8.9-59.2 μg/ml) in controls (n = 68) (p < 0.001, Table 1). Adiponectin concentrations in women with endometrial polyps (n = 20) was 29.94 μg/ml (14.1-38.0 μg/ml) (p < 0.001 as compared with endometrial cancer, Table 2). The difference in adiponectin levels between patients with endometrial polyps and controls was not significant (Table 3).

<table>
<thead>
<tr>
<th>Group</th>
<th>Adiponectin μg/ml</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>15.28</td>
<td>22.7</td>
</tr>
<tr>
<td>Range</td>
<td>3.7-26.5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Median</td>
<td>15.3</td>
<td>19.2</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>13.1-17.5</td>
<td>16.9-28.5</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>5.74</td>
<td>13.37</td>
</tr>
</tbody>
</table>

**Group** R - patients with endometrial cancer or endometrial hyperplasia with atypia; Group K - patients with normal endometrium; p - statistical significance; N - number of patients.

Table 2. — Concentrations of adiponectin in the serum of obese women (group R and group P).

We next compared adiponectin levels depending on the presence of risk factors of endometrial cancer. Mean concentrations in the B1 subgroup was 14.41 μg/ml (7.9-22.1 μg/ml) for patients with endometrial cancer and hyperplasia with atypia, as compared with 23.3 μg/ml (17.3-29.2 μg/ml) in controls (p < 0.001, Table 4). For two risk factors (B2), the results were 15.78 μg/ml (3.7-22.2 μg/ml) versus 22.87 μg/ml (13.2-28.1 μg/ml) in controls (p < 0.001, Table 5). When only obesity was present (B3), adiponectin levels were 15.9 μg/ml (9.4-26.5 μg/ml) in patients with endometrial cancer and hyperplasia with atypia as compared with 27.8 μg/ml (9.4-56.1 μg/ml) in controls (p < 0.001, Table 6).

The mean adiponectin level in Stage 3 and 4 endometrial cancer was 14.97 μg/ml (3.7-36.8 μg/ml) and did not differ significantly from 15.4 μg/ml (13.9-20.2 μg/ml) in Stage 1 (Table 7). Patients with grade 1 tumor (n = 12) demonstrated a mean adiponectin concentration of 19.04 μg/ml (7.9-36.8 μg/ml), as compared with 12.86 μg/ml (9.4-36.1 μg/ml) in patients with G2 (n = 13) and 12.86 μg/ml (10.8-14.0 μg/ml) in patients with grade 3 (n = 8). The difference between G1 and G3 was significant (p < 0.05, Table 8), whereas the difference between G1 and G2 was not (Table 9).

Discussion

It is believed that obesity in some way favors neoplastic transformation in the endometrium. The adipose tissue is the site of peripheral aromatization of adrenal
Adiponectin levels were at their lowest (12.9-112.2 ng/ml, kg/m²) were at greatest risk of endometrial cancer when were not published. In our study, patients with normal BMI values (< 25 kg/m²) were at greatest risk of endometrial cancer depending on stage.

Table 7. — Concentrations of adiponectin in the serum of patients with endometrial cancer depending on stage.

<table>
<thead>
<tr>
<th>Group</th>
<th>G1 (n = 28)</th>
<th>G2 (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>15.4</td>
<td>14.97</td>
</tr>
<tr>
<td>Range</td>
<td>13.9-20.2</td>
<td>3.7-36.8</td>
</tr>
<tr>
<td>Median</td>
<td>15.3</td>
<td>NS</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>12.42-20.7</td>
<td>9.89-21.32</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>2.62</td>
<td>8.19</td>
</tr>
</tbody>
</table>

1, 3, 4 - stage of endometrial cancer; 1 - includes stages 1a, 1b, and 1c; p - statistical significance (NS - not significant); N - number of patients.

Table 8. — Concentrations of adiponectin in the serum of patients with endometrial cancer depending on grade.

<table>
<thead>
<tr>
<th>Group</th>
<th>G1 (n = 12)</th>
<th>G2 (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>19.04</td>
<td>12.86</td>
</tr>
<tr>
<td>Range</td>
<td>3.7-36.8</td>
<td>10.8-14.0</td>
</tr>
<tr>
<td>Median</td>
<td>18.85</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>11.1-26.9</td>
<td>11.3-14.4</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>9.43</td>
<td>1.25</td>
</tr>
</tbody>
</table>

G1, G3 - grade of histological differentiation of endometrial cancer; p - statistical significance (NS - not significant); N - number of patients.

Table 9. — Concentrations of adiponectin in the serum of patients with endometrial cancer depending on grade.

<table>
<thead>
<tr>
<th>Group</th>
<th>G1 (n = 12)</th>
<th>G2 (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>19.04</td>
<td>13.48</td>
</tr>
<tr>
<td>Range</td>
<td>3.7-36.8</td>
<td>7.9-26.1</td>
</tr>
<tr>
<td>Median</td>
<td>18.85</td>
<td>NS</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>11.1-26.9</td>
<td>9.89-17.1</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>9.43</td>
<td>5.95</td>
</tr>
</tbody>
</table>

G1, G2 - grade of histological differentiation of endometrial cancer; p - statistical significance (NS - not significant); N - number of patients.

Adiponectin is a hormone with anti-diabetic, anti-atherosclerotic, anti-inflammatory, and anti-tumor action, produced by adipose tissue [4, 6, 13, 15]. We have now shown that obese patients with endometrial cancer or hyperplasia with atypia have significantly lower levels of this adipocytokine than obese patients with a normal endometrium (p < 0.05). Levels in patients with endometrial cancer were lower than in endometrial polyps (p < 0.001). Similar findings were reported by Soliman et al. [16] for patients with endometrial cancer (88.8 ± 63.3 ng/ml, n = 117) as compared with normal controls (148.2 ± 68.3 ng/ml, n = 238; p < 0.01). Moreover, the risk of endometrial cancer in that study was greatest for patients with the lowest levels of adiponectin. Although subgrouping according to tumor stage and grade was done by these researchers, adiponectin levels per stage or grade were not published.

In our study, patients with normal BMI values (< 25 kg/m²) were at greatest risk of endometrial cancer when adiponectin levels were at their lowest (12.9-112.2 ng/ml, p = 0.002). Our interpretation of this finding is that hypoadiponectinemia is a risk factor for endometrial cancer independently of BMI. Similar data were provided by Cust et al. [17], Dal Maso et al. [18], and Petridou et al. [19]. Dal Maso and colleagues [18] reported lower values of adiponectinemia in patients with endometrial cancer (mean 11.4, range 6.5-17.1 μg/ml) as compared with controls (mean 16.0, range 8.4-22.5 μg/ml). Petridou et al. [19] found that an increase of one standard deviation in adiponectin concentration reduced the risk of endometrial cancer by 50%.

A pan-European study in 135,953 women published in 2007 clearly demonstrated a link between adiponectin levels and endometrial cancer [17]. This tumor was diagnosed in 284 patients after a mean follow-up of 5.1 years. Cust et al. [17] reported that adiponectin levels in endometrial cancer were 15% lower than in normal controls. Moreover, rising adiponectin concentrations were associated with decreasing risk of endometrial cancer. This beneficial effect of adiponectin was largely independent of concentrations of other risk factors associated with obesity, such as peptide C, IGFBP-1, IGFBP-2, SHBG, estrone, and testosterone.

In the present study, adiponectin levels were higher in G1 as compared with G3 tumors (p < 0.05). We are tempted to relate this finding to the report of Takemura et al. [20] who found both isoforms of the adiponectin receptor (AdipoR1 and AdipoR2) on epithelial cells and cells of the endometrial matrix, and interpreted this finding in support of the direct action of adiponectin on the endometrium.

The present findings and those reported by others [16, 17] are in agreement with a protective action of adiponectin against endometrial cancer. Possible mechanisms of adiponectin activity could involve enhancement of fatty acid oxidation in skeletal muscles, suppression of hepatic gluconeogenesis, facilitation of insulin signaling transduction, or promotion of insulin sensitivity in peripheral tissues [21, 22].

Acknowledgment

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References

Serum adiponectin in relation to endometrial cancer and endometrial hyperplasia with atypia in obese women


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Tamoxifen in women with breast cancer and mammographic density

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Summary

Purpose of investigation: To evaluate the effect of tamoxifen on mammographic density using a qualitative and a semiquantitative method. Methods: Mammograms from 148 women treated for breast cancer before and after surgery were reviewed: 68 were administered tamoxifen; 80 did not receive tamoxifen. The mammograms were classified in one of the four BIRADS density categories by two radiologists blinded to the treatment and by a computer-assisted method after digitizing images. Results: At mammographic one-year-follow-up density was reduced in both groups and remained stable in the following years. A comparison of mammograms performed before surgery and after one year showed a statistically significant difference in density reduction between the tamoxifen and the non-tamoxifen-treated group. Good agreement was obtained between the qualitative and semiquantitative method. Conclusion: Breast density reduction observed in women treated with tamoxifen may help in the detection of small tumors in dense breasts by means of reducing the masking effect of parenchyma.

Key words: Mammographic density; Breast cancer; Tamoxifen.

Introduction

High breast density has been reported as one of the greatest breast cancer risk factors: a radiologically assessed breast density of more than 50% has an attributable risk of approximately 30% [1]. Dense breast tissue furthermore reduces the ability to detect small cancers due to possible “masking” [2]. A reduction in breast density may lower the risk of breast cancer and increase the possibility of detecting small breast neoplasms. In 1976 Wolfe first described the association between a qualitative classification of dense mammographic patterns and the risk of breast cancer [3] and several other cohort studies have confirmed this association [4]. However, whether breast density is an independent risk factor or if it is linked to other risk factors is still unclear [3, 5]. Mammographic breast density can be caused by various internal and external factors, and research is under way to determine whether it is the result of genetic and/or environmental factors, lifestyle factors, hormonal levels at different phases of a woman’s life or a result of her reproductive history [6, 7]. Many authors have shown interest in the evaluation of the effects of exogenous hormone drug administration on breast mammographic density in women with previously excised breast cancers mainly for two reasons: 1) patients with a personal history of cancer have a relatively high-risk of a new breast cancer and mammograms are definitively important to assess each new little alteration suggestive of tumor; 2) follow-up by mammography is mandatory and unavoidable, and mammograms acquired before and after treatment are accessible to be compared. In particular special attention has been paid to tamoxifen citrate, a selective estrogen-receptor modulator (SERM) which has been evaluated for its efficacy as an adjuvant treatment in women with breast cancer [8] and as a prophylactic treatment in women considered to be at high risk for subsequent disease [9] or at average risk for breast cancer [10]. Whereas hormone replacement therapy (HRT) seems to increase breast density, tamoxifen seems to reduce breast density [4, 11] even though the changes that occur are reversible [12]. Boyd et al. [5] and Chow et al. [13] both concluded that “tamoxifen causes a decrease in mammographic density with use; an effect that is better quantitated by semiquantitative criteria or computer-aided calculation of digitized images”. Byng et al. proposed an “analysis of digitized mammograms which facilitate computer analysis” in order to detect small changes in breast density [1]. Whether a reduction in mammographic density is associated with a reduced individual risk of breast cancer is still unclear. However, tamoxifen-induced reduction in density can be a marker for the effectiveness of action in the single patient and also facilitate the reading of mammograms and thereby the ability to detect early breast cancer. The aim of this study was to evaluate the possibility to assess the effect of tamoxifen on breast density during and after completion of therapy using a qualitative (BIRADS) and semiquantitative (computer-aided calculation of digitized images) method.
Materials and Methods

This study is a retrospective, nonrandomized, blinded review of mammograms from 148 women (age range 41-78 yrs), who were surgically treated for monolateral breast cancer from January 1988 to December 1998 and underwent follow-up evaluation for six years in our department. All mammograms were obtained using the same equipment with the same high quality film-screen combination and amount of compression. Patients, who were hormone-receptor-positive received tamoxifen treatment, whereas patients who were hormone-receptor-negative received no hormonal treatment. The tamoxifen-receiving group consisted of 68 women who received tamoxifen alone or tamoxifen combined with chemotherapy and/or radiation therapy after surgery, administered postoperatively at 20 mg/day for five years. The second group consisted of 80 women who received only chemotherapy and/or radiation therapy after surgery. In both groups there was a homogeneous distribution of pre and postmenopausal patients despite the different age range (tamoxifen-receiving group: age range 41-78 yrs, mean age 58.5 ± 9.3 yrs, median 56.3 yrs; non-tamoxifen-treated group: age range 49-78 yrs, mean age 63.9 ± 9.2 yrs, median 63.3 yrs). Ethical approval for the study was granted by the Medical Research Ethics Committee of our University, and informed consent was obtained from all patients. The study is divided in two parts. In the first part of the work mammographic breast density was classified using a qualitative subjective assessment of glandular densities according to the four standard criteria of The American College of Radiology’s Breast Imaging Reporting and Data System (BI-RADS) and percent density: BI-RADS A indicates that the breast is almost entirely fatty (<35% dense tissue), BI-RADS B that there are scattered fibroglandular densities (10-49% dense tissue), BI-RADS C that the breast is heterogeneously dense (50-75% dense tissue), and BI-RADS D that the breast is extremely dense (>75% dense tissue). In the second part of the work the analogic film screen mammograms were digitalized and the digitized images were computed and processed with two graphical softwares (Corel Photo-Paint and AutoCad 2004.0.0) for the detection of areas with glandular density, the quantification of their percent of extension and successively for the final classification into one of the four BI-RADS categories. Data obtained with the two methods (qualitative and semiquantitative method) were compared. All measurements were made on one craniocaudal view of the unaffected breast taken before surgery and annually for six years for each patient. In the tamoxifen-receiving group, first follow-up was performed one year after the start of tamoxifen therapy and last follow-up one year after completed tamoxifen therapy. In the non-tamoxifen-treated group first follow-up was performed one year after completion of collateral therapies. The mammograms were classified with consensus by two radiologists, both familiar with mammogram reading and with BI-RADS classification, and blinded to the treatment the patients had received. Fisher’s exact test was used to analyze the associations between categorical variables, the relationship between the groups and variations in mammographic density and the odd ratio (OR) was calculated. The Wilcoxon signed-rank test was used to evaluate the homogeneity in mammographic density distribution in the groups. Intraclass correlation ICC (two-way mixed) was used to assess the agreement between qualitative and quantitative methods. All statistical analyses were performed using SPSS 13.0 software package (SPSS, Chicago, USA) and a p value < 0.05 was considered significant.

| Table 1. — Variation in density in the tamoxifen-receiving group. |
|-----------------------------|------------|-----------|-----------|-----------|-----------|
| Qualitative/ semiquantitative method | A | B | C | D | Total |
| Mammmography after one year | | | | | |
| Basal | 22/21 | 0/0 | 0/0 | 0/0 | 22/21 |
| mammography | | | | | |
| C | 0/0 | 9/9 | 13/13 | 0/0 | 22/13 |
| D | 0/0 | 0/0 | 4/4 | 6/6 | 10/10 |
| Total | 23/23 | 22/22 | 17/17 | 6/6 | 68/68 |

| Table 2. — Table 2. — Variation in density in the non-tamoxifen-treated group. |
|-----------------------------|------------|-----------|-----------|-----------|-----------|
| Qualitative/ semiquantitative method | A | B | C | D | Total |
| Mammmography after one year | | | | | |
| Basal | 30/28 | 0/0 | 0/0 | 0/0 | 30/28 |
| mammography | | | | | |
| C | 0/0 | 11/12 | 24/24 | 0/0 | 26/12 |
| D | 0/0 | 0/0 | 3/3 | 9/9 | 12/12 |
| Total | 31/31 | 13/13 | 27/27 | 9/9 | 80/80 |

Results

Distribution of dense breasts in the tamoxifen (cases) and the non-tamoxifen-treated group (controls) was homogeneous before surgery. Tables 1 and 2 list the distribution of the four BI-RADS categories before surgery and at the first follow-up after one year in the cases and in the controls as assessed with the qualitative and semiquantitative method. The variations were stable throughout the remaining five-year follow-up period. At the first follow-up, totally 20 variations in breast density were observed with the qualitative method (14 cases and 6 controls) and 22 with the semiquantitative assessment (15 cases and 7 controls): all variations concerned breast density reduction and no increase was observed with either method. The Wilcoxon signed-rank test showed a statistically significant difference between preoperative and first follow-up mammograms with both the two assessment methods (p < 0.0001 and p < 0.0001) and a statistically significant difference in breast density reduction was assessed between the cases and the controls (p = 0.021). Good agreement in the BI-RADS assessment was detected while comparing the qualitative and the semiquantitative method for preoperative mammograms (ICC = 0.994 p < 0.00001, ICC = 0.985 p < 0.00001) and mammograms at the first follow-up after one year (ICC = 1, ICC = 1), respectively, in cases and controls. There was a statistically significant difference (p < 0.0001) between mean age in the two groups, however at the first mammographic follow-up after one year all patients were in menopause. In relation to the median age of 59 yrs in the cases, 12/14 cases of density reduction occurred in patients < 59 yrs while among the controls all the six cases of density reduction occurred in patients < 59 yrs. Fisher’s test showed a statistically significant relationship between age and variation in breast density in both groups (p = 0.035, p = 0.004) with an estimated OR for the cases of 3.2 times (95% CI 1.15-8.86) with qualitative assessment and 2.95 (95% CI 1.13-7.74) with semiquantitative assessment greater than the controls of achieving reduced breast density.
Discussion

Mammographic breast density is associated either with an increased risk of benign proliferative breast disease that includes a wide range of pathological conditions associated with varying risk of breast carcinoma [14] and with an increased risk of false-negative results at mammography, and a substantial decline in mammographic sensitivity for cancer detection. A reduction in breast density would therefore be important and desirable to reduce both the risk for benign proliferative disease and diagnostic errors. This study showed a statistically significant difference in breast density reduction between the tamoxifen and the non-tamoxifen-treated group (p = 0.021) thus confirming previous studies concerning reduction in mammographic breast density using tamoxifen in women with breast cancer and in healthy women at high risk for breast cancer [4, 11, 13]. All changes in breast density were observed at the first follow-up after one year both in the cases and in the control; these data disagree with Cuzick et al. [4] who reported the greatest breast density reduction within 18 months of treatment and a continued reduction in density until 54 months of treatment but this difference may be explained by the different characteristics of the patient population and by the fact that all patients in our study were in menopause at the first follow-up. Nonetheless our study is a nonrandomized review, a fact that may have influenced the results: the tamoxifen-receiving group all had hormone-receptor-positive breast cancer, whereas the non-tamoxifen-treated group had hormone-receptor-negative breast cancer. One year after completed tamoxifen treatment no further changes in breast density were observed. The effect seems not to be reverted in postmenopausal women, whereas the reversibility of the effect in premenopausal women still requires further investigation. Fisher’s exact test performed on the results obtained in the cases shows a statistically significant relationship between patient age and variation in breast density with a greater breast density reduction in younger and premenopausal women that may be linked to different types of density. The definition “dense breast” refers in fact to a quantitatively and qualitatively highly heterogeneous group: quantitatively it depends on the relative amounts of fat, connective and epithelial tissue and water content. Fat is radiologically lucent and appears dark on a mammogram, whereas connective, epithelial tissue and water are radiologically dense and appear light. Qualitatively there are dense breasts containing mainly connective tissue or mainly mammary-gland tissue with varying water content which characterizes breasts of women of reproductive age. It is possible that the different composition of the so-called dense breast causes a different response to menopause and to hormonal therapy as dense breasts with more mammary-gland tissue combined with an elevated percentage of water have been reported to be more sensitive than other combinations to age, hormonal situation and hormone treatments [15]. To evaluate mammographic density and tamoxifen-based treatment, a qualitative assessment of mammographic density is required. However, classification in categories has certain limitations because the reading of mammograms is operator-dependent and because it is difficult to measure small variations, which are particularly important in preventive treatments. Some authors have proposed computerized methods for this purpose, which have proved very helpful [1, 13, 14]. Despite the criticism subjective interpretation of mammograms has received, a qualitative classification and assessment of percent of mammographic density is useful in daily clinical practice, and in a team of experts, differences in readings are insignificant. Nonetheless the possibility that a simple digitalization process and the availability of two simple image softwares may offer to semiquantitative assessment of breast density is in our opinion to be noted as this method may avoid mammogram reader dependence. In our work a very good agreement in the BIRADS assessment was obtained with the two methods, probably because of the great experience of the readers. Moreover the semiquantitative assessment method may be more valid when compared to a subjective one performed by radiologists with less experience even if requiring a further training in breast density assessment. In our study, the greatest reduction in breast density was achieved after 12 months in postmenopausal women who received 20 mg/day tamoxifen with both the qualitative and semiquantitative method. Additional research is needed to assess the minimum dose and treatment time required to obtain the necessary reduction in density in order to improve diagnostic accuracy in very dense breasts, and areas of ongoing investigation include evaluating a potential specific treatment before mammographic examinations.

Conclusion

A substantial reduction in breast density in women treated with tamoxifen verified both with a subjective qualitative method and with a semiquantitative method could reduce the “masking” effect in the detection of small tumors.

References

Tamoxifen in women with breast cancer and mammographic density


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A 15-year report of pathological and benign ovarian tumors in teenagers

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Summary

The purpose of this retrospective study was to determine the frequency, clinical aspects and surgical management of ovarian masses in 52 adolescent patients, in whom surgery was deemed necessary, from 1991-2006. We considered age, symptoms, ultrasound investigations, CA 125 levels, family history, operative treatment, surgical complications tumor size, histopathological examinations, pregnancy rate and follow-up. Ovarian lesions in teenagers include a broad array of pathologic diagnoses that have variable and non-specific presenting symptoms. The most common presenting complaint was abdominal pain in 34 (65.4%). Forty-seven patients (90.4%) had benign lesions, two (3.8%) had borderline tumors and three patients had malignant lesions (5.8%). Most of the patients who wanted to conceive subsequently did so. For benign ovarian disorders the operation should be designed to optimize future fertility while in patients with malignancy, complete staging and resection of the lesion should be the first concern.

Key words: Adolescence; Ovarian tumours; Borderline ovarian tumours; Ovarian carcinoma; Surgical treatment.

Introduction

The presence of ovarian tumors in adolescence is of great significance because of the possibility of malignancy and the probable long-term effect on reproduction. Ovarian neoplasms constitute 1-2% of all childhood and adolescent malignancies, and represent the most common gynecological tumor (60-70%) during this period of a woman’s life [1, 2]. Ovarian masses span a spectrum of pathology from benign to highly aggressive malignant neoplasms [3]. Non-neoplastic conditions include follicular cysts, corpus luteal cysts, and endometriomas. Neoplastic processes include both benign tumors such as mature cystic teratomas as well as highly malignant tumors. In addition, there are tumors of low malignant potential that frequently follow a benign clinical course [4]. Benign neoplasms and functional cysts are the most common ovarian masses during childhood and adolescence [5]. Surgical intervention may be required depending on the diagnostic evaluation and possible trial of treatment that has failed. Certain conditions require immediate intervention such as possible torsion, medically refractory tub ovarian abscess, and intraabdominal hemorrhage with hemodynamic instability [6]. These problems may, to various degrees, affect the reproductive potential of these women [7-9]. In this report we analyzed cases from a Greek population for preoperative and intraoperative tumor evaluation, operative treatment, staging, follow-up and pregnancy rate.

Material and Method

This is a retrospective study of 52 adolescent girls with a diagnosed ovarian mass between 1/1/1991-31/12/2006. They were referred and evaluated at the Department of Obstetrics & Gynecology and Department of Pediatrics (2 cases) of Democritus University Alexandroupolis in Greece.

The following data were analyzed: age, age of menarche, present symptoms and signs (including the presence of fever and rebound abdominal tenderness or peritonitis, abdominal distension and menstrual disorders), preoperative diagnostic workup, operative procedure, histology of tumor, and postoperative follow-up including pregnancy rate. The following laboratory evaluations were analyzed: white blood count, the levels of beta human chorionic gonadotropin (β-hCG), carcinoembryonic antigen (CEA), CA-125 and alpha-fetoprotein (αFP), and the results of further endocrinologic workup, where appropriate. We reviewed all radiology reports including the results of abdominal X-rays, ultrasound (US) scans, computed tomography (CT), nuclear magnetic resonance (NMR) scans, all operative reports, and recorded the size of all ovarian masses as documented at surgery or in the pathology record. US was used to define the size of the lesion and to characterize its gross morphologic condition as solid, simple cyst or complex cyst. A transvaginal sonographic examination, accompanied if necessary by transabdominal examination, was performed on all patients using an (GE-LOGIC™ 400) US machine with color and power Doppler capability, equipped with a 2.5-5.5-MHz convex transabdominal transducer and a 5.5-8.5-MHz transvaginal probe. Size and echostucture of the uterus, endometrial thickness and any irregular findings and inperitoneal free fluid (pouch of Douglas or ascites) were recorded.

The morphology of each adnexal mass was described according to the following different types of sonographic morphological tumor characteristics:

1) Unilocular cyst: smooth-walled unilocular cyst with clear fluid or dense (echogenic) fluid content.
2) Cyst with septa: smooth-walled cyst with clear fluid or dense (echogenic) fluid content and only septa inside the cyst.
3) Cyst with papillae: cyst with clear fluid or dense (echogenic) fluid content and papillae.
4) Tumors with fluid/solid content: cyst with clear fluid or dense (echogenic) fluid and solid content.
5) Pure solid tumors: tumors composed of only solid tissue.

The main indication for surgery was the presence of the ovarian mass. The diagnoses of the presence of an ovarian mass were the following: acute abdominal pain and recurrent abdominal pain despite conservative treatment, abdominal distension and menstrual bleeding. The operative procedure differed based on the size, type of lesion (cystic, solid or mixed) as well as the age of the young woman.

Laparoscopy was performed in 15 cases, while laparotomy was carried out in 37 cases. All the adnexal masses which were suspicious of malignancy at the time of laparoscopy were evaluated by frozen section evaluation intraoperatively. In those cases in which malignancy was suspected laparotomy was performed and the final histological diagnosis was provided post-operatively.

Results

The characteristics of the 52 subjects are presented in Table 1. The majority of operated women 39 (75.5%) were under 17 years of age. The mean age was 16.64 ± 5 years (range min 14 – max 19 years). We identified 47 postmenarchal subjects and five premenarchal. The most common presenting complaint was abdominal pain which was present in 34 (65.4%); in 11 of these the suspected diagnosis was appendicitis but a pelvic mass was diagnosed instead. The other presenting symptoms were abdominal distention in 10 (19.2%) and menstrual disorders in eight (15.4%) cases, respectively (Table 2). On physical examination ten (19.2%) had abdominal tenderness, 37 (71.2%) had a palpable mass or increased abdominal girth. In another five (9.6%) cases there were no findings on physical examination but the ovarian cysts were detected through US.

Forty patients underwent preoperative transvaginal and 12 transabdominal examination because they were virgins. The US findings of the 52 subjects are presented in Table 3. To further evaluate the source of the pelvic mass an abdominal CT scan was performed in five cases (11.5%) and a MRI scan in four cases (7.7%). Serum tumor markers and hormonal status evaluation was performed only in the non emergency cases. CA-125 was normal (< 35 mIU/ml) in 41 patients and elevated in eight patients 15.3%. The preoperative average CA-125 level was 45.1 ± 5.19 mIU/ml. Serum CA-125 levels were elevated in one case of extraovarian ovarian cancer, in two cases of dysgerminoma, two cases of teratoma, one case of mucinous cystadenoma and in two cases of endometrioid cysts (Table 4). The levels of other tumor markers – human chorionic gonadotropin, a-fetoprotein and carcinoembryonic antigen – were normal in all cases, except the two patients with dysgerminoma and the patient with extraovarian ovarian cancer.

Three patients (emergency cases) were operated on for adnexal torsion and the remaining 49 (non emergency cases) had ovarian masses with various conditions. Two of the patients had bilateral lesions (3.8%). The associated cysts were of a functional nature in both cases. From the 52 patients, 15 (28.8%) (Group A = 15) underwent the laparoscopic approach while in 37 patients (71.2%) (Group B = 37) exploratory laparotomy was done. Surgical duration ranged from 30-100 min. The most common laparoscopic procedure was cystectomy in ten patients, aspiration and electrocoagulation of ovarian cysts in four and salpingo-oophorectomy in one. During laparotomy salpingo-oophorectomy was performed in five patients and cystectomy in 32 patients. Histological findings in bleeding. All the non emergency cases (49) underwent complete preoperative diagnostic work-up, while in the three emergency cases only sonography with Doppler assessment of the ovarian pathology and laboratory examination were performed. Forty patients underwent transvaginal and 12 transabdominal examination because they were virgins. The US findings of the 52 subjects are presented in Table 3. To further evaluate the source of the pelvic mass an abdominal CT scan was performed in five cases (11.5%) and a MRI scan in four cases (7.7%). Serum tumor markers and hormonal status evaluation was performed only in the non emergency cases. CA-125 was normal (< 35 mIU/ml) in 41 patients and elevated in eight patients 15.3%. The preoperative average CA-125 level was 45.1 ± 5.19 mIU/ml. Serum CA-125 levels were elevated in one case of extraovarian ovarian cancer, in two cases of dysgerminoma, two cases of teratoma, one case of mucinous cystadenoma and in two cases of endometrioid cysts (Table 4). The levels of other tumor markers – human chorionic gonadotropin, a-fetoprotein and carcinoembryonic antigen – were normal in all cases, except the two patients with dysgerminoma and the patient with extraovarian ovarian cancer.

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Table 1. — Patient characteristics and symptoms.

<table>
<thead>
<tr>
<th>Age</th>
<th>16.6 ± 5 SD, range min 14 – max 19 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenarchal</td>
<td>47 (90.4%)</td>
</tr>
<tr>
<td>Premenarchal</td>
<td>5 (9.6%)</td>
</tr>
<tr>
<td>Non emergency - symptomatic</td>
<td>49 (94.2%)</td>
</tr>
<tr>
<td>Emergency - symptomatic</td>
<td>3 (5.8%)</td>
</tr>
</tbody>
</table>

Table 2. — Signs and symptoms leading to diagnosis of ovarian mass.

| Abdominal pain | 34 (65.4%) |
| Abdominal distention | 10 (19.2%) |
| Menstrual disorders | 8 (15.4%)   |

Table 3. — Preoperative transvaginal (TV) - or transabdominal (TA) ultrasound, CT, MRI.

<table>
<thead>
<tr>
<th>Ovarian cysts</th>
<th>US</th>
<th>CT</th>
<th>MRI</th>
<th>Mean tumor size cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple</td>
<td>16</td>
<td>–</td>
<td>–</td>
<td>4.8 (min 3.8 - max 8.3)</td>
</tr>
<tr>
<td>Complex</td>
<td>27</td>
<td>2</td>
<td>1</td>
<td>5.3 (min 4.6 - max 9.8)</td>
</tr>
<tr>
<td>Solid</td>
<td>9</td>
<td>3</td>
<td>3</td>
<td>5.1 (min 3.5 - max 7.5)</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. — Correlation between CA-125 levels and histological findings.

<table>
<thead>
<tr>
<th>HCG (U/ml)</th>
<th>AFP (U/ml)</th>
<th>CEA (U/ml)</th>
<th>CA-125 &gt; 35 U/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 5</td>
<td>&gt; 0.7</td>
<td>&gt; 2.5</td>
<td></td>
</tr>
<tr>
<td>1/1 100%</td>
<td>1/1 100%</td>
<td>1/1 100%</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>0/7 0%</td>
<td>0/7 0%</td>
<td>0/7 0%</td>
<td>Endometrioid cysts</td>
</tr>
<tr>
<td>2/17 11.76%</td>
<td>2/17 11.76%</td>
<td>2/17 11.76%</td>
<td>Gynec cell tumor</td>
</tr>
<tr>
<td>0/6 0%</td>
<td>0/6 0%</td>
<td>0/6 0%</td>
<td>Epithelial cysts</td>
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<td>0/12 0%</td>
<td>0/12 0%</td>
<td>0/12 0%</td>
<td>Functional cysts</td>
</tr>
<tr>
<td>0/3 0%</td>
<td>0/3 0%</td>
<td>0/3 0%</td>
<td>Parovarian cysts</td>
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<td>0/2 0%</td>
<td>0/2 0%</td>
<td>0/2 0%</td>
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</tr>
<tr>
<td>0/1 0%</td>
<td>0/1 0%</td>
<td>0/1 0%</td>
<td>Granulosa-cell tumor</td>
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<td>Total 3/49</td>
<td>Total 3/49</td>
<td>Total 8/49</td>
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</tbody>
</table>
A histological examination confirmed two borderline epithelial ovarian tumors, two dysgerminomas in Stage IA, one granulosa sertoli cell tumor, and only one metastasis to the ovary, a Stage IVb carcinoma. The ovarian carcinoma was a mixed tumor in which only partial tumor excision was performed whereas in the other five cases salpingo-oophorectomy and, if needed, extirpation of peritoneal implants was the treatment of choice. The patient with an extraovarian primary tumor had a low symptomatic ovarian mass in the left ovary which was discovered with bimanual abdominal examination one week before the operation. During the surgery she was found to have extensive intraabdominal metastases from an occult primary extraovarian tumor with histological characteristics of primary ovarian cancer. This lesion was composed of epithelioid cells containing clear or focally granular pale cytoplasm with slightly enlarged hyper chromatic nuclei. Tumor infiltrating lymphocytes, mitoses or endothelial-lined space invasion, increased proliferative activity and tumor necrosis were also identified. Immunohistochemically, tumor cells stained positively for monoclonal antibodies EMA (epithelial membrane antigen), pankeratins, CEA and negative for CLA (common leukocyte antigen), myosin, vimentin, desmin, actin, cytokeratins 8-18-19, NSE, and S-100 protein. No additional treatment was recommended in this patient because she had generalized metastases.

Concerning the two presenting dysgerminomas, Stage IA ovarian tumors, one of them lacked extensive infiltrative invasion but the other one was associated with unexpectedly aggressive behavior. In the latter case postoperative radiation was administered. This patient received six rounds of first-line adjuvant chemotherapy with platinex. During a four-year follow-up and postsurgery, the patient who initially had Stage IA dysgerminoma disease developed recurrent tumor.

In the six histologically suspicious cases the final histological examination confirmed two borderline epithelial ovarian tumors, two dysgerminomas in Stage IA, one granulosa sertoli cell tumor, and only one metastasis to the ovary, a Stage IVb carcinoma. The ovarian carcinoma was a mixed tumor in which only partial tumor excision was performed whereas in the other five cases salpingo-oophorectomy and, if needed, extirpation of peritoneal implants was the treatment of choice. The patient with an extraovarian primary tumor had a low symptomatic ovarian mass in the left ovary which was discovered with bimanual abdominal examination one week before the operation. During the surgery she was found to have extensive intraabdominal metastases from an occult primary extraovarian tumor with histological characteristics of primary ovarian cancer. This lesion was composed of epithelioid cells containing clear or focally granular pale cytoplasm with slightly enlarged hyper chromatic nuclei. Tumor infiltrating lymphocytes, mitoses or endothelial-lined space invasion, increased proliferative activity and tumor necrosis were also identified. Immunohistochemically, tumor cells stained positively for monoclonal antibodies EMA (epithelial membrane antigen), pankeratins, CEA and negative for CLA (common leukocyte antigen), myosin, vimentin, desmin, actin, cytokeratins 8-18-19, NSE, and S-100 protein. No additional treatment was recommended in this patient because she had generalized metastases.

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Correlation with surgical management are shown in Table 5. In nine patients of Group B after initial diagnostic laparoscopy, the procedure was converted to laparotomy in three patients with Stage 4 endometriosis and extensive bowel adhesions, in three patients with large-volume dermoids, and in three patients with suspicious ovarian and peritoneal tumors. Tumorectomy with salpingo-oophorectomy was performed in five cases with suspicious results on frozen section (two borderline tumors, BOT, two dysgerminomas and one granulosa cell tumor) and in one more case of extraovarian carcinoma on frozen section. Excision of the ovarian cyst was performed in 42 patients, while cyst aspiration only was done in four cases. After removal of the ovarian masses and satisfactory hemostasis in 36 cases the ovarian bed was not sutured. In six cases the wound in the ovary was closed with repair sutures, initially using PDS (polydioxanone) 4/0, and later with either PDS 2/0 or 4/0. A histologic diagnosis was obtained in every patient. Forty-seven patients (90.38%) had benign lesions, two had borderline tumors (3.85%) and three patients (two dysgerminoma and one ovarian cancer) had malignant lesions (5.77%). The two BOTs consisted of two epithelial tumors. Histological findings in correlation with age distribution of the ovarian tumors are shown in Table 6. Of the 52 study
In the rare case of a 16-year-old girl with a granulosa cell tumor, the preoperative US finding was a solid, predominantly cystic, hypoechoic tumor and the CA-125 level measured normal. Tumor size was Stage I at presentation and was 5.0 cm or less in mean size. No symptoms of premature pubarche, thelarche, menarche, or hirsutism were observed. Hormonal laboratory (FSH, LH, estradiol, progesterone) analysis revealed values in normal levels.

A mature cystic teratoma or dermoid cyst, seen in 15 patients, was the commonest benign neoplasm, and 74.6% of these girls were under 17 years old. Three girls had malignant ovarian neoplasms, two of which were germ cell in origin. Malignant neoplastic ovarian lesions were commonly greater than 5 cm in diameter. The greatest tumor diameter (about 10 cm) appeared in epitheloid cysts. Lesions < 5 cm in postpubertal girls were significantly more likely to be non-neoplastic, functional cysts. Endocrine manifestations include early or precocious puberty and virilization, which were not encountered in our patients.

There was a great diversity of US patterns and histological results, especially for borderline tumors and one case of the endometroid cyst (Table 7). An interesting case was found in the endometroid cyst group; a 14-year-old girl with normal menstruation, normal development of secondary sexual characteristics and chronic pelvic pain. The karyotype was normal (46XX) and her urinary system was normal as well. Laparoscopy revealed a double uterus with a rudimentary left horn, normal left ovary, and a cystic mass in the right ovary, but the left fallopian tube was distended and filled with chocolate-like fluid. The cystic mass, rudimentary left uterine horn and left fallopian tube were immediately excised.

Two postoperative complications were noted. The first was bleeding in the place of the trocar installation, in one graft on the trocar site after laparoscopic extraction of one endometroid-type tumor, and the second one was fever postoperatively after dermoid cyst enucleation per laparotomy. Important clinical information concerning complications were not reported. The overall complication rate of surgically managed adnexal masses was very low. Fifty patients are under our follow-up and are in remission, alive with no evidence of disease after a mean follow-up of 36 months. Only two patients died; the first one had extraovarian cancer and died three weeks postoperatively due to rapid progression of the disease, and the second one with dysgerminoma died in the fourth year of the treatment as a result of liver metastases related to the ovarian pathology. Forty-four patients tried to conceive during a period of four to 36 months after surgery. Our overall intrauterine pregnancy rate was 72.7% (32/44) in women aged from 17 to 21 years; of these, one 20-year-old patient had an ectopic pregnancy (2%; 1/32). All of these intrauterine pregnancies (31) went to term and no fetal abnormalities or other problems were reported.

### Table 7. — Correlation between ultrasound and histopathological findings of ovarian cysts.

<table>
<thead>
<tr>
<th>Histopathological findings</th>
<th>Ultrasound findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simple</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>12</td>
</tr>
<tr>
<td>Functional cysts</td>
<td>9</td>
</tr>
<tr>
<td>Endometroid cysts</td>
<td>1</td>
</tr>
<tr>
<td>Epithelial cysts</td>
<td>1</td>
</tr>
<tr>
<td>Paraovarian cysts</td>
<td>3</td>
</tr>
<tr>
<td>Borderline tumor</td>
<td>2</td>
</tr>
<tr>
<td>Sex-cord stromal tumor</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
</tr>
</tbody>
</table>

### Discussion

One of the major problems in adolescent gynecology is the presence of an ovarian tumor [10]. Although tumors in this age group are less frequently observed than in adult women, they require immediate and careful investigation. The causes of ovarian enlargement in adolescence include functional cysts, paraovarian cysts, benign neoplasms, ovarian torsion and malignant neoplasms. The vast majority of ovarian masses which occur in children and adolescents have no malignant characteristics [11-13]. Physiological or functional ovarian cysts are the most common ovarian lesions seen in the pediatric age group and malignant neoplasms are rare [14, 15]. Ovarian teratomas (OTs) may be of mature or immature morphologies. Mature cystic teratomas (MCTs), often referred to as dermoid cysts, are the most common germ cell tumors of the ovary in women of reproductive age [16]. Ovarian cancer on the other hand, although rare in this age group, is the most common genital tract malignancy [17, 18]. Despite their rarity the incidence of malignant or premalignant degeneration of neoplasms is higher than in adult women [19, 20]. Ovarian malignant neoplasms in young girls and teenagers are unusual [21]. The most frequent histological subtypes found are those derived from germ cells, followed by epithelial cysts and sex-cord stromal tumors [22]. Sex-cord stromal tumors consist of epithelial (granulosa-Sertoli cells) and mesenchymal elements in a variety of combinations. Granulosa cell tumor is the most common subtype, presenting as the juvenile form in young females. It is of low malignant potential and is adequately treated only with salpingo-oophorectomy [23]. Malignant germ cell tumors account for approximately 20% of ovarian masses in children and adolescents [24]. This was also confirmed in our study. In three malignant cases histopathological assessment showed the following results: two dysgerminomas, and one extraovarian ovarian cancer which was a mixed tumor. Clinical and therapeutic particularities differentiate them from the same tumors of older women [25]. Clinical symptoms are generally not helpful in distinguishing benign from malignant masses. Ovarian masses often present with abdominal complaints that can mimic other diseases, in particular, appendicitis [26]. The most early common clinical features in our patients were abdominal pain pelvic mass and abnormal vaginal bleed-
ing. Patients with large tumors were admitted with compression symptoms or abdominal distension. In our study the appearance of acute symptoms in the non-emergent cases is usually attributed to emergency reasons such as adnexal torsion, torsion of the adnexa with paraovarian cyst and ruptured lutein cysts with ovarian bleeding. It is important in these serious conditions to begin treatment at an early stage without the risk of future decreased fertility. In 30% of the patients, there is torsion of a normal adnexa, while the majority of the cases are associated with ovarian pathology [27, 28]. In our study the torsion was associated with normal adnexa. The use of sonography, Doppler US, and abdominal CT and/or MRI scans may give important additional information to the preoperative detection of ovarian cyst pathology [29-31]. This was confirmed in our patients but it was not possible preoperatively to determine if the ovarian lesion was benign or malignant. Consideration should be given to order preoperatively ovarian tumor markers, to help with intraoperative management and pathology diagnosis [32]. Serum CEA, alpha-fetoprotein and beta-hCG are routine tests for organic tumors. The most common cause of chronic pelvic pain in adolescents is endometriosis, affecting up to 70% of girls with chronic pelvic pain unresponsive to medical management (oral contraceptives and no steroid anti-inflammatory drugs) [33]. Endometroid cysts occur more rarely compared to diffuse endometriosis in adolescents [34, 35]. Early diagnosis and medical management may prevent the development of the disease [36]. Intraoperatively, in five patients with endometroid cysts diffuse pelvic endometriosis was detected and in two cases endometriomas. Parovarian cysts can show a wide range of sonographic features. Their risk of malignancy is low if no papillary projections are detected at transvaginal sonography, but when mural proliferations are present, a borderline tumor can be found at pathological examination [37]. The characteristic laparoscopic differentiation of ovarian cysts is the crossing of vessels over them [38]. Parovarian cysts are not always benign; two previous studies reported a malignancy rate of 2-2.6% [39, 40]. Ovarian cystic tumors are the most frequent ovarian disease in adolescence. Although the majority of ovarian masses during this period are benign, the possibility of ovarian encountering an unexpected ovarian malignancy could not be excluded. In the absence of effective systemic medical treatment, immediate surgery is recommended. During surgical treatment of ovarian tumors in young girls, consideration should be given to the preservation of future fertility [41-43]. In cases of low malignant potential, tumor is possible in that particularly cystectomy increases the risk for disease recurrence, but recurrence does not affect survival. Conservative treatment can retain the potential for spontaneous pregnancy [44]. From our results, we conclude that fertility following successful conservative treatment of adnexal cysts is very high. Cyst enucleation was the most commonly applied procedure either with laparoscopy or with laparotomy. Oophorectomy or salpingo-oophorectomy is the safest treatment only when malignancy is suspected.

References


A 15-year report of pathological and benign ovarian tumors in teenagers


Concurrent chemoradiation with carboplatin for elderly, diabetic and hypertensive patients with locally advanced cervical cancer


Unidad de Investigación Biomédica en Cáncer, Inst Inv. Biomédicas UNAM, INCAN (México)

Summary

Introduction: Chemoradiation based on cisplatin is the standard treatment of locally advanced cervical cancer, however, a subset of patients are either elderly and/or have comorbidities such as diabetes and hypertension. These conditions may compromise the administration of cisplatin. We report our Institution experience with weekly carboplatin as a radiosensitizer for the management of this subset of patients. Patients and Methods: We reviewed the files of 59 patients with locally advanced cervical cancer who were treated with primary chemoradiation with weekly carboplatin. Response rate, toxicity and survival were analyzed. Results: Mean age was 62 years (range, 36-83 years). The majority of cases were squamous cell carcinoma (88.14%), and distribution according to FIGO Stage was IB2 8.4%, IIA 13.5%, IIB 52.5%, IIIA 3.3% and IIIB 18.6%; Overall, 100% and 91% of patients completed external beam and intracavitary therapy. Seventy-nine percent received from five to six planned cycles of weekly carboplatin. Complete responses were achieved in 49 (83.05%) patients, whereas ten patients (16.95%) had either persistent or progressive disease. The most common toxicities were grades 1 and 2 hematological and gastrointestinal. At median follow-up (20 months; range 2-48 months), 16 patients (32.65%) have relapsed. Estimated 30-month overall survival is 63%.

Conclusions: Weekly carboplatin concurrent with pelvic radiation is well tolerated in patients with locally advanced carcinoma of the cervix who are older than 70 years and/or have diabetes mellitus and/or high blood pressure, however, the apparently slightly lower survival observed cautious against its routine use.

Key words: Chemoradiation; Cervical cancer; Carboplatin.

Introduction

Cervical carcinoma is the most frequent cause of death by cancer in women from developing countries [1]. For early stages of the disease, radiation and surgery are equally effective treatment modalities [2], however, the prognosis of patients with locally advanced disease is still unsatisfactory despite the 12% absolute benefit on 5-year survival from concomitant cisplatin-based chemoradiation [3]. Data from the GOG 120 study [4] shows that weekly cisplatin at 40 mg/m² for six applications is equally effective yet less toxic than the combination of cisplatin-5-fluorouracil. Thus, weekly cisplatin is commonly employed as a radiosensitizer in cervical carcinoma patients.

Cancer is a disease of aging, with a steep increase in cancer cases after the age of 60 years. Cervical cancer has always been known as a neoplasm that affects women in middle-age, however due to the alteration in the demographics of cancer because of the aging in our societies, more and more often we are treating elderly patients with this neoplasia who may have age-related changes in pharmacokinetics and pharmacodynamics of antineoplastic therapy which may result in increased toxicity. For instance, renal excretion is affected by a gradual decline in function with age. There is a decrease in the glomerular filtration rate [GFR] by approximately 1 ml/min for every year over the age of 40. The reduction in GFR is not reflected by an increase in serum creatinine because of the simultaneous loss of muscle mass. [5, 6].

Diabetes mellitus and hypertension are both highly prevalent and increasing diseases in the general population [7, 8]. It is considered that 20-30% of patients with diabetes will develop diabetic nephropathy. The progressive stages in the natural history of diabetic nephropathy are glomerular hyperfiltration, microalbuminuria, hypertension, macroalbuminuria and after seven to ten years of persistent proteinuria, an increase of serum creatinine and end-stage renal disease start [9]. Hypertensive nephropathy appears as a complication of persistent high blood pressure which leads to vasoconstriction and a progressive decrease of the renal plasmatic flow which provokes a decrease of the renal mass due to ischemia and could end in renal failure [10].

Carboplatin is less nephrotoxic and emetogenic than cisplatin although it is more myelosuppressive [11, 12]. In cervical cancer, preclinical and clinical studies demonstrate that it is equally effective yet better tolerated than cisplatin [13-18]. In addition, it is a radiosensitizer [19, 20]. We previously reported that the recommended dose of carboplatin to be used weekly with radiation was 133 mg/m² (total of 800 mg/m²) [21]. Since that study we adopted chemoradiation with carboplatin as routine treatment in our Institution for patients with locally advanced cervical cancer, patients with high-risk conditions to...
develop renal dysfunction by cisplatin, such as diabetes mellitus, high blood pressure and/or ≥ 70 years old. Hence, we wanted to analyze our results of treatment with carboplatin chemoradiation as routine management in this specific subgroup of cervical cancer patients.

Materials and Methods

Patients. We conducted a retrospective review of 59 consecutive newly diagnosed and previously untreated patients who received radiotherapy and concurrent carboplatin at the INCAN between January 2002 and June 2006. All patients had a histological diagnosis of cervical carcinoma and were staged according to the FIGO classification using the standard pretreatment workup (pelvic examination without anesthesia). Carboplatin was used for sensitization if patients had at least one of the following criteria: age older than 70 years, diabetes mellitus and/or high blood pressure. As this was a retrospective review on patients treated on a routine basis, no ethical approval was required by our Institution.

Treatment. Patients received external beam radiation (EBRT) using megavoltage machines (Co60 or linear accelerator equipment) with a minimum photon-beam energy of 2.25 MV with an isocenter technique to the whole pelvis for a total dose of 50 Gy (5 weeks, 2 Gy fractions from Monday to Friday) followed by one or two intracavitary cesium (low-dose rate) applications within two weeks of finishing EBRT. The planned total dose to point A was at least 85 Gy. Patients were treated with the conventional 4-field box technique. Irradiated volume was to include the whole uterus, paracervical, parametrial, and uterosacral regions, as well as external iliac, hypogastric, and obturator lymph nodes. Carboplatin was administered for six weeks during external radiation, beginning on the first day of radiation. Carboplatin infusion was used at a dose of 133 mg/m2 and administered via a peripheral vein to patients in an outpatient setting as follows: carboplatin diluted in 500 ml of glucose solution at 5% for 60 min intravenously.

Statistical analysis. Overall survival was analyzed on an intention-to-treat basis and was registered from date of diagnosis to date of death or date of last visit. The curve was constructed using the Kaplan-Meier method.

Results

Patient characteristics. A total of 59 patients were analyzed. Patient clinical characteristics are shown in Table 1. The majority of cases were squamous cell carcinoma (88.14 %), and distribution according to FIGO stage was IB2 8.4%, IIA 13.5%, IIB 52.5%, IIA 3.3% and IIIB 18.6%; there were only two IVA cases (3.3%). Mean hemoglobin at diagnosis was 13.8 g/dl with ranges between 8.1 and 16.8. Mean age was 62 years (range, 36-83 years). Twenty-two (37%) patients had high blood pressure, 28 (47%) were diabetic (9 of these 50 patients had both conditions) and nine (15%) patients were aged > 70.

Follow-up. Upon treatment completion, patients were evaluated every three months for the first year, every four months during the second year, every six months during the third year, and annually thereafter. At each visit, a physical and pelvic examination, blood counts, clinical chemistry, and chest X-rays were performed. Computed tomography (CT) scan, ultrasound (US), and other imaging studies were conducted when appropriate. Suspected cases of persistent or recurrent disease were confirmed by biopsy whenever possible.
Table 3. — Acute common toxicity criteria of the National Cancer Institute (CTC NCI) version 2 criteria (59 patients).

<table>
<thead>
<tr>
<th>Grade</th>
<th>0 N (%)</th>
<th>1 N (%)</th>
<th>2 N (%)</th>
<th>3 N (%)</th>
<th>4 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>2 (3.4)</td>
<td>7 (11.8)</td>
<td>50 (84.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fever</td>
<td>59 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>58 (98.3)</td>
<td>1 (1.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 (21)</td>
<td>40 (38)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Proctitis</td>
<td>56 (94.9)</td>
<td>2 (3.4)</td>
<td>1 (1.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (11.9)</td>
<td>17 (28.8)</td>
<td>35 (59.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (16.9)</td>
<td>19 (32.2)</td>
<td>30 (50.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>48 (81.3)</td>
<td>11 (18.6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19 (32.2)</td>
<td>4 (6.8)</td>
<td>28 (47.4)</td>
<td>8 (13.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>21 (35.6)</td>
<td>1 (1.7)</td>
<td>27 (45.8)</td>
<td>8 (13.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>51 (86.4)</td>
<td>6 (10.2)</td>
<td>2 (3.3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>54 (91.5)</td>
<td>2 (3.4)</td>
<td>3 (5.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>54 (91.5)</td>
<td>3 (5.0)</td>
<td>2 (3.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>57 (96.6)</td>
<td>1 (1.7)</td>
<td>2 (3.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>56 (94.9)</td>
<td>1 (1.7)</td>
<td>2 (3.4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>58 (98.3)</td>
<td>1 (1.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

**Treatment Response.** Treatment response was evaluated by intention-to-treat. Complete responses were achieved in 49 (83.05%) patients, whereas ten (16.95%) patients had either persistent (5 patients, 8.47%) or progressive (5 patients, 8.47%) disease. Among patients with progressive disease, all had systemic progression, and four of these additionally had uncontrolled local disease.

**Toxicity.** Overall, treatment was very well-tolerated. Toxicity during chemoradiation is shown in Table 3. As expected, the most common toxicities were hematological and gastrointestinal but were mainly grades 1 and 2. Of note, the rate of grade 3 neutropenia and leukopenia was only 13.6% with no grade 4 episodes. So far, two (3.4%) and seven (11%) patients have presented grade 1 and 2 late proctitis.

**Survival.** At a median follow-up time of 20 months (range, 2-48 months), 16 patients (27.11%) have presented grade 1 and 2 late proctitis. Estimated 30-month overall survival was 63% (Figure 1). The small number of patients precluded any analysis on influence of age and these comorbidities on survival.

**Discussion**

Diabetes mellitus and hypertension are two of the most prevalent chronic diseases which affect populations worldwide. Both conditions damage renal structures through their evolution, despite optimal glycemic and blood pressure control [9, 10]. Likewise, aging is accompanied by decreasing renal function which has a negative impact on the degree of toxicity resulting from chemotherapy, in particular, cisplatin. Thus, older patients demonstrate reduced clearance of total and unbound platinum, with increased severity of cisplatin-induced nephrotoxicity [25-27]. Since in our Institution a substantial proportion of patients with newly diagnosed cervical cancer are older than 70 years and/or have diabetes and hypertension we adopted carboplatin as the radiosensitizer of choice for these patients.

The majority of the studies using carboplatin as a radiosensitizer for the primary treatment of cervical cancer are small phase I or II trials. Despite these limitations, most of these agree on the safety and efficacy of this drug. Micheletti et al. reported a complete response rate of 75% in 12 Stage IIB-IIIB patients using a schedule of 12 mg/m²/day for a total dose of 504 mg/m² in 42 days which was equivalent to 250 mg/m² every 21 days for two courses [28]. In another study done on IIA-IIIB patients a complete response rate of 86.3% was reported. Fifteen of these 19 patients in complete response were reported alive and disease free at a median follow-up of 15 months [29]. Higgins et al. [30] evaluated 31 patients with Stage IIB-IIIB cervical cancer using an initial dose of carboplatin (AUC of 2) which was administered on the first day of radiation therapy and repeated on a weekly basis for six courses. A complete response rate was documented in 28 of 31 patients (90%). Hematological toxicity was observed in less than two percent. After a mean follow-up time of 12 months, 23 patients (74%) remained disease-free. Dubay et al. [31] reported the outcomes of 21 Stage IIB-IVA cervical cancer patients who received carboplatin (300 mg/m²) administered every three weeks at the start of radiation. All patients completed at least three courses of chemotherapy during their radiation therapy. Two patients had grade 3 granulocytopenia, two patients had grade 3 anemia and one patient had grade 3 gastrointestinal toxicity. Thirteen patients (62%) went on to complete all six planned cycles. The average follow-up time was 51.6 months; the pelvic control rate was 76% and overall survival rate was 71%.

In our Institution we have adopted a weekly dose of 133 mg/m² based on our dose-finding study where we reported that this dose-level produced 33% of grade 3 leukopenia/neutropenia with no other grade 3 toxicity, except for the skin and lower gastrointestinal tract in less than 20% of patients [21]. This dosing allowed the application of carboplatin for six and five weeks in 78% of patients which is comparable to the number of times cisplatin is administered in a weekly regimen at 40 mg/m² [32]. Likewise, chemotherapy did not compromise the dose or time radiation was delivered, and most patients (92%) completed both EBRT and intracavitary therapy.
Chemoradiation with weekly cisplatin or a regimen of cisplatin and 5-fluorouracil at 21-day cycles for locally advanced cervical cancer produces 5-year survival rates between 65% and 83% depending on the proportion of FIGO stages accrued in both protocol [4, 33-35] and non-protocol settings [32]. In this report the expected survival at 30 months follow-up time was 63% which appears slightly lower to that obtained with cisplatin. However, whether this could be the result of the patient population treated or due to the use of cisplatin is not clear. It has previously been reported that comorbidities and age can have an adverse prognostic influence in cervical cancer patients [36-38]. In contrast, this dose of carboplatin was very well tolerated, with leukopenia and neutropenia below 15% which is remarkable as myelosuppression is the limiting toxicity of this agent.

While the present study suggests that carboplatin is well suited for aged, diabetic and/or hypertensive patients, there are issues that deserve discussion. Although cisplatin has been shown to impair glucose tolerance in rats [39], to induce hyperglycemia [40-42], and to elevate blood pressure in patients [43], these morbidities and age are not contraindications for using cisplatin. In addition, it has been reported that cisplatin is well tolerated in elderly lung cancer patients [44]; and that hyperglycemia, may paradoxically protect the kidney from cisplatin nephrotoxicity in rats [45]. On the contrary, although the literature supports the equivalent efficacy of cisplatin and carboplatin in cervical cancer [11-18], and a recent randomized non-inferiority trial reported no differences in outcome of nasopharyngeal cancer patients receiving either cisplatin or carboplatin concurrent with radiation [46], the apparently slightly lower survival observed in our patients is disturbing, although it could be the result of the small number of patients or the presence of comorbidities. On this basis, we can not recommend the routine use of carboplatin for hypertensive, diabetic or elderly patients. Nevertheless, there is little doubt that carboplatin is better tolerated and to easy administer than cisplatin, therefore a prospective randomized head to head comparison of these agents is merited.

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References


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Preoperative transforming growth factor-beta 1 (TGF-beta 1) plasma levels in operable breast cancer patients

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Summary

Objectives: The aim of this project was to search for new risk prognostic markers in the early stage of breast cancer. We tested preoperative plasma transforming growth factor - beta 1 (TGF-beta 1) levels in patients with operable breast cancer. Correlation with traditional prognostic markers and with positivity/negativity sentinel lymph node was evaluated. Materials and Methods: Between 2003 and 2005, 36 patients with operable breast cancer (T1-2, N0-1, M0) with positive or negative sentinel lymph nodes were evaluated for their plasma TGF-beta 1. Twenty-seven healthy individuals (9 premenopausal and 18 postmenopausal) served as controls. Patients were evaluated for the traditional prognostic markers including tumor characteristics, positivity and negativity of sentinel lymph node, TNM, tumor grade, expression of tumor markers CA 15-3 and CEA, hormonal status (pre- or postmenopausal patients, estrogen and progesteron receptor expression), ERB and p53 expression. Predictive value of TGF-beta 1 level and correlation with either of the assessed parameters was tested by one way ANOVA analysis. Results: Measurements of preoperative plasma TGF-beta 1 levels in patients with operable breast cancer were significantly higher compared with healthy individuals (median 15293 and 3983 pg/ml p < 0.0001). TGF-beta 1 level in plasma of patients with a positive sentinel lymph node was significantly higher than in patients with negative sentinel lymph nodes (high vs low, median 18,9 and 14,5 ng/ml, respectively, p = 0.05). Conclusion: The determination of TGF-beta 1 status might help to identify a high-risk population early in tumor progression, for which a more appropriate therapy should be established. In the node-negative population, the up-regulation of TGF-beta 1 might constitute an early event that promotes further progression of breast tumors.

Key words: Operable breast cancer; Transforming growth factor-beta 1 (TGF- beta1); Preoperative assessment; Sentinel lymph node; Risk factor; Prognostic marker.

Introduction

Breast cancer is the most frequent cancer in females and its incidence in developed countries of the world is still increasing [1, 2]. Most patients in early stage of disease (with negative regional lymph node, without signs of primary tumor metastasis) can be effectively treated with surgery and local radiotherapy. Patients with positive axillary lymph nodes are indicated for adjuvant chemotherapy. Besides involvement of local lymph nodes, other parameters, such as size of the prime tumor, histology of the tumor, grade of tumor cells, and hormone receptor Her2/neu status help in choosing the appropriate therapy. Unfortunately, those criteria are not sufficient. Although lymph node status is one of the best prognostic factors in breast cancer, it is not sufficiently accurate to predict the clinical course of the disease. Indeed, 20-30% of node-negative breast cancer patients will experience disease recurrence and metastatic dissemination [3].

This is the reason new markers need to be searched for which could, as soon and as objective as possible, determine the exact situation of breast cancer patients and consequently adequate therapy could be planned and therapy response monitored. Transforming growth factor-beta 1 (TGF-beta 1) is thought to be implicated in breast cancer progression. TGF-beta is a pleiotropic growth factor, which affects many different cell functions such as proliferation and extracellular matrix synthesis. TGF-beta can stimulate tumor angiogenesis, alter the stromal environment and cause local and systemic immunosuppression, all of which contribute to tumor progression and metastatic dissemination [4-7].

This study was conducted to further analyze the role of TGF-beta 1 in breast cancer and to evaluate its significance as a prognostic marker in early stages of breast cancer. The aim was to compare preoperative plasma TGF-beta 1 levels in early breast cancer patients and to compare them with those of healthy individuals and with the patients with advanced stage of disease (positive sentinel lymph node).

The association between preoperative plasma level of TGF-beta 1 and traditional prognostic markers (lymph node status, TNM classification, tumor grade, hormonal status, expression of tumor markers CA 15-3, CEA) was studied for all patients by two way ANOVA analysis.

Those investigations should help to find markers which will allow us to precis the diagnosis in early stages of disease and to help adjust the aggressivity of standard therapy.
Materials and Methods

This study involved 36 patients diagnosed and treated in the Obstetrics and Gynecology Department of our institution, between early 2003 and late 2005. Patients were selected according to the following criteria: (1) primary unilateral breast tumor; (2) no evidence of metastatic disease or any other malignancy at the time of diagnosis; (3) cT1,T2, N0/N1 status according to UICC criteria; (4) surgery as the first treatment - operable breast cancer study entrance criteria:

- size of prime tumor ≤ 1 cm with negative lymph nodes (T1a,b, N0);
- size of prime tumor ≤ 1 cm with positive lymph nodes (T1a,b, N1);
- size of prime tumor > 1 cm and < 5 cm with negative lymph nodes (T1c,T2, N0);
- size of prime tumor > 1 cm and < 5 cm with positive lymph nodes (T1c, T2, N1).

The diagnosis of breast cancer was done by core-cut or open biopsy. All patients included in the research study were routinely examined prior to operation, including palpation, mammography and/or breast sonography. In patients who were breast cancer positive for tumor markers CEA and CA 15-3 (normal values till 32.4 for CA 15-3 and 2.5 for CEA), chest X-ray, liver sonography and skeleton scintigraphy were done. Data on age, primary tumor stage, TNM staging (according to the Union Internationale Contre le Cancer) [8-10] and immunohistochemistry (determination of hormone receptors, mitotic tumor index) were reviewed and recorded. Grade was established according to the Nottingham Grading System [11-12]. Estrogen and progesterone receptor positivity was tested by monoclonal antibody kits ER/PR (Immunotech Company, USA). Her2/neu was tested by Hercep Test (DAKO Company, UK), Her2/neu 3+ were considered positive.

Venous blood samples were collected before the surgery. Plasma samples were obtained by centrifugation and stored at -70°C until assayed. TGF-beta 1 plasma level was determined by modified ELISA (enzyme-linked immunoabsorbent assay) using monoclonal anti TGF-beta 1 antibodies from R&D Systems®.

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In all patients detection for sentinel lymph nodes was performed. Most of the patients [26] underwent technetium-guided detection 18-20 hours after subareolar injection of technetium radiocolloid 99mTc Senti-scint, Radiob, H). Seven patients underwent blue dye perioperative-guided detection (Blue Patent© V, Guerbet) and in three cases detection was performed under blue dye perioperative-guided detection (Blue Patent© V, Guerbet) and in three cases detection was performed under blue dye perioperative-guided detection (Blue Patent© V, Guerbet) and in three cases detection was performed under blue dye perioperative-guided detection (Blue Patent© V, Guerbet).

Patients not included in the study: size of prime tumor > 5 cm, and patients with neoadjuvant therapy (hormonal, radio- or chemotherapy). The study was approved by the ethical board and patients signed informed consents regarding blood drawing and presentation of results.

Statistics

The association between preoperative plasma levels of TGF-beta 1 and traditional prognostic markers (lymph node status, TNM classification, tumor grade, hormonal status, expression of tumor markers CA 15-3, CEA, Ki 67) was studied for all patients by two-way ANOVA analysis. Statistical analysis was performed with the Mann-Whitney U-test. Data were presented as mean ± SEM or as percentage; a p-value of < 0.05 was considered to be statistically significant.

Results

Clinical and pathological characteristics (Table 1)

The patients were 38-78 years old at diagnosis, with a median age of 56 years. In total, 33.3% of patients were premenopausal. A total of 12 patients presented a tumour size less than 1 cm; 72.2% of patients were node-negative, 25.0% presented one to three axillary invaded nodes and 2.8% had more than three invaded nodes. Ductal carcinomas were diagnosed in 77.8% of patients and invasive lobular carcinomas in 22.2% of patients.

The primary treatment was segmentectomy (69.4%) or modified radical mastectomy (30.6%) with axillary dissection. Twenty-six patients underwent technetium-guided detection of SLN, seven patients underwent blue dye perioperative guided detection, and in three cases detection was performed by combinations of both methods. The patients did not have any other therapy at the time of study entrance.

<table>
<thead>
<tr>
<th>Feature Category</th>
<th>No. of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 50</td>
<td>8</td>
<td>22.2</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>28</td>
<td>77.8</td>
</tr>
<tr>
<td>Hormonal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premenopausal</td>
<td>12</td>
<td>33.3</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>24</td>
<td>66.7</td>
</tr>
<tr>
<td>Tumor size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>7</td>
<td>19.4</td>
</tr>
<tr>
<td>T2</td>
<td>29</td>
<td>80.6</td>
</tr>
<tr>
<td>Histology</td>
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<td></td>
</tr>
<tr>
<td>Ductal</td>
<td>32</td>
<td>88.9</td>
</tr>
<tr>
<td>Lobular</td>
<td>4</td>
<td>11.1</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>II</td>
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<td>III</td>
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<tr>
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<td>25</td>
</tr>
<tr>
<td>ER+ PR+</td>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>26</td>
<td>72.2</td>
</tr>
<tr>
<td>Positive</td>
<td>10</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Biological characteristics of the breast cancer patients

A wide inter-patient variability in the levels of biological factors in breast cancer samples could be observed. Thirty-one out of 36 patients (86.1%) showed ER positivity, 75.0% (27/36) were PR positive, three out of 35 were Her2/neu positive (8.3%). Three patients showed triple negativity for all three markers. Fifteen out of 34 patients (44.1%) showed p53 positivity, eight of those 15 showed p53 positivity less than 10%. Only three patients showed CA 15-3 positivity and two for CEA.

From the total of 36 eligible patients, 26 (72.2%) showed negativity of the sentinel lymph node, whereas
Preoperative transforming growth factor-beta 1 (TGF-beta 1) plasma levels in operable breast cancer patients

Ten were sentinel lymph node positive. There was no correlation between above mentioned markers expression and sentinel lymph node positivity.

**TGF-beta 1 levels (Table 2, Figure 1)**

TGF-beta 1 level in plasma of cancer patients was significantly higher compared with healthy individuals (median 15293 and 3983 pg/ml p < 0.0001). TGF-beta 1 level in the plasma of patients with positive sentinel lymph nodes was significantly higher than that in patients with negative sentinel lymph nodes (high vs low, median 14.5 and 18.9 ng/ml, respectively, p = 0.05). There was no difference between pre- and postmenopausal patients.

**Discussion**

High levels of TGF-beta has recently been a discussed topic in correlation to patient therapy response, stage of disease and poor prognosis. Recent evidence continues to support a central role for TGF-beta in tumor maintenance and progression [14, 15].

There is evidence that TGF-beta acts as a suppressor of tumor initiation but also as a promoter of tumor progression, when the antiproliferative effect of the TGF-beta signaling pathway has been overridden by other oncogenic mutations [16, 17]. In addition, there is increasing evidence that after malignant cells lose their sensitivity to TGF-beta 1 - mediated growth inhibition, autocrine TGF-beta signalling may promote tumorigenesis [18]. TGF-beta was shown to be produced by tumor cells and mainly by macrophages and T-regulatory cells of cancer patients [19]. TGF-beta is a pleiotropic cytokine with powerful immunosuppressive functions. Recent investigations have highlighted the role of TGF-beta in suppression of T-cell mediated anti-tumor immunity as well as cytotoxicity of NK immune cells and dendritic cells (DC) [20-22].

Immune response of cancer patients is often insufficient, supporting immunosuppression and tumor growth [23-28]. Transforming growth factor-beta inhibits the antigen-presenting functions and antitumor activity of dendritic cell vaccines [29]. Targeting tumor-associated macrophages and T-regulatory cells producing TGF-beta seems to be a novel strategy against breast cancer.

Whereas TGF-beta 1 seems to be confirmed as a poor prognostic marker in a number of human tumors such as ovarian [30], colorectal, gastric [31], and prostatic [32] cancers, glioma [33] and in metastatic breast cancer [34]. The impact of TGF-beta 1 on the progression of breast cancer remains uncertain. Desruisseau et al. [3] described increased TGF-beta 1 protein level in breast cancer tissue samples and correlated with a shorter disease-free survival. This suggests that secreting higher levels of TGF-beta 1 may provide an advantage to tumor cells. The hormonal influence on activation of the TGF-beta system adds an additional layer of complexity.

Ivanovic et al. [34] showed that elevated plasma TGF-beta 1 levels correlate with decreased survival of metastatic breast cancer patients. In our study, we focused on patients with early stages of disease.

We proved for the first time that TGF-beta 1 levels are already elevated in early stages of the disease in patients with operable breast cancer. Moreover, TGF-beta 1 in plasma of patients with positive sentinel lymph nodes was significantly higher compared to patients with negative sentinel nodes. The fact that a high level of TGF-beta 1 was observed in a node-negative population strongly
suggests that TGF-β1 interferes at early stages of tumor progression, probably by making cell environment favorable for metastatic spread. Thus, in the node-negative population, the upregulation of the TGF-β1 group might constitute an early event that promotes further progression of breast tumors.

Whereas numerous predictive factors have been characterized thus far, early prognostic markers that interfere in the beginning of tumor progression are scarce. High TGF-β1 levels observed in node-negative breast cancer patients suggest that the determination of TGF-β1 status might help to identify a high-risk population early in tumor progression, for which a more appropriate therapy should be established. In this context, it appears fundamental to confirm the prognostic value of TGF-β1 in a large cohort of node-negative patients.

References


The effect of combined therapy on activity of cathepsin D and alpha-1-antitrypsin in the blood serum of women with cervical cancer

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Summary

Purpose of investigation: The aim of the study was to determine the activity of cathepsin D (CTSD) and alpha-1-antitrypsin (AAT) in the blood serum of women with cervical carcinoma treated with different modes of therapy. Methods: The study was conducted on 68 women suffering from carcinoma of the uterine cervix, that were irradiated intracavitarily by a Selectron LDR brachytherapy unit. Additionally, all patients were treated with different therapy methods according to clinical stage. Results: In women with cervical cancer, CTSD activity was higher while AAT activity was lower both before and after brachytherapy sessions as compared to controls. Six months after the end of therapy, the activity of CTSD and AAT reverted back to the values characteristic for healthy women. Conclusion: The estimation of cathepsin D and alpha-1-antitrypsin activity during the course of cervical cancer management may be useful in early detection of potential recurrence and/or widespread metastasis formation.

Key words: Cathepsin D; Alpha-1-antitrypsin; Cervical cancer; Therapy.

Introduction

Cervical cancer is the most commonly occurring neoplasm in women. The recommended management of this carcinoma is prinal surgery and adjuvant or neoadjuvant radiotherapy as external beam radiotherapy and/or intracavitary brachytherapy. There is no treatment of choice for early-stage cervical carcinoma in terms of overall or disease-free survival, but the combination of surgery and radiotherapy has the worst morbidity [1]. In advanced stages the results of radiotherapy are not satisfactory and more recently concurrent chemoradiation, particularly with cisplatin-based regimens are successfully applied [2]. With the aim of yielding the best cure with minimum complications, the mode of treatment or combination of different treatment methods should depend not only on the neoplastic process grade, but also on the age, any concomitant illnesses, histological type, cervical diameter and menopausal status of patients [3].

For the early diagnosis of uterine cervical carcinoma, cytological, histological and biochemical tests are of great importance [4]. Although potential cervical cancer markers are considered to be of prognostic value, they in fact have no significant role in the clinical management of cervical cancer. Squamous cell carcinoma antigen (SCC) together with other assays, seems to be a useful tool in the determination of response to chemotherapy [5], but yet large trials are needed to validate it. The invasive and metastatic potential of malignant cells results from complex interactions of numerous factors. An important role in the occurrence and development of neoplasms, and also in the formation of widespread metastasis is attributed to lysosomal enzymes [6].

It is suggested that novel approaches for the selection of specific prognostic factors that would be valuable as indications for administration of different management are needed. The aim of the paper was to determine the activity of lysosomal protease - cathepsin D (CTSD) and activity of alpha-1-antitrypsin (AAT) - one of the protease inhibitors in the blood serum of women with cervical cancer before and after the combined therapy.

Patients and Methods

The study was performed on 68 women (an average age 50) being treated for carcinoma of the uterine cervix in the Regional Center of Oncology in Bydgoszcz. The patients were divided into three groups as regards the management, which was planned individually, depending on the degree of clinical advancement of the neoplasm according to the FIGO scale and the general state of patients' health. Intracavitary brachytherapy (Selectron LDR unit) was used in all of the patients. The 1st group consisted of 37 patients in clinical Stage I and early Stage II. In those women neoadjuvant brachytherapy was used (45-50 Gy, Cs¹³⁷). After four or six weeks, the patients underwent surgery (the Werthein-Neigs method). Twenty-one patients in clinical Stage II and III were included in the 2nd group. They were given combined treatment as neoadjuvant brachytherapy (50-60 Gy, Cs¹³⁷) prior to external telecobalt therapy (45 Gy, cobalt 60) and chemotherapy (cisplatin + 5-fluorouracil). Ten

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women from the 3rd group were given brachytherapy and adjuvant external teletherapy. The given doses were the same as in the 2nd group.

Blood samples were taken before the brachytherapy, after two brachytherapy sessions and about six months later, during a check-up. A set of control blood samples was obtained from 25 healthy women without any known disease (average age 56). Venous blood was taken, alongside other diagnostic tests and was placed in dry sterile tubes to obtain blood serum. The serum was then frozen and kept at the temperature of -20°C until the activity of CTSD and AAT was evaluated.

Cathepsin D activity was determined according to the Anson method [7], while alpha-1-antitrypsin activity was determined using the method of Eriksson [8]. CTSD activity was expressed in 10^2 nM of tyrosine released during hemoglobin hydrolysis per mg of protein per min and AAT concentration was expressed in mg inhibited activity of trypsin in 1 ml of blood serum.

All the data were statistically analyzed by means of a one-way ANOVA test. Correlation coefficients of examined parameters were also calculated. The statistically significant level of p < 0.05 was accepted.

Results

The activity of CTSD (Table 1) in the blood serum of patients from all three groups both before therapy and after two brachytherapy sessions was about three-fold higher than in healthy women (p < 0.05). During the period of treatment the activity of the enzyme did not alter in a statistically significant way. After six months of therapy CTSD activity in all three groups of patients decreased and reverted back to the values observed to those in healthy women. At this time a significant improvement in the clinical state of patients was also observed. When comparing patients treated with different modalities, there were no statistically significant differences in CTSD activity among the 1st, 2nd and 3rd groups.

In women suffering from cervical cancer the activity of AAT (Table 1) was lower compared to the controls (p < 0.05). As a result of six-month treatment, an increase in AAT activity occurs and then there were no statistically significant differences in comparison to the control group. The activity of the protease inhibitor was found to be unaltered after two brachytherapy sessions as compared to the value before the start of therapy. No statistically significant differences in AAT activity among patients from the three groups were found.

Moreover, comparing the activity of CTSD with AAT activity, we found that in the blood serum of women suffering from cervical cancer both before and after the treatment, high enzyme activity is accompanied by low inhibitor activity (r = -0.80; p < 0.05).

Discussion

Cathepsin D plays the main proteolytic role within the cells, but the quantity and activity of this enzyme depends on the type of cell and its metabolism [9]. The high CTSD activity in fibroblasts of tumor tissue is known to facilitate the hydrolysis of intercellular structures, detachment of neoplastic cells from the primary tumor followed by their migration, and then invasion of other tissues [10]. Cathepsins are probably responsible for proteolytic degradation of the extracellular matrix which may be the reason for cancer cell spreading and metastasis formation [11]. Lysosomes in neoplastic cells possess very labile membranes which cause the easy release of enzymes into the cytoplasm and consequently the dynamics of the lysosomal enzyme activity in blood serum is closely connected with the enzymatic activity within the tumor tissue [12]. Higher cathepsin D activity observed in different carcinomas as compared to healthy controls is supposed to be related to a shorter disease-free interval and overall survival of cancer patients [13]. Nevertheless, in the literature there are very few data concerning CTSD activity in cervical cancer patients. In the present study we revealed higher cathepsin D activity in the blood serum of women with cancer of the uterine cervix both before the therapy and after two brachytherapy sessions in comparison to the control group. The increased activity of other lysosomal enzymes such as cathepsin B, alkaline phosphatase and acid phosphatase in women suffering from cervical cancer was previously reported by some authors [14-16]. Utrera-Barillas et al. [17] demonstrated that the complex interaction between increased cathepsin B activity and expression of some genes associated with invasiveness of a neoplasm in cervical cancer patients may have an effect on the clinical behavior of the tumor.

Protease inhibitors fulfill an important role in maintaining the proteolytic balance of the organism, thus intensified proteolysis in tumor tissue as well as in surrounding tissues may be related to the disturbed inhibition of lysosomal proteases in cancer cells. In this paper we revealed a high negative correlation between CTSD and its inhibitor activity (r = -0.80; p < 0.05) in women with cervical cancer. The level of alfa-1-antitrypsin is thought to have a direct relationship with cervical cancer conditions [18]. In this paper we showed the decreased AAT activ-

Table 1. — Activity of cathepsin D (CTSD) and alpha-1-antitrypsin (AAT) in the blood serum of women with cervical cancer treated with combined methods and the control group (values are given as means ± SD).

<table>
<thead>
<tr>
<th>Control Group (healthy women)</th>
<th>before the treatment</th>
<th>patients after two therapy sessions</th>
<th>six months after the end of therapy</th>
</tr>
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<tbody>
<tr>
<td>CTSD (10^2 nM tyrosine/mg protein/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st group</td>
<td>7.26 ± 2.28</td>
<td>7.72 ± 2.62</td>
<td>2.91 ± 1.02</td>
</tr>
<tr>
<td>2nd group</td>
<td>7.64 ± 0.45</td>
<td>7.87 ± 3.29</td>
<td>2.46 ± 0.78</td>
</tr>
<tr>
<td>3rd group</td>
<td>8.03 ± 4.35</td>
<td>10.06 ± 4.63</td>
<td>3.01 ± 1.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AAT (mg impeded trypsin/ml serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st group</td>
</tr>
<tr>
<td>2nd group</td>
</tr>
<tr>
<td>3rd group</td>
</tr>
</tbody>
</table>

1st group – brachytherapy prior to surgery, 2nd group – teletherapy before brachytherapy + chemotherapy, 3rd group – external beam radiation adjuvant to brachytherapy.

- statistically significant differences in comparison with the control group: p < 0.05;
- statistically significant differences in comparison with patients before therapy: p < 0.05;
ity in the blood serum of cervical cancer patients before the start of therapy, and after two brachytherapy sessions it was still lower than in the control group. The defective inhibition of the proteases of cervical carcinoma cells was discussed concerning its in vivo significance for invasion of neoplasm [19]. It seems that measurement of CTSD activity together with AAT activity in blood serum may be significant in predicting recurrence in cervical cancer patients.

Biochemical tests that play a significant role as the designation of so-called neoplastic markers, do not always reflect the management efficacy as well as the response of patient organisms to the administration of different treatment methods. In the present study, no statistically significant alterations were found among the three groups of patients with the differently applied management. It may prove the fact that the mode of therapy has no effect on the recovery of lysosomal enzymes in those women. However, treating cervical cancer patients with surgery, radiotherapy and chemotherapy improves the clinical state of patients and it seems that the proteolytic balance plays an important role in this phenomenon. In this study we demonstrated that the activity of cathepsin D as well as alpha-1-antitrypsin in the blood serum of women with cervical carcinoma had been brought back to normal after six months of combined therapy, which may testify to the treatment efficacy. As multiple lysosomal enzymes are involved in invasion and metastasis, the most useful information may be obtained by the combined measurement.

Conclusion

Determination of the activity of cathepsin D along with alpha-1-antitrypsin activity during the course of cervical cancer may not be useful in monitoring the treatment process itself, but it may help to estimate the efficacy of applied management with the aim of early detection of potential recurrence and/or widespread metastasis formation.

References


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Tragic results of suboptimal gynecologic cancer operations

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Summary

Objective: The goal of this study was to analyze gynecological cancer patients who underwent suboptimal or failed surgeries with unsatisfactory and undesired results. Study design: During 1997-2007, 74 women were referred to our gynecological oncology service after suboptimal or failed surgeries for ovarian, cervix, endometrium and vulvar cancers. Medical records were evaluated retrospectively to determine the reasons of suboptimal surgery. Results: Optimal cytoreduction was achieved in ten women (21.7%), 32 women (69.5%) had suboptimal surgical cytoreduction and four women (8.6%) had failed surgery. Seven patients were recurrences (3 had liver metastasis, 2 had pelvic metastasis, 2 had bladder metastasis); two patients died due to bladder metastasis, one patient died six days after surgery due to a pulmonary embolism in the suboptimal cytoreduction group, and one patient died due to ascites in the failed surgery group. Optimal surgery was achieved in three women (27.2%) and eight women (72.7%) had suboptimal surgery in the cervical cancer population. One patient had a recurrence with pelvic metastasis in the suboptimal group. Suboptimal surgery was achieved in one woman with vulvar cancer. Optimal surgery was achieved in seven women (43.7%) and nine women (56.2%) had suboptimal surgery in the endometrial cancer population. One patient died 11 days after surgery due to sepsis in the optimal surgery group. One patient died 21 months after primary surgery and the other patient had a recurrence with paraaortic lymph nodes, ascites and omental thickening in the suboptimal surgery group. The prognosis of 30 (65.2%) women in the ovarian cancer population, eight (72.7%) women in the cervical cancer group, 11 (68.7%) women in the endometrial cancer group, and one woman (100%) in the vulvar cancer population was unknown. The unknown cases of all genital cancers were missed during follow-up and we could not reach them using their phone or address information. Conclusion: If a gynecologist does not have enough experience or expertise about gynecological cancer operations, he or she must consider the possible harm that any surgical intervention might do, as the latin phrase "primum non nocere" means and should refer patients to a gynecological oncology center without performing any surgery. Optimal gynecologic surgery can only be carried out correctly when education becomes available throughout the world. Thus postgraduate fellowship programs should be considered urgently to extend the general gynecologists’ surgical experience and expertise in developing and undeveloped countries.

Key words: Gynecological cancer; Optimal cytoreduction; Suboptimal surgery; Optimal surgery.

Introduction

Gynecological cancers are the leading cause of morbidity and mortality in the world with varying incidences and outcomes depending on the country, and account for between 10% and 15% of women’s cancers [1].

Surgical management is usually the first choice of treatment for many genital tract malignancies depending on the site of tumor involvement. For carcinoma of the endometrium, ovary and vulva, surgery is the primary choice of treatment and is usually therapeutic, while a radical operation is often used as a curative procedure for early-stage carcinoma or for central tumor recurrence [2]. Despite clear, clinically accepted guidelines, and advanced surgical techniques for gynecological cancer, considerable numbers of patients with genital cancers are treated unintentionally by suboptimal or failed surgeries [3-5].

The goal of the present study was to analyze gynecological cancer patients who underwent suboptimal or failed surgeries with unsatisfactory and undesired results. We analyzed suboptimal surgeries in gynecological cancer patients. These results may highlight the importance of postgraduate fellowship programs for general gynecologists and patient education.

Material and Methods

Between September 1997 and August 2007, 74 women were referred to our gynecological oncology service after suboptimal or failed surgeries for ovarian, cervix, endometrium and vulvar cancers. From the available patient medical records, we retrospectively extracted clinical data, including age at diagnosis, education status, number of children, radiographic or physical examination findings, preoperative histopathology, preoperative CA-125 values, clinical diagnosis, surgical staging (type of surgery, omentectomy, pelvic and paraaortic lymph node sampling, appendectomy), surgical stage, postoperative histopathology, recurrence, recurrence interval after primary surgery, recurrence treatment, mortality and mortality interval after primary surgery.

Results

The characteristics of the women are shown in Table 1a. Optimal surgery was achieved in ten women (21.7%) (patient nos.1-10), 32 women (69.5%) had suboptimal surgery (patient nos. 11-42), and four women (8.6%) had failed surgery (patient nos. 43-46) in the ovarian cancer population. Mean age for the ovarian cancer population was 49 years (range 13 to 82). The majority of optimal surgery (n = 6, 13%) and suboptimal surgery (n = 23, 50%) cases had serous histology in the ovarian cancer population. The four (8.6%) cases with metastatic ovarian cancer (Signet ring cell carcinoma) had failed surgery. The major-
Table 1a.

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<th>Patient</th>
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<th>Preoperative biopathology</th>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>1a</td>
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carcinoma; ca, unilateral salpingo-oophorectomy; USO, bilateral salpingo-oophorectomy; BSO, total abdominal hysterectomy; TAH, extirpation; ext; squamous cell carcinoma; SCC; carcinosarcoma; CS; adenocarcinoma; AC.
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<td>Cervical SCC</td>
<td>–</td>
<td>Cervical ca</td>
<td>Type 3 hysterectomy</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>–</td>
</tr>
<tr>
<td>53</td>
<td>48</td>
<td>No</td>
<td>–</td>
<td>Cervical SCC</td>
<td>–</td>
<td>Cervical ca</td>
<td>Type 3 hysterectomy</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>54</td>
<td>36</td>
<td>No</td>
<td>–</td>
<td>Cervical SCC</td>
<td>–</td>
<td>Cervical ca</td>
<td>Type 3 hysterectomy</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>55</td>
<td>58</td>
<td>No</td>
<td>–</td>
<td>Cervical SCC</td>
<td>–</td>
<td>Cervical ca</td>
<td>Type 3 hysterectomy</td>
<td>–</td>
<td>Yes</td>
<td>No</td>
<td>–</td>
</tr>
</tbody>
</table>
Tragic results of suboptimal gynecologic cancer operations

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ity of optimal surgery (n = 3, 6.5%) cases had Stage IIIB disease and the majority of suboptimal surgery (n = 10, 21.7%) cases had Stage IIIC disease (Table 2).

Prognoses of the optimal surgery group in the ovarian cancer population were as follows: the prognosis of three cases (patient nos. 1-3) was unknown. The other seven cases were under control and follow up regularly (patient nos: 4-10) (Table 1b).

The prognosis of the suboptimal surgery group in the ovarian cancer population was as follows; prognoses of 24 women (patient nos. 11, 13-15, 17, 19, 22-26, 28-35, 37-40, 42) were unknown. Seven women had recurrences (patient nos. 12, 16, 18, 20, 21, 36, 41). Three had liver metastases, two had pelvic metastases, and two had bladder metastases. One woman died three months after bladder metastasis (patient no: 12), one woman died six days after surgery due to a pulmonary embolism (patient no. 27), and one woman died one month after bladder metastasis (patient no. 36) (Table 1a).

The prognosis of failed surgery patients in the metastatic ovarian cancer population was as follows: three were unknown, and one died due to ascites after six months of recurrence (patient no. 43) (Table 1b).

Optimal surgery was achieved in three women (27.2%) (patient nos. 47-49), and eight women (72.7%) had suboptimal surgery (patient nos. 50-57) in the cervical cancer population. Mean age for the cervical cancer population was 51 years (range 28 to 78). The majority of optimal surgery (n = 2, 18.1%) and suboptimal surgery (n = 6, 54.5%) cases had squamous histology in the cervical cancer population. All of the optimal surgery (n = 3, 27.2%) cases had Stage 1b1 disease and the majority of suboptimal surgery (n = 6, 54.5%) cases had Stage 1b1 disease (Table 3).

The prognosis of the optimal surgery cases in the cervical cancer population was as follows: the prognosis of one case (patients no. 47) was unknown. The other two cases were under control and follow-up regularly (patients nos. 48, 49) (Table 1b).

The prognosis of the suboptimal surgery patients in the cervical cancer population was as follows: the prognosis
<table>
<thead>
<tr>
<th>Patient</th>
<th>Histopathological diagnosis after surgery</th>
<th>Recurrence</th>
<th>Recurrence interval after primary surgery (months)</th>
<th>Recurrence treatment</th>
<th>Survival</th>
<th>Mortality interval after primary surgery (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ovarian dysgerminoma</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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<td>Unknown</td>
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<tr>
<td>2</td>
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<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>3</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>Ovarian BST</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>Ovarian serous papillary AC (grade 3)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>12</td>
<td>Ovarian transitional cell ca</td>
<td>4x4x4 cm solid mass originating from bladder posterior</td>
<td>46</td>
<td>2 cycles hycamtn chemotherapy</td>
<td>Exitus</td>
<td>49</td>
</tr>
<tr>
<td>13</td>
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<td>Unknown</td>
<td>Unknown</td>
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<td>Unknown</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
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<td>6x5x5 cm cystic mass originating from liver/ascites</td>
<td>24</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
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<td>Pelvic mass extraction and left iliaca external lymph node extraction</td>
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<td>Unknown</td>
<td></td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>20</td>
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<td>Multiple liver metatases/ascites</td>
<td>5</td>
<td>6 cycles PT</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>21</td>
<td>Ovarian serous papillary AC</td>
<td>14x12x10 cm liver metatases</td>
<td>48</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>22</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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<td>Unknown</td>
<td>Unknown</td>
</tr>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>26</td>
<td>Ovarian GCT (dysgerminoma + yolk sac)</td>
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<td>Unknown</td>
<td>Exitus</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>27</td>
<td>Ovarian serous papillary AC</td>
<td>–</td>
<td>–</td>
<td>Exitus</td>
<td>Unknown</td>
<td>6 days after primary surgery due to PE</td>
</tr>
<tr>
<td>28</td>
<td>Ovarian serous papillary AC</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
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<td>Unknown</td>
<td>Unknown</td>
</tr>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
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<tr>
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<td>Unknown</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
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<td>34</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>35</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>36</td>
<td>Ovarian yolk sac ca</td>
<td>8x8x7 cm solid mass originating from bladder</td>
<td>11</td>
<td>No</td>
<td>Exitus</td>
<td>12</td>
</tr>
<tr>
<td>37</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>38</td>
<td>Ovarian yolk sac ca</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>39</td>
<td>Ovarian BBT</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>40</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>41</td>
<td>Ovarian serous papillary AC</td>
<td>12x7x7 cm solid pelvic mass</td>
<td>Unknown</td>
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<td></td>
</tr>
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<td>42</td>
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<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>43</td>
<td>Metastatic ovarian ca</td>
<td>Asciites 18</td>
<td>6 cycles 5 FU</td>
<td>Exitus</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Metastatic ovarian ca</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

of seven cases (patient nos. 51-57) was unknown. One patient had recurrence (patient no. 50) with pelvic metastasis and underwent radiotherapy treatment (Table 1b).

Suboptimal surgery was achieved in a 48-year-old woman with Stage II squamous type vulvar cancer (patient no. 58). The prognosis of this case was unknown (Tables 1b and 3).

Optimal surgery was achieved in seven women (43.7%) (patient nos. 59-65) and nine women (56.2%) had suboptimal surgery (patient nos. 66-74) in the endometrial cancer population. Mean age for the endometrial cancer population was 59 years (range 32 to 75). The majority of optimal surgery (n = 5, 31%) and suboptimal surgery (n = 8, 50%) cases had adeno-carcinoma histology in the uterine cancer population. The majority of optimal surgery (n = 4, 25%) cases had Stage Ib and Ic diseases and the majority of suboptimal surgery (n = 5, 31.2%) cases had Stage Ic disease (Table 3).

The prognosis of the optimal surgery patients in the endometrial cancer population was as follows: the prognosis of four cases (patient nos: 60-63) was unknown. One patient died 11 days after surgery due to sepsis (patient no. 59). The other two cases were under control and follow-up regularly (patients nos. 64-65) (Table 1b).

The prognosis of the suboptimal surgery patients in the endometrial cancer population was as follows: the prognosis of seven cases (patient nos. 68-74) was unknown. One patient died 21 months after primary surgery (patient no. 66) and the other patient had a recurrence with paraortic lymph node involvement, ascites and omental thickening (patient no. 67) (Table 1b).

The unknown cases of all genital cancers were missed.
combination modalities often required [1].

**Discussion**

Therapeutic interventions for gynecological cancers include surgery, chemotherapy and radiotherapy, with combination modalities often required [1].

---

**Table 2.**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Optimal (n = 10, 21.7%)</th>
<th>Suboptimal (n = 32, 69.5%)</th>
<th>Failed (n = 4, 8.6%)</th>
<th>Total (n = 46, 100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous</td>
<td>6 (13)</td>
<td>23 (50)</td>
<td>–</td>
<td>29 (63)</td>
</tr>
<tr>
<td>Borderline serous</td>
<td>1 (2.1)</td>
<td>–</td>
<td>–</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>–</td>
<td>2 (4.3)</td>
<td>–</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Borderline mucinous</td>
<td>1 (2.1)</td>
<td>–</td>
<td>–</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Transitional cell</td>
<td>–</td>
<td>1 (2.1)</td>
<td>–</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Borderline brener</td>
<td>–</td>
<td>1 (2.1)</td>
<td>–</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Granulosa cell</td>
<td>1 (2.1)</td>
<td>–</td>
<td>–</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Yolk sac</td>
<td>–</td>
<td>2 (4.3)</td>
<td>–</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Dysgerminoma</td>
<td>1 (2.1)</td>
<td>2 (4.3)</td>
<td>–</td>
<td>3 (6.5)</td>
</tr>
<tr>
<td>Mixed type germ cell tumor</td>
<td>(dysgerminoma + yolk sac)</td>
<td>–</td>
<td>–</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Metastatic ovarian cancer</td>
<td>(signet ring cell carcinoma)</td>
<td>–</td>
<td>4 (8.6)</td>
<td>4 (8.6)</td>
</tr>
</tbody>
</table>

**Stage**

IA 1 (2.1) 2 (4.3) 3 (6.5)
IC – 1 (2.1) 1 (2.1)
IIA 2 (4.3) – 2 (4.3)
IIIB 2 (4.3) 4 (8.6) 6 (13)
IIIA – 1 (2.1) 1 (2.1)
IIIB 3 (6.5) 10 (21.7) 11 (23.9)
IVA – 3 (6.5) 3 (6.5)
IVB 1 (2.1) 6 (13) 4 (8.6) 11 (23.9)

---

**Table 3.**

<table>
<thead>
<tr>
<th>Cervical cancer histology</th>
<th>Optimal (n = 3)</th>
<th>Suboptimal (n = 8)</th>
<th>Total (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell</td>
<td>2 (18.1)</td>
<td>6 (54.5)</td>
<td>8 (72.7)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1 (9.0)</td>
<td>2 (18.1)</td>
<td>3 (27.2)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ib1</td>
<td>3 (27.2)</td>
<td>6 (54.5)</td>
<td>9 (81.8)</td>
</tr>
<tr>
<td>Ib2</td>
<td>–</td>
<td>1 (9)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>IIa</td>
<td>–</td>
<td>1 (9)</td>
<td>1 (9)</td>
</tr>
</tbody>
</table>

| Uterine carcinosarcoma    | 5 (31)          | 8 (50)            | 14 (87.5)     |
| Uterine leiomyosarcoma    | 1 (6.2)         | 1 (6.2)           | 2 (12.5)      |
| Uterine carcinosarcoma    | 1 (6.2)         | –                 | 1 (6.2)       |
| Stage                    |                 |                   |               |
| Ib                       | 2 (12.5)        | 3 (18.7)          | 5 (31.2)      |
| Ic                       | 2 (12.5)        | 5 (31.2)          | 7 (43.7)      |
| Ia                       | 1 (6.2)         | –                 | 1 (6.2)       |
| Ib                       | 1 (6.2)         | –                 | 1 (6.2)       |
| Iib                      | 1 (6.2)         | –                 | 1 (6.2)       |
| Ice                      | 1 (6.2)         | –                 | 1 (6.2)       |
| IVa                      | –               | 1 (6.2)           | 1 (6.2)       |

<table>
<thead>
<tr>
<th>Vulvar cancer histology</th>
<th>Optimal (n = 1)</th>
<th>Suboptimal (n = 1)</th>
<th>Total (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1 (100)</td>
<td>1 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Ovarian cancer requires intensive and complex therapies and is demanding of the patient’s psychological and physical energy. Ovarian cancer is the fifth most common cause of death from malignancy in women. Currently, the most widely accepted treatment for advanced stage epithelial ovarian cancer is cytoreductive surgery. The principal goal of cytoreductive surgery is removal of tumor to < 1.5 cm, followed by platinum/taxane combination chemotherapy [2].

Despite the advances in ovarian cancer treatment, optimal cytoreduction rates vary between 20% and 80%, and are dependent on tumor volume, tumor location, and the surgeon’s education and experience [3]. Bristow et al. reviewed 53 studies with advanced stage ovarian carcinoma, and the average rate of optimal cytoreduction among all 53 studies was 42% [6]. Everett et al. detected 56 patients with ovarian carcinoma and the rate of optimal cytoreduction among patients was 48% [3]. Forty-six of the ovarian cancer cases that had been treated by optimal and suboptimal surgeries were referred to a gynecologic oncology service. Optimal cytoreduction was achieved in ten women (21.7%); 32 women (69.5%) had suboptimal surgical cytoreduction and four women (8.6 %) had failed surgery. Prognoses of ovarian cancer patients were as follows: three cases in the optimal surgery group, 25 cases in the suboptimal surgery group and three cases in the failed surgery group had unknown prognoses. Six patients had recurrences in the suboptimal surgery group (three - liver metastases, two - pelvic metastases, one - bladder metastasis). One patient died six days after surgery due to a pulmonary embolism in the suboptimal surgery group and one death was due to ascites in the failed surgery group.

Behtash et al. showed inadequate evaluation of 62 cases with invasive cervical carcinoma that had been treated by simple hysterectomy [5]. Eleven of the cervical cancer cases that had been treated by optimal and suboptimal surgeries were referred to a gynecology oncology service. Optimal cytoreduction was achieved in three women (27.2%) and eight women (72.7%) had suboptimal surgery [5]. Prognoses of cervical cancer patients were as follows: one case in the optimal surgery group and seven cases in the suboptimal surgery group had unknown prognoses. One patient had a recurrence with pelvic metastasis in the suboptimal surgery group. Suboptimal surgery was achieved in one woman in the vulvar cancer group with unknown prognosis.

Sixteen cases of endometrial cancer that had been treated by optimal and suboptimal surgeries were referred to a gynecologic oncology service. Optimal surgery was achieved in seven women (43.7%) and nine women (56.2%) had suboptimal surgery [5]. Prognoses of endometrial cancer patients were as follows: four cases in the optimal surgery group and seven cases in the suboptimal surgery group were unknown. One patient died 11 days after surgery due to sepsis in the optimal surgery group, one patient died at home, and the other patient had a recurrence with paraortic lymph node involvement, ascites and omental thickening in the suboptimal surgery group.

during follow-up and we could not reach them with their phone or address information because the information was wrong or had changed (Table 1b).

---
Reasons for suboptimal surgery in gynecologic cancer patients were as follows:

– Gynecologic cancer management requires close cooperation between the gynecologic oncologist, radiotherapist, medical oncologist and pathologist. These suboptimal cases were managed with lack of this cooperation.

– The idea of retaining all responsibility of cancer patients with a gynecologist or obstetrician has proven invaluable. These suboptimal cancer patients were operated on by a single physician.

– Many centers in the world recognize the need to develop gynecologic oncology as a subspeciality within the larger speciality of obstetrics and gynecology. The patients in the included studies were operated on without a gynecological oncologist.

– The United Nations have 191 member countries worldwide [7]. To the best of our knowledge gynecologic cancer operations are not carried out properly (except in developed countries) in most of the member countries (consequences of inadvertent, suboptimal primary surgery in carcinoma of the uterine cervix [3-5]).

– Poverty is much more complex than simply income deprivation. Poverty entails also lack of education and lack of healthcare systems. Referred patients to our clinic lacked basic school education (98.6%) (except case no. 2).

– Our clinic planned a multidisciplinary approach (second operation to complete suboptimal surgeries, radiotherapy, chemotherapy, etc.) in suboptimal surgery patients who underwent gynecologic surgeries, but we were not successful because the unknown cases of all genital cancers were missed during follow-up and we could not reach them with with their phone or address information because the information was wrong or had changed.

Based on these unsatisfactory findings and undesired results, we have reached the conclusion that:

– It is imperative that gynecologists and other primary care providers give a full and frank explanation to gynecologic cancer patients (even if they are uneducated) about their illness, surgical procedure and medical therapy plans pre- and postoperatively.

– Phone numbers and address information of gynecologic cancer patients are very important for follow-up visits after surgery. Thus it is imperative that patient information is verified.

– If a gynecologist has no experience or expertise about gynecologic cancer operations, he or she must consider the possible harm that any surgical intervention might do, as the latin phrase means “primum non nocere”, and he or she should refer the patient to a gynecological oncology center for intervention.

– Optimal surgical gynecological surgeries can only be performed correctly when education becomes available throughout the world. Thus postgraduate fellowship programs need to be urgently considered to extend general gynecologists’ surgical experience and expertise in developing and undeveloped countries. Recognition of the need for subspecialist units will improve the multidisciplinary approach to gynecological cancer patients. A well-trained gynecological oncologist will then be able to integrate with surgical and oncological colleagues to provide the highest treatment standards for patients.

References


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Clinical audit of patients with cervical cancer in Slovenia. Data analysis from 2003-2006

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Summary
Purpose of Investigation: From 2003 to 2006 the data on Slovenian cervical cancer patients who regularly attended a gynecologist were gathered. Data were analyzed in order to improve the efficiency of the cervical cancer screening program. Methods: Data on all patients newly diagnosed with cervical cancer were collected at three central clinics in Slovenia. The results are a presentation and comparison of detailed information on some characteristics of cervical cancer patients of the group that regularly visited a gynecologist and of the other group who did not. Data were processed by descriptive epidemiological methods. Mantel-Haenzel $\chi^2$ and Fisher’s p tests were used to evaluate statistical significance. Results: On average, 55% of patients with cervical cancer underwent a gynecological examination five years before the diagnosis. The patients who regularly attended their gynecologist were, in all age groups, statistically significantly younger, the stage of cervical cancer at diagnosis was statistically significantly lower ($p = 0.01$) and were, in statistically significantly higher percentage, treated surgically ($p < 0.01$). From 2003 to 2006, each patient had on average five examinations at her gynecologist within the period of five years to six months before the diagnosis of cervical cancer. The average number of collected smear samples was 3.2. Conclusion: From the results of our analysis, it may be concluded that improvements are needed in Slovenia in the field of screening for and early detection of cervical cancer.

Key words: Clinical audit; Cervical cancer; State screening program; Premalignant cervical disease.

Introduction
In addition to a sufficiently large number of women recruited through screening, the most important measures to be taken to assure successful cervical cancer screening are effective detection of premalignant cervical disease and prompt, as well as high-quality, treatment. However, it is of key importance that all individual processes included in the entire screening program, such as data gathering and storing in the screening program registry and in the Cancer Registry of Slovenia, proper functioning of the information system, collection of cervical smear samples, treatment of cervical diseases, and follow-up treatment as well as the work in cytopathology laboratories, are running smoothly and in tune with each other. Had one of these processes included in the program not met the required quality criteria, others would not have been able to replace the resulting deficit, though they would have exceeded all quality standards with their extreme assiduousness [1, 2].

Hence, the success in screening for cervical cancer may hardly be expected if the quality control indicators of individual processes included in the multidisciplinary program are not regularly followed-up, if no critical analyses are performed, and if regular checks for eventual inadequacies of these processes and immediate corrective measures are not carried out. Very often, the availability of the results obtained from appropriate analyses may be of great help in the endeavors to suppress the rate of shortcomings. At the same time, the staff working in the screening program should be given the chance to continuously improve their knowledge as well as to have access to the latest analysis results, the data on the proposed improvements, and the innovations carried out in specific fields within the program. The last is particularly important in case the staff in charge is performing highly subjective examination methods, i.e., cervical cancer smear tests and evaluation of colposcopic examination findings [3, 4].

In Slovenia, systematic screening for cervical cancer was started in 1998. At first it was implemented as a pilot program and in 2002, as a national cervical cancer screening program aimed at reducing the cervical cancer incidence in Slovenia. The major reason that compelled us to start working within a highly organized and planned system rather than within an opportunistic program was the increasing cervical cancer incidence that was first observed after the year 1994. The incidence was the highest in 1997 (23.6/100,000), but after the year 1998, it dropped slightly to 20/100,000 [5]. The most recent data for the year 2004 showed that the cervical cancer incidence was still 19.1/100,000 (in 2003, 20.4/100,000). In 1994 and 1993, the CIN 3 incidence was 94.4/100,000 and 85.2/100,000, respectively [6].

To facilitate the evaluation of certain parameters applied in the national cervical cancer screening program in Slovenia, we started with gathering the data on Slovenian patients with cervical cancer who regularly attended a gynecologist, but despite that, contracted invasive cervical cancer. The gathered data were then analyzed to
find any deficiencies that would help us to improve the efficiency of the cervical cancer screening program and the detection of premalignant cervical disease.

Methods

In 2003, a research study was started on patients who were regularly attending a gynecologist and who were diagnosed with cervical cancer that same year. The data on all patients newly diagnosed with cervical cancer were collected at the same time at three clinics in Slovenia: Institute of Oncology Ljubljana, University Medical Centre, Department of Gynaecology and Obstetrics, Ljubljana, and University Medical Center Maribor, Clinic for Gynaecology and Perinatology, Maribor. The synchronous gathering of data on the patients with newly diagnosed cervical cancer in three clinics was chosen because we expected that we would thus have easier access to the data, better control over the then circumstances, and better chances of taking prompt and proper measures. Moreover, we also avoided the gathering of the data of deceased patients. The same method of data gathering was applied also in 2004, 2005, and 2006. The data were gathered through interviews with patients, from hospital files, and from the patients’ questionnaires which were handed over to us by their gynecologists upon having obtained consent from the patients. A few patients who reported that they had not attended the appointment with their gynecologists despite having received an invitation were classified into the group of patients who did not attend gynecologists. From earlier analyses made by other authors from Slovenia on the data provided by cervical cancer patients, it could be assumed that the patients did not always supply the exact data on their visits to gynecologists; this assumption could not be confirmed even by the present analysis [7].

The analysis results are a presentation and comparison of detailed data on some characteristics of cervical cancer patients of the group that regularly visited a gynecologist and of the other group who did not. In the second part, some screening data of the patients who regularly attended gynecologists are presented; these are the data on cervical smear test results, diagnostic procedures, and symptoms. The screening time covered by the analyses goes back to the period extending from five years before the diagnosis of cervical cancer and the year of diagnosis.

In the years between 2003 and 2006, the total number of patients with newly diagnosed cervical cancer was 585. Of 585 patients, 323 (55.21%) had visited a gynecologist in the last five years before the diagnosis (Table 1). The remaining 44.89% of patients did not visit their gynecologists, sometimes for 15 years or even more. Our results reconfirm the assumption made in our earlier paper that the women who do not regularly visit a gynecologist hardly ever make a decision on their own to visit a gynecologist for an examination. In the recent past, conization was performed in 7.43% of the cervical cancer patients who regularly attended a gynecologist and in 1.9% of those who did not (p < 0.01).

The data were processed by descriptive epidemiological methods. Mantel-Haenszel $\chi^2$ and Fisher’s p tests were used to evaluate statistical significance.

Table 1. — Distribution of patients with cervical cancer by gynecological examinations performed within the last five years before the diagnosis of cervical cancer and the year diagnosis was established.

<table>
<thead>
<tr>
<th>Gynecological Examinations</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>91</td>
<td>79</td>
<td>72</td>
<td>81</td>
<td>323</td>
</tr>
<tr>
<td></td>
<td>55.21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>58</td>
<td>88</td>
<td>62</td>
<td>54</td>
<td>262</td>
</tr>
<tr>
<td></td>
<td>44.89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>149</td>
<td>167</td>
<td>134</td>
<td>126</td>
<td>585</td>
</tr>
<tr>
<td></td>
<td>100.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

Age of patients, pathohistological status of cervical cancer, disease stage and therapy of the group of patients who regularly attended a gynecologist and of the other group who did not.

Mean age of the patients who regularly attended a gynecologist and of the other group who did not was 43.6 and 57.2 years, respectively. The patients who regularly attended a gynecologist were statistically significantly younger in all age groups than those of the other group who were not visiting a gynecologist. The percentage of patients aged < 49 years in the group of patients regularly attending a gynecologist and of the other group who did not was 75.62% and 32.82%, respectively (p < 0.01). The percentage of patients aged ≥ 70 years in the group of patients who regularly attended a gynecologist and of the other group who did not was 2.74% and 21.76%, respectively (Table 2).

Table 2. — Distribution by age and year diagnosis of cervical cancer was established in patients who visited (YES) or did not visit (NO) regularly a gynecologist.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>Total %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>up to 29</td>
<td>9</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>30-39</td>
<td>29</td>
<td>5</td>
<td>22</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>40-49</td>
<td>32</td>
<td>16</td>
<td>27</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>50-59</td>
<td>11</td>
<td>15</td>
<td>19</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>60-69</td>
<td>8</td>
<td>11</td>
<td>3</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>70-79</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>80 or more</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>91</td>
<td>58</td>
<td>79</td>
<td>88</td>
<td>72</td>
</tr>
</tbody>
</table>

The most frequent carcinoma that was diagnosed in the patients included in our study in the period 2003 to 2006 was squamous cell carcinoma (80.86%), the second was adenocarcinoma (12.83%), and the third adenosquamous carcinoma (4.95%), followed by other types of carcinomas (1.36%). Adenocarcinoma was detected more frequently in the patients who regularly visited a gynecologist (15.78%) than in those who did not (9.16%; p = 0.01). Squamous cell carcinoma was statistically significantly more frequently detected in the patients who did not regularly visit a gynecologist (84.74%) than in those who did (77.69%); the difference was statistically significant (p = 0.02).

In the patients who regularly attended a gynecologist, the stage of cervical cancer at diagnosis was statistically significantly lower (p = 0.01) (Table 3). This difference is the most obvious in disease Stage I A. In patients who
regularly visited a gynecologist and in those who did not, this disease stage was detected in 35.29% and in 7.63%, respectively. The comparison of the disease Stages IA1 and IA2 did not show statistically significant differences between the two groups \( (p = 0.69) \).

The differences between the two groups with regard to disease stage were also related to the selection of treatment modality. A statistically significantly higher percentage of patients who regularly visited a gynecologist were surgically treated more often (85.44%) than those who did not (38.16%; \( p < 0.01 \)). Radiotherapy (with or without systemic treatment) was performed in 13.93% of patients who regularly visited a gynecologist and in 57.63% of those who did not (\( p < 0.01 \)). Symptomatic treatment was applied in 0.63% of patients who regularly visited a gynecologist and in 4.21% of those who did not (\( p < 0.01 \)).

Data on screening the patients who regularly visited a gynecologist: number of gynecological examinations, cervical smear test results, diagnostic procedures and symptoms.

From 2003 to 2006, each patient had on average five examinations at a gynecologist within the period of five years to six months before the diagnosis of cervical cancer (in 2003, 7.0 examinations; in 2004, 5.2 examinations; in 2005, 4.9; and in 2006, 3.6 examinations). The average number of collected smear samples was 3.2 (in 2003, 3.7; in 2004, 3.4; in 2005, 3.0; and in 2006, 2.8). On average, 55% of patients with cervical cancer had undergone a gynecological examination five years before the diagnosis.

In line with our expectations, the percentage of negative smear test results (75.33%) was the highest in the patients who were tested five years before the diagnosis of cervical cancer. In the following years, the percentage of negative test results gradually decreased; four years before the diagnosis of cervical cancer, the percentage of negative smear test results was 57.83%, three years before the diagnosis it was 62.02%, two years before 51.95%, and 7-12 months before the diagnosis, as much as 25% of patients still had negative test results (Table 4). On the other hand, the closer the date of the diagnosis, the more the percentage of pathologic cervical smear test results increased in inverse proportion to normal test results. In the period of 7-12 months before the diagnosis, the percentage of moderate dyskaryosis was 23.45%. These smears most frequently tested positive for initial pathologic changes, such as ASCUS or AGNUS or mild dyskaryosis. Five years and 7-12 months before the diagnosis, 5.19% and 1.56% of collected smear samples, respectively, were inadequate (Table 4).

From 2003 to 2006, colposcopy was performed in 70.3% of patients, biopsy or curettage in 20.3%, and excision (LLETZ, cone biopsy) or destructive surgical techniques in 9% of patients. HPV tests were carried out in 4.85% of patients. More detailed data on diagnostic procedures performed within specific time periods before the diagnosis are presented in Table 5.

Table 4. — Distribution of cervical smear test results by periods ranging from 6 to 60 months before diagnosis in the years 2003 to 2006.

<table>
<thead>
<tr>
<th>Period</th>
<th>Inadeq smear</th>
<th>Neg smear</th>
<th>Reactive changes</th>
<th>ASCUS or AGC</th>
<th>Mild dyskaryosis</th>
<th>Moderate or severe dyskaryosis</th>
<th>Suspic. or malignant cells</th>
<th>All</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6 M till</td>
<td>1</td>
<td>16</td>
<td>6</td>
<td>13</td>
<td>14</td>
<td>1</td>
<td>64</td>
<td>100.00</td>
<td></td>
</tr>
<tr>
<td>&lt; 12 M</td>
<td>(1.56%)</td>
<td>(25%)</td>
<td>(9.37%)</td>
<td>(20.31%)</td>
<td>(20.31%)</td>
<td>(21.88%)</td>
<td>(1.57%)</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>12 M till</td>
<td>4</td>
<td>40</td>
<td>2</td>
<td>13</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>77</td>
<td>100.00</td>
</tr>
<tr>
<td>&lt; 24 M</td>
<td>(5.19%)</td>
<td>(51.95%)</td>
<td>(2.69%)</td>
<td>(16.89%)</td>
<td>(18.18%)</td>
<td>(3.9%)</td>
<td>(1.30%)</td>
<td>79</td>
<td>100.00</td>
</tr>
<tr>
<td>24 M till</td>
<td>2</td>
<td>49</td>
<td>7</td>
<td>9</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td>79</td>
<td>100.00</td>
</tr>
<tr>
<td>&lt; 36 M</td>
<td>(2.54%)</td>
<td>(62.02%)</td>
<td>(8.86%)</td>
<td>(11.39%)</td>
<td>(10.13%)</td>
<td>(5.06%)</td>
<td>9</td>
<td>97</td>
<td>100.00</td>
</tr>
<tr>
<td>36 M till</td>
<td>5</td>
<td>56</td>
<td>5</td>
<td>13</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>97</td>
<td>100.00</td>
</tr>
<tr>
<td>&lt; 48 M</td>
<td>(5.25%)</td>
<td>(57.83%)</td>
<td>(5.15%)</td>
<td>(13.40%)</td>
<td>(6.25%)</td>
<td>(4.12%)</td>
<td>7</td>
<td>97</td>
<td>100.00</td>
</tr>
<tr>
<td>48 M till</td>
<td>4</td>
<td>58</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>77</td>
<td>100.00</td>
</tr>
<tr>
<td>&lt; 60 M</td>
<td>(5.19%)</td>
<td>(75.33%)</td>
<td>(5.19%)</td>
<td>(3.9%)</td>
<td>(9.09)</td>
<td>(1.30%)</td>
<td>7</td>
<td>77</td>
<td></td>
</tr>
</tbody>
</table>

Cervical diseases, e.g., premalignant cervical disease or cervical cancer, are accompanied by the development of certain discomforts. The patients who were diagnosed with cervical cancer had often complained to their gynecologist of the problems they had before the diagnosis. These disorders were already dealt with by our earlier studies; however, the data gathered in 2003 again demonstrated the occurrence of some clinical symptoms typical of cervical cancer that had been reported by the patients before the diagnosis. These symptoms described by the patients who regularly visited a gynecologist were different, depending on the time lapse until the diagnosis. Five years before the diagnosis the majority of women did not complain of any gynecological problems, three years before the diagnosis they reported vaginal discharge and...
inflammation, and one year before the diagnosis they described symptoms typical of premalignant cervical disease or cervical cancer (Table 6).

Table 6. — Symptoms by periods ranging from 6 to 60 months before the diagnosis in the years 2003 to 2006.

<table>
<thead>
<tr>
<th>Symptoms Period</th>
<th>Without Inflammation</th>
<th>MTG</th>
<th>Mixture</th>
<th>Lumbar pain</th>
<th>Other</th>
<th>All</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 6 M till 25</td>
<td>25</td>
<td>10</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>50 100.00</td>
</tr>
<tr>
<td>&lt; 12 M (50.00%)</td>
<td>(20.00%) (22.00%) (2.00%) (2.00%) (4.00%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 M till 29</td>
<td>23</td>
<td>16</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>54 100.00</td>
</tr>
<tr>
<td>&lt; 24 M (42.59%)</td>
<td>(32.05%) (16.66%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 M till 21</td>
<td>21</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>41 100.00</td>
</tr>
<tr>
<td>&lt; 36 M (51.22%)</td>
<td>(34.14%) (7.31%) (2.34%) (4.87%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 M till 27</td>
<td>27</td>
<td>8</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>41 100.00</td>
</tr>
<tr>
<td>&lt; 48 M (65.85%)</td>
<td>(19.51%) (4.87%) (2.34%) (7.31%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 M till 30</td>
<td>30</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>38 100.00</td>
</tr>
<tr>
<td>&lt; 60 M (96.77%)</td>
<td>(9.67%) (6.45%) (9.67%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Discussion

The present study is an analysis of the data on patients with newly detected cervical cancer in the period between 2003 and 2006. Our main interest was to find out whether any changes in clinical data occurred within the four-year period of organized screening for cervical cancer in Slovenia.

No significant difference was observed between the years 2003 and 2006 in the percentage of patients who had a gynecological examination within the period of five years before the diagnosis of cervical cancer (please note that the examinations performed six months before the diagnosis with the aim of confirming the diagnosis were not included). In 2006 and in 2003, the percentages of the patients who had gynecological examinations within the period of five years before the diagnosis of cervical cancer were 57.9% and 60.0%, respectively. The data gathered throughout the period between 2003 and 2006 indicate a trend of a gradually increasing percentage of patients who had not visited a gynecologist or had not had cervical sample tests for 15 or more years. In the years 2003, 2004, 2005, and 2006, the percentages of these patients were 42%, 45%, 50%, and 44%, respectively. One fourth of the patients who had not been regularly visiting a gynecologist had the gynecological examination within the period of less than ten years before the diagnosis (in 2006 and 2003, 22% and 29%, respectively).

In 2006, the mean age of all patients was 49.8 years, and in 2003, 48.2 years. In 2006 the majority of patients contracted cervical cancer at the age of 40-44 years, and in 2003 at the age of 45-49 years. One third of the patients included in these two observation periods were older than 50 years. The data from 2006 indicate a greater percentage of patients older than 69 years and of those aged between 30 and 34 years.

The mean age of patients who had a gynecological examination was statistically significantly lower than the mean age of the patients who were not visiting a gynecologist. Similar data are also reported in studies by other authors [8]. No statistically significant difference was observed between the years 2003 and 2006 in comparing the mean age of patients. However, the difference between the two years was obvious when comparing the mean age of the patients who were not regularly visiting a gynecologist; in 2006, the mean age of these patients was higher (58.6 years) than in 2003 (55.5 years). In both observation periods, the majority of the patients who were not regularly visiting a gynecologist were diagnosed with cancer at the age of 60-69 years.

The data on pathohistological findings also demand closer attention. A higher percentage of adenocarcinoma in the patients who regularly attended a gynecologist may support the hypothesis that the cervical smear test results of these patients have been indicating a pathological process in initial stages in the endocervix, but, due to insufficient diagnostic procedures, the pathological changes could not be detected. This assumption may be also confirmed by a high percentage of the disease detected in Stage I in patients who regularly visited a gynecologist. From the comparison of the data of 2003 and 2006, a gradual increase of the disease detected in Stage I and Stage IA was noted in patients who regularly attended a gynecologist, which could be an indication of a positive change resulting from effective screening and early detection of cervical cancer in Slovenia.

The average number of gynecological examinations and cervical smear tests performed in the patients with cervical cancer who visited a gynecologist within the last five years before the diagnosis dropped significantly in 2006, which is in line with the new recommendations for detecting, treating and following-up patients with premalignant cervical disease [11]. In 2006 the average number of gynecological examinations per patient was 3.6, while in 2003 it was 7.03. The number of cervical smear tests performed per patient in 2006 was 2.8, whereas in 2003 it was 3.7.

The percentage of our patients with consistently negative cervical smear test results is similar to the percentage reported by other authors [8-10]. A systematic and independent re-evaluation of negative cervical smear test results has not been made yet. The results also reveal a considerable number of cervical cancer patients who had negative cervical smear test results a few years before the diagnosis. Atypical glandular cells are still a frequent result of cervical smear tests in patients who later develop glandular cervical cancer. With regard to some new developments observed in cervical smear test results, certain changes will be introduced in diagnostic procedures, such as colposcopy with biopsy. A high percentage of colposcopies in comparison to the number of biopsies is a problem that demands an urgent solution [12]. It is however not yet certain what steps should be taken to provide proper and high-quality preventive measures in case of glandular premalignant cervical disease detection and also how to have open access to the use the HPV test as an effective tool in the diagnostics of cervical cancer [13-15].

From the results of our analysis, it may be concluded that improvements are urgently needed in Slovenia in the
field of screening for and early detection of cervical cancer [17]. It is first and foremost important, – to continue with data gathering and analyzing the procedures performed in patients who were regularly attending a gynecologist before they were diagnosed with cervical cancer;  
– to analyze individual cases, including independently reevaluating cervical smear samples or other pathohistological samples collected in the period within five years before the diagnosis of cervical cancer;  
– to determine, similarly to organized screening programs for cervical cancer in other countries, the dates of refresher courses on colposcopy and time interval between two courses intended for all who are regularly performing colposcopy in order to improve the quality of performance of this procedure and of cervical smear collection, and to pay greater attention to the drawbacks observed in the follow-up findings of cervical cancer patients;  
– to consistently urge following the recommendations for detecting, treating, and following-up patients with premalignant cervical disease;  
– to facilitate as soon as possible systemic application of a HPV test as an additional diagnostic procedure in women with initial stage pathologic changes of a cervical smear and in those who were treated for CIN;  
– to redirect a part of the activities of the departments of gynecology and obstetrics in Slovenian hospitals into more effective colposcopy clinics, which should be able to provide high-quality diagnostics, and fast and effective treatment of premalignant cervical disease in line with national guidelines imposing also the follow-up of quality indicators;  
– to urge women to perform gynecological examinations regularly particularly in cases of pathologic changes of a cervical smear and other gynecological disorders associated with premalignant cervical diseases, as well as in women treated for CIN.

Acknowledgement

The authors sincerely thank all colleagues, gynecologists and others who helped in data gathering and Mrs. Mojca Čakš for the English translation.

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References


Uterine sarcoma diagnosed during colon surgery - a complete precise diagnosis

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University Hospital “Narodni Front”, Belgrade (Serbia)

Summary

Uterine sarcomas are very rare tumors with the greatest malignant potential of all uterine tumors, and they differ significantly from endometrial carcinoma by their specific course, propagation and prognosis. A 54-year-old patient, after three vaginal deliveries and negative personal and family history, as well as regular cycles, presented with secondary problems related to occasional constipation with sporadic diarrhea and bloody stools. Colonoscopy revealed a colon tumor.

Key words: Uterus; Uterine sarcoma; Colon tumor.

Case Report

Uterine sarcomas are very rare cases of tumors with the greatest malignant potential of all uterine tumors, and they differ significantly from endometrial carcinoma by their specific course, propagation and prognosis. Uterine sarcomas make up 3-5% of all tumors of the uterus [1]. Homologous uterine sarcomas originate from endometrial glands or endometrial stroma (endometrial stromal sarcoma) or the muscular layer of the uterus (leiomyosarcoma). Other types of homologous sarcomas (angiosarcoma or lymphosarcoma) originate from other tissues that are normally found in the uterus – blood and lymph vessels. Table 1 shows the classification of uterine sarcomas. The incidence of uterine sarcoma in combination with pregnancy is rare in older primigravidas, and the course of pregnancy becomes questionable in medical and ethical terms.

A 54-year-old patient, after three vaginal deliveries and negative personal and family history, as well as regular cycles, presented with secondary problems related to occasional constipation with sporadic diarrhea and bloody stools. After performing colonoscopy, a colon tumor was found. The patient had had no gynecological examination for two years.

During the surgical procedure, it was established that colon changes were not of primary intestinal etiology but a consequence of prominence and destruction of the colon wall by a long-term or aggressive pathologically changed uterus. Hysterectomy with salpingo-oophorectomy was performed (Figures 1, 2). Histopathological analysis confirmed primary uterine pathology, uterine sarcoma, which was an atypical alteration in the colon wall without inflammation and ascites.

Additional information received from the patient revealed suspected prolonged bleeding and routine uterine revision after each delivery. Histopathological analysis of the placenta was not performed after the deliveries.

After her last delivery, 20 years before, the patient had three abortions performed in appropriate institutions, but with severe secondary inflammatory processes of the endometrium and parametrium bilaterally.

Table 1. — Classification according to Ober [14].

<table>
<thead>
<tr>
<th>Homologous</th>
<th>Heterologous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure</td>
<td></td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>Rhabomyosarcoma</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Fibrosarcoma</td>
<td>Osteosarcoma</td>
</tr>
<tr>
<td>Mixed</td>
<td>Mixed mesodermal (Mullerian) tumor</td>
</tr>
</tbody>
</table>

Classification according to GOG* [9]

Leiomyosarcoma
Endometrial stroma sarcoma
Mixed Mullerian tumor (carcinosarcoma)
Mixed heterologous Mullerian tumor (mixed mesodermal sarcoma)
Other uterine sarcomas

*Gynecologic Oncology Group.

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as a whole”. Was our patient’s hemorrhage a consequence of revisions? In the future, should we perform not only hematological examination and antibody and infection analyses, but also explorative curettage in conditions of suspected ultrasonography changes? Should diagnosis of the colon and small pelvis and vice versa be carried out in postmenopausal women?

References


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Malignant germ cell tumors of the ovary: a review of 41 cases and risk factors for recurrence

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3Department of Obstetrics and Gynecology, Dumlupinar University, Katalya (Turkey)

Summary

Objective: To review the outcome of treatment in patients with malignant ovarian germ cell tumors and to define the risk factors for recurrence. Material and Methods: Forty-one patients with malignant ovarian germ cell tumors were reviewed retrospectively. Survival time and survival rate were obtained. Risk factors such as stage, histological type, and type of operation were evaluated for recurrence. Results: Twenty-three (56%) had dysgerminomas, eight (19.5%) had mixed germ cell tumors, three (7.3%) had yolk sac tumors, three (7.3%) had immature teratomas, two (4.8%) had squamous cell carcinoma arising from a mature teratoma, one (2.4%) had embryonal carcinoma and one choriocarcinoma. Most of the cases (73%) were in Stage I. Twenty-nine patients (70.7%) underwent conservative surgery and 12 patients (29.3%) had at least bilateral salpingo-oophorectomy. Thirty patients were operated on optimally with surgical staging and 11 suboptimally. Seven patients (17%) had recurrence after remission. The overall survival time was 187 ± 8.43 months for all cases, 195 ± 8.49 for dysgerminoma and 161 ± 10.96 for non-dysgerminoma cases with a median follow-up time of 98.52 (8-204) months. Non-dysgerminoma histologic type, being operated on suboptimally and radically, and advanced tumor stage have been found to be risk factors for recurrence. Conclusion: Regardless of histologic types and stages the prognosis of germ cell tumors are satisfactory with current therapeutic strategies.

Key words: Malignant germ cell; Recurrence; Ovary; Risk factors.

Introduction

Malignant ovarian germ cell tumors (MOGCT) are rare tumors of the ovary (2-5%) [1]. Unlike their epithelial counterparts they are usually seen in childbearing age and at an earlier stage. Therefore it is essential to maintain fertility in selected patients [2, 3]. MOGCT are much more curable than epithelial ovarian tumors. The prognosis of these tumors has improved over the past years due to introduction of cisplatin, and the survival rates in patients treated with platinum-containing regimens have been reported to be more than 70% [4-6]. Although not often, recurrences can be seen in MOGCT [2, 7-9] but risk factors for recurrence have not been clearly outlined. In this retrospective study, we review the outcome of treatment in patients with MOGCT and define the risk factors for recurrence.

Material and Methods

Forty-one patients with MOGCT who were operated on in Istanbul University, Istanbul Medical Faculty Department of Obstetrics and Gynecology between 1988 and 2006 were reviewed retrospectively. Clinical, pathological, surgical and postoperative treatment data were collected. Follow-up data were obtained either from patient files or by telephone interviews with the patients or relatives.

Patients were grouped as dysgerminoma and nondysgerminoma cases. Survival time and survival rates were obtained according to this classification. The median follow-up time was 98.52 (8-204) months.

In patients who desired children fertility sparing surgery was performed and radical operations were performed on other patients. Surgical staging was performed according to the guidelines of the International Federation of Gynecology and Obstetrics [10]. Histopathological diagnosis was performed according to the World Health Organization recommendations [11]. Postoperative multiple-agent chemotherapy was given in our medical oncology department. Risk factors such as stage, histology, and type of operation were evaluated for recurrence.

Kaplan Meier and Cox proportional hazard analysis were used for survival time and survival rate comparison and Fisher’s exact test was used for comparison of risk factors in statistical analysis.

Results

Forty-one patients were evaluated. The median age was 25.048 ± 8.4 (11-68). Twenty-three (56%) had dysgerminomas, eight (19.5%) had mixed germ cell tumors, three (7.3%) had yolk sac tumors, three (7.3%) had immature teratomas, two (4.8%) had squamous cell carcinoma arising from a mature teratoma, one (2.4%) had embryonal carcinoma and one choriocarcinoma (Table 1). Sixteen women presented with Stage I A, two with Stage IB, 12 with Stage IC, one with Stage IIC, two with Stage IIE, four with Stage IIIB, and four with Stage IIEB disease (Table 2).

Twenty-nine patients (70.7%) underwent conservative surgery and 12 patients (29.3%) had at least bilateral salpingo-oophorectomy. Thirty patients had been operated on optimally with surgical staging, 11 had been operated suboptimally. Seven patients had recurrence after remission (Table 3). Nondysgerminoma histologic
Table 1. — Distribution of tumors according to histological types.

<table>
<thead>
<tr>
<th>Histology</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
<td>23</td>
<td>56%</td>
</tr>
<tr>
<td>Mixed germ cell tumor</td>
<td>8</td>
<td>19.5%</td>
</tr>
<tr>
<td>Endodermal sinus tumor</td>
<td>3</td>
<td>7.3%</td>
</tr>
<tr>
<td>Immature teratoma</td>
<td>3</td>
<td>7.3%</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>1</td>
<td>2.4%</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>1</td>
<td>2.4%</td>
</tr>
<tr>
<td>Squamous cell carcinoma derived from mature cystic teratoma</td>
<td>2</td>
<td>4.8%</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2. — Stage distribution of the tumors.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>16</td>
</tr>
<tr>
<td>IB</td>
<td>2</td>
</tr>
<tr>
<td>IC</td>
<td>12</td>
</tr>
<tr>
<td>IIA</td>
<td>1</td>
</tr>
<tr>
<td>IIC</td>
<td>2</td>
</tr>
<tr>
<td>IIIB</td>
<td>4</td>
</tr>
<tr>
<td>IIIIC</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3. — Risk factors for tumor recurrence.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>n</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td>Nondysgerminoma</td>
<td>6/18</td>
<td>33</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Dysgerminoma</td>
<td>1/23</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Operation</td>
<td>Suboptimal</td>
<td>5/11</td>
<td>45</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Optimal</td>
<td>2/30</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Operation</td>
<td>Conservative</td>
<td>3/29</td>
<td>13.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radical</td>
<td>3/12</td>
<td>25</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Stage</td>
<td>Stage I</td>
<td>2/30</td>
<td>6.6</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Stage II</td>
<td>5/8</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. — Survival time in dysgerminoma and non-dysgerminoma cases.

<table>
<thead>
<tr>
<th></th>
<th>Survival time (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Total</td>
<td>41 187 ± 8.43</td>
</tr>
<tr>
<td>Dysgerminoma</td>
<td>23 195 ± 8.49</td>
</tr>
<tr>
<td>Non-dysgerminoma</td>
<td>18 161 ± 10.96</td>
</tr>
<tr>
<td></td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

Discussion

Ovarian germ cell tumors account for 20-25% of all ovarian neoplasms and only about 3% of these are malignant [1]. Unlike their epithelial counterpart, 75% of MOGCT are diagnosed in Stage I. Dysgerminomas are the most common, comprising up to 50% of MOGCT. Mixed component germ cell tumors account for approximately 10% of all germ cell tumors, with dysgerminoma being the most commonly occurring element [7, 12]. In accordance with the literature most of our cases consisted of dysgerminomas (56%); mixed germ cell tumors accounted for 19.5% (Table 1). Regarding stage, 30 of 41 (73%) cases were in Stage I, three of 41 (7.5%) were in Stage II and eight of 41 (19.5%) were in Stage III (Table 2).

Germ cell tumors are broadly classified as dysgerminomas and non-dysgerminomas. This is important because their natural history and response to treatment, prognosis and survival times are very different [13, 14]. The largest series in literature about MOGCT belong to Zhang et al. [9] with 233 cases. They reported that 5-year survival rate differed between dysgerminoma and non-dysgerminomatous tumors being 84.2% for the former and 44.6% for the latter. In patients with non-dysgerminomatous tumors, chemotherapy with PVB and BEP regimens gave a 5-year survival rate of 66.0% and 73.3%, respectively. We found similar results with the findings of Zhang et al. [9]. In our series, we also classified the patients as dysgerminomas and non-dysgerminomas and compared their survival time and survival rate. The survival time was 195 ± 8.49 months for dysgerminoma and 161 ± 10.96 for nondysgerminoma cases with a median follow-up time 98.52 (8-204) months. The difference in survival time was statistically significant (p < 0.05) (Table 4). The survival rate was 88% for dysgerminoma and 68% for nondysgerminoma in the 132th month (p < 0.05).
Malignant germ cell tumors of the ovary: a review of 41 cases and risk factors for recurrence

We concluded that for young women who wish to preserve childbearing capacity, regardless of the stage of the tumor, fertility-preserving surgery with complete surgical staging followed chemotherapy is an appropriate and definitive treatment. For patients in whom childbearing capacity is not an issue, surgery should include total abdominal hysterectomy and bilateral salpingo-oophorectomy with complete staging.

In the literature there has been not been data about the risk factors for recurrence. Peccatori et al. [7] found recurrence in ten out of 129 patients (7.7%). Recurrence was observed in three out of 66 patients in De Backer et al.’s series [8], seven recurrences out of 74 patients (9.5%) in Low et al.’s series [9], and 43 out of 233 (18.4%) in Zhang et al.’s series [10]. However none of them discussed the risk factors. Our study mainly focused on the risk factors for tumor recurrence. We evaluated whether histologic type (dysergerminoma/non-dysergerminoma), stage of disease (early/late), and type of operation (optimal/suboptimal, radical/conservative) have any effect on recurrence rate. Out of 41 patients, seven (17%) had recurrences. While only one patient (Stage IIIB) out of 23 dysgerminoma cases (4%) had recurrence, six patients out of 18 nondysgermima cases (33%) had recurrence (p < 0.005). Patients with dysgerminoma had lower recurrence rates as compared with nondysgerminoma types. In patients operated on optimally the recurrence rate was 6% (2 patients out of 30). In contrast, in 11 of the suboptimally operated patients five had recurrences (45%) (p < 0.005). These findings support the fact that optimal staging surgery is essential in managing malignant germ cell tumors. As the relation between the stage of tumor and recurrence was compared, we found higher recurrence rates in advanced stage of tumors. In 30 patients with Stage I disease, only two patients (6.6%) had recurrence. On the contrary, in eight patients with higher than Stage I, five patients (62%) had recurrence. Higher recurrence rate in advanced stage is an expected finding. Interestingly, the patients operated on conservatively had lower recurrence rates as compared with those operated on radically (at least bilateral salpingo-oophorectomy) (3/29 13.7% vs 3/12 25%, respectively). However when keeping in mind that the patients operated on radically were in higher stages this finding seems reasonable.

In conclusion, we observed that histology of the tumor (being nondysgerminoma), advanced stage, suboptimal operations, radical operations (due to advanced stage) carried higher risk factors for recurrence in malignant germ cell tumors of the ovary. These patients should be followed with high attention. More studies with more cases are needed to define the risk factors for recurrence of MOGCT.

References


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Fascin can be an auxiliary immunomarker of ovarian granulosa cell tumors: comparison with calretinin and inhibin-α

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⁴Laboratory of Cytogenetics and Molecular Genetics, University Hospital of Larissa, Larissa (Greece)

Summary

The histopathologic diagnosis of granulosa cell tumor adult type (AGCT) can be supported by the use of established immunomarkers such as inhibin-α and calretinin. Previously unreported data is presented on the detection of fascin in AGCT, in nonneoplastic granulosa cells and in other types of sex-cord stromal tumors. In addition, by staining a panel of various tumors, potentially markers such as inhibin-α might become problematic since they are rare, present variable histologic patterns and can recur unpredictably [1, 2]. The application of immunohistochemical markers has assisted the morphologic assessment [3-11], but the available immunomarkers may show limitations regarding sensitivity or specificity.

Fascin-1 or simply fascin is a 55kDa actin-bundling protein [12-15]. Fascin cross-links actin filaments into tightly packed bundles, thus having a role in the formation of various actin-based cellular structures [16, 17]. Fascin is normally found in mesenchymal and neural tissues. Its expression is low or absent in non-neoplastic adult epithelial tissues, but may be increased in carcinomas [18]. Recent reports suggest that fascin may be a new prognostic indicator in several types of human carcinoma [19-29], probably due to its involvement in the formation of cellular surface protrusions and cellular motility. In vitro studies, based on transfection experiments, have shown that elevated levels of fascin increased the speed of cell migration and emphasized the association between fascin expression and motility of transformed cells [30].

In a previous study that examined fascin immunoreactivity in epithelial ovarian tumors [24] we observed strong staining in granulosa cells of ovarian follicles. The aim of the present study was to analyze fascin immunoreactivity in ovarian granulosa cell tumors and in a range of tumors that could potentially enter in their differential diagnosis. Thus, we could evaluate the possible role of fascin as a surrogate immunomarker in granulosa cell tumors.

Key words: Fascin; Ovary; Granulosa; Immunohistochemistry; Inhibin-α, calretinin.

Introduction

The histopathologic evaluation of adult granulosa cell tumors (AGCT) may become problematic since they are rare, present variable histologic patterns and can recur unpredictably [1, 2]. The application of immunohistochemical markers has assisted the morphologic assessment [3-11], but the available immunomarkers may show limitations regarding sensitivity or specificity.

Fascin-1 or simply fascin is a 55kDa actin-bundling protein [12-15]. Fascin cross-links actin filaments into tightly packed bundles, thus having a role in the formation of various actin-based cellular structures [16, 17]. Fascin is normally found in mesenchymal and neural tissues. Its expression is low or absent in non-neoplastic adult epithelial tissues, but may be increased in carcinomas [18]. Recent reports suggest that fascin may be a new prognostic indicator in several types of human carcinoma [19-29], probably due to its involvement in the formation of cellular surface protrusions and cellular motility. In vitro studies, based on transfection experiments, have shown that elevated levels of fascin increased the speed of cell migration and emphasized the association between fascin expression and motility of transformed cells [30].

In a previous study that examined fascin immunoreactivity in epithelial ovarian tumors [24] we observed strong staining in granulosa cells of ovarian follicles. The aim of the present study was to analyze fascin immunoreactivity in ovarian granulosa cell tumors and in a range of tumors that could potentially enter in their differential diagnosis. Thus, we could evaluate the possible role of fascin as a surrogate immunomarker in granulosa cell tumors.

Materials and Methods

Patients and surgical specimens

Twenty-two ovarian granulosa cell tumors were included in the study, 21 adult-type (AGCTs) and one juvenile-type (JGCT). Nine of them were retrieved from the archives of the Pathology Department of the University Hospital of Larissa. The rest were seen in consultation and paraffin blocks were obtained from other hospitals in Greece. The age of the patients ranged from 23 to 67 years old. Nine of the patients showed various effects of hyperstimen. Metastasis was histologically documented in only one case and multiple samples from the metastatic deposits were included in the study. The maximum dimension of the tumors ranged from 1-24 cm, whereas the median was 7 cm. The microscopic features of the tumors were conventional and represented most of the morphologic spectrum seen in AGCT.

The study also included 14 cases of ovarian sex-cord stromal tumors of other histologic types and 101 cases of various neoplasms that could potentially enter in a differential diagnosis with AGCT. The sex-cord stromal tumors included four fibromas, one thecoma, three fibrothecomas, two Sertoli-Leydig cell tumors, two sclerosing stromal tumors and two unclassified sex-cord stromal tumors. In the group of various neoplasms we included 42 ovarian carcinomas, 15 breast lobular carcinomas, eight carcinoids (of lung, GI tract, ovary and uterine cervix), 14 small cell carcinomas (of lung or urinary bladder), six melanomas (three of them metastatic), seven mesotheliomas, two endometrioid stromal sarcomas and seven high-grade sarcomas. In each case one sample was included with the exception of lobular carcinomas where we added ten samples from metastatic sites. Additionally, we studied samples from six cases of peritoneal mesothelial hyperplasia.

Immunohistochemical procedures

We applied the following antibodies: for fascin (clone IM20, dilution 1:300, 20 min at room temperature [RT], Novocastra, Newcastle upon Tyne, U.K.), for inhibin-α (clone BC/R1, dilution 1:30, 20 min [RT], Biocare Medical, Walnut Creek, CA).
and for calretinin (polyclonal, dilution 1:50, 20 min [RT], Biocare Medical, Walnut Creek, CA). Immunohistochemistry was performed using a streptavidin-biotin-peroxidase method in a commercially available automated immunostainer (Bond Max, Vision Biosystems, Australia). For antigen retrieval Bond Epitope Retrieval Solution 2 (30 min, Vision BioSystems, Mount Waverley, Australia) was used for fascin and calretinin, while Bond Epitope Retrieval Solution 1 (20 min, Vision BioSystems, Mount Waverley, Australia) was used for fascin and calretinin, respectively. Antigens were unmasked using Bond Refine Solution 2 (30 min, Vision BioSystems, Australia). The primary antibodies were visualized with the Bond Polymer Refine Detection (Vision Biosystems, Newcastle upon Tyne, U.K.), with DAB as a chromogen. Antigens for inhibinα and calretinin were applied only to granulosa cell tumors. Two aspects of fascin immunoreactivity were semiquantitatively evaluated, intensity and extent. Intensity was estimated by comparing tumor cell staining to that of adjacent endothelial cells, the latter being used as internal positive controls. Immunostaining was considered as "intense" when it was similar to that of endothelial cells (score 2), and "weak to moderate" (score 1) when it was less intense than that of endothelial cells. The extent of immunoreactivity was categorized according to the percentage of immunostained neo-
Figure 1. — AGCTs showing extensive and intense staining for fascin.

Figure 2. — Immunostaining for fascin was cytoplasmic.

Figure 3. — Rare foci lacking obvious epithelioid arrangements showing less intense staining.

Figure 4. — One metastatic focus showing weaker fascin staining. Theca-like cells in metastasis were negative for fascin (a), but strongly positive for calretinin (b).

Figure 5. — Two sclerosing stromal tumors showing weak or absent immunoreactivity. Note positivity in endothelial cells.

Figure 6. — Immunostaining for calretinin (a) and inhibin-α (b) was often uneven or patchy.
Fascin can be an auxiliary immunomarker of ovarian granulosa cell tumors: comparison with calretinin and inhibin-α

In fibrothecomatous tumors there was intense and extensive fascin staining. Fascin immunostaining differed from that of calretinin and inhibin-α in several ways. Fascin stained more tumors and more cells in each tumor (Table 2). In addition, fascin staining was uniform whereas that of calretinin and inhibin-α was uneven or patchy (compare Figures 1 and 6a-b). Furthermore, fascin did not stain theca cells in the immediate vicinity of AGCT cords and nests (Figure 7a). Calretinin (Figure 7b) and inhibin-α stained these cells strongly.

Calretinin immunostaining was seen in 20 out of 21 AGCTs. Extensive calretinin staining (>75% of tumor cells) was seen in 28.6% of the cases. Inhibin-α immunostaining was seen in 19 out of 21 AGCT. Extensive inhibin staining (>75% of tumor cells) was seen in 14.3% of the cases. Immunoreactivity for calretinin and inhibin-α is summarized in Table 2.

From the 101 miscellaneous tumors and lesions, only ten showed fascin immunoreactivity comparable to that of AGCT, i.e., similar IHS. These included four ovarian carcinomas, three non-ovarian small cell carcinomas, two sarcomas and one endometrioid stromal sarcoma. Almost 50% of this group of cases showed no fascin staining at all.

**Discussion**

This is the first study that demonstrates the presence of fascin in AGCT and in non-neoplastic granulosa cells. Detection of fascin in normal granulosa cells raises questions regarding fascin activity in these cells. Fascin could be related to microvillous processes observed in granulosa cells. The latter extend cytoplasmic projections, through zona pellucida, to connect with oocytes via gap junctions [31-33]. These connections are considered important for the proper preservation of the oocytes. Filopodia have been observed in AGCTs by electron microscopy [34]. In general, the formation of filopodia requires intensified actin assembly and in several cell types it is associated with overexpression of fascin [17]. Thus, fascin could be related to filopodia formation in granulosa cells.

Given the above comments, fascin immunoreactivity in neoplastic granulosa cells could be expected. Fascin is still expressed after neoplastic transformation as a preserved element of the granulosa cell phenotype. With the help of electron microscopy, astute observers have described interdigitating filopodia within Call-Exner bodies [35]. Since fascin could be a feature of well differentiated granulosa cell tumors, we looked in areas showing patterns considered to represent tumor with poorer differentiation. Overall, we did not observe a relationship of fascin immunostaining with the degree of differentiation in AGCT, although few areas showed slightly less fascin staining. Thus, fascin might not be a surrogate marker in grading AGCT.

The histopathologic diagnosis of AGCT depends primarily on the identification of traditional morphologic features. Immunohistochemistry plays an ancillary role. It may become critical in cases with poor preservation of morphology coupled with relative inexperience of the observer. The introduction of a new candidate immunomarker for AGCT should prompt comparison with two markers already applied routinely, inhibin-α and calretinin [3-11, 36]. Both of them appear to be more specific and less sensitive than fascin. However, fascin may still have a “role” in some diagnostic “scenarios”. Absence of fascin immunoreactivity could help in excluding AGCT when the latter is low in a diagnostic list. On the contrary, finding uniform-strong fascin staining could reassure a pathologist issuing a diagnosis of AGCT without convincing immunoreactivity for inhibin-α or calretinin. AGCT-negative for these two markers was seen in 4.8% of our cases. Thus, the diagnostic contribution of fascin may be based on its negative predictive value.

The value of a new immunomarker may not always depend on its high diagnostic contribution. Occasionally, it may help in highlighting histogenetic points. In the case of AGCT, a neoplastic theca cell component has
References


Abdominal pillow for the sparing of small bowel in four-field conventional pelvic radiotherapy

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Summary

From 2003 through 2004, 88 patients with gynecological cancer were referred to Istanbul University Oncology Institute for pelvic radiation therapy. All patients underwent small bowel evaluation within the pelvic radiotherapy field in both the supine and prone positions with and without an abdominal pillow. The small bowel area included in radiation fields and intestinal movement were compared on PA films. All patients were treated by using the abdominal pillow. The median external beam pelvic radiation dose of 5040cGy (range, 3220-5400cGy) was administered. The mean distance of upward displacement of small bowel in the prone position on abdominal pillow compared with in the prone position alone and in the supine position was 3.6 cm (range, 0-14 cm) and 4.7 cm (range, 0-14 cm). Using the abdominal pillow, the mean small bowel area was reduced by 45% and 55% compared to the prone position alone and the supine position, respectively (p = 0.0001). In patients who had pelvic surgery intestinal movement was significantly reduced. The incidence of G1, G2 and G3 acute radiation toxicity was 18%, 36% and 3%, respectively. This study demonstrates that the small intestines can be displaced out of the radiation field by an abdominal pillow in the prone position. Also, this noninvasive technique provides for reduction of acute gastrointestinal morbidity.

Key words: Gynecologic tumors; Pelvic radiotherapy; Radiotherapy techniques; Patient positioning; Small bowel toxicity.

Introduction

Radiation therapy is a critical component in the treatment of gynecologic tumors; however, it has clinical limitations due to the complications, mainly damage to adjacent normal tissues. Radiation therapy regimens are formulated to maximize the chances for cure while incurring the smallest amount of damage to normal tissues. In gynecologic cancers, the most serious complications are those involving the gastrointestinal or genitourinary systems.

Intestinal complications of radiation therapy are classified as either acute or chronic. The acute effects of radiotherapy are caused by ionizing radiation on the epithelium of the intestine. The chronic effects of radiotherapy result from the induction of vasculitis and fibrosis, and they are more serious than the acute effects.

Small bowel tolerance is a highly significant dose-limiting factor, because of early and late adverse effects. The incidence and severity of problems are related to the total dose and dose per fraction, volume of intestine irradiated, the daily use of single-field treatment, use of concomitant chemotherapy, comorbidities, previous abdominal surgery and observation time [1].

Particularly, treatment of late toxicity on the small bowel is difficult after clinical symptoms have developed. Therefore, preventing intestinal toxicity must be of maximum importance. Advances in the techniques of delivery of radiotherapy to pelvic organs may decrease the incidence of intestinal complications.

Several methods may be used to prevent intestinal toxicity. For example, use of computerized radiation dosimetry to design the best treatment plan and to use high-energy treatment machines, such as linear accelerators, that deliver a high dose to tumor volume while sparing the normal structures [2]. Other methods are to move out of the pelvis with surgical methods, to change radiation techniques, and to use radioprotectants during the radiotherapy.

The small bowel is a mobile structure and segments of the small bowel can move in and out of the irradiated volume. Numerous surgical techniques have been used to reduce small bowel volume. Repositioning of normal tissues can be accomplished by mechanical rather than invasive surgical techniques. For this reason, the position techniques such as the use of a belly board, an open table top and an up-down table have been described [3-5].

The main aim of this study was to try to reduce the small intestine within the pelvic treatment field, and in this way to reduce acute and chronic complications of pelvic radiotherapy by using the abdominal pillow.

Methods

Eighty-eight patients with gynecological malignancies (cervical cancer in 48, endometrial cancer in 35, vaginal cancer in 3, and endometrial sarcoma in 2) were selected for this study. All 37 patients with endometrial tumor and six patients with cervical carcinoma underwent total hysterectomy and bilateral salpingo-oophorectomy. Pelvic lymph node sampling or dissection was performed in 31 patients (35%). Patient characteristics are summarized in Table 1.

Information about the treatment and complications of the treatment were explained to the patients, and they accepted the
treatment in question. After the procedure, in all patients simulations were done in supine and prone positions with or without an abdominal pillow. The footplate and the prone pillow were used for patient stabilization. The treatment position is represented in Figure 1. We made the abdominal pillow using air equivalent foam material. We had three devices made. One was placed within the simulation room and the other two were placed within the treatment rooms. They measured 50 cm (bottom length), 29 cm (width), and 12 cm (thickness).

During the simulation procedure, the small bowel was visualized using barium contrast. The patients were given about 500 ml of barium sulfate and then one to three hours elapsed to allow the contrast to fill in the small bowel. The patients were placed in the supine position and next in the prone position on the simulator table; pelvic field borders were set according to bone structure and posterior anterior simulation films were taken. Then the abdominal pillow was placed under the lower abdomen of the patient and a pause of a few minutes was sustained because the small bowel had to be moved out of the pelvis. In this position, the posterior-anterior and lateral orthogonal simulation films were obtained (Figures 2 and 3).

The films were then visually analyzed. The target volume was drawn from each set of simulation films. The fields with the least amount of small bowel overlying the target volume were chosen. The small bowel inside the treatment fields was shielded with cerrobend blocks. The treatment fields were checked with portal films once a week and the faults were corrected.

We did not take lateral simulation films at each position, since it costs too much and we had limited time for each patient.
simulation. We took lateral simulation films only at the treatment positions. The intestinal movement was evaluated according to the distance between the bottom of the small bowel and inferior border of the radiation field. Later, small bowel areas on the simulation films were separated into squares so that we could calculate the amount of bowel out of the field. Finally we calculated the intestinal area and the total irradiation area and compared these statistically.

In the X-ray simulation, limits were L4-L5 or L5-S1 vertebral interspaced superiorly and ischial tuberosity or below the foramina obturatoria inferiorly according to diagnosis and stage of disease.

The standardized irradiation protocol consisted of whole-pelvis external irradiation 45-50.4 Gy with a daily dose 1.8-2.0 Gy, which is specified at the isocenter for four-field techniques with 15 MV linear accelerator.

Initial studies with MR imaging were done six months or more after completion of radiation therapy.

Enteric toxicity was evaluated in accordance with the Radiation Therapy Oncology Group (RTOG) criteria [6].

All data were analyzed with the SPSS for Windows program package (Version 7.5, SPSS Inc.). The differences between the two groups were evaluated with the chi-square test and the coupled data were paired with the Student’s t-test.

### Results

The patients’ median age was 56 years (range, 27-77). Body weight of the patients ranged between 48-132 kg and median weight was 70 kg. Forty patients who had cervical cancer were administered concomitant chemotherapy with pelvic radiotherapy. During the post-radiotherapy period, the median follow-up was 24 months (range, 10-55 months). Forty-three of 88 patients (49%) were treated with postoperative radiotherapy, 34 patients (39%) were treated with curative chemoradiotherapy, five patients (5%) were treated with curative radiotherapy alone, and six patients (7%) were treated with postoperative chemoradiotherapy (Table 1).

While in the prone position using an abdominal pillow the median intestinal area within the fields was 41.2 cm² (range, 0-161 cm²), in the prone position and in the supine position these median areas were 85.7 cm² (range, 9-220 cm²) and 105.3 cm² (12-257 cm²), respectively. Mean small-bowel area ratio to whole pelvic radiation field with the abdominal pillow, in the prone position and in the supine position were 13.5% (range, 0-50%), 29% (range, 3-72%) and 39% (range, 5-83%), respectively (p = 0.0001). In other words, using the abdominal pillow, average reductions of small bowel area in the pelvic radiation field were 54% (range, 0-100%) and 45% (range, 0-100%) on PA films compared to the supine position and the prone position alone, respectively (p = 0.0001) (Table 2).

The mean distance of upward displacement of small bowel in the prone position with an abdominal pillow compared to the prone position alone and supine position were 3.6 cm (range, 0-14 cm) and 4.7 cm (range, 0-14 cm). Both of these are statistically significant (p = 0.0001). In prone position, this distance was 1.5 cm (range, 1-2 cm) compared to the supine position (p = 0.0001). Mean values of vertical distance, small bowel area, small bowel area/treatment area in the supine, prone and prone with the pillow positions are shown in Figure 4.

In six out of 88 patients (7%), there was no small bowel present in the treatment field after using an abdominal pillow. On the contrary in four patients the small bowel

### Table 1. — Characteristics of 88 patients treated for gynecological tumors.

<table>
<thead>
<tr>
<th>Patients characteristics</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Habits and Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine cervical cancer</td>
<td>48</td>
<td>54</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Vaginal cancer</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Corpus sarcoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative radiotherapy</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td>Postoperative chemoradiotherapy</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Curative chemoradiotherapy</td>
<td>34</td>
<td>39</td>
</tr>
<tr>
<td>Radiotherapy alone</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

### Table 2. — Mean and median values of small bowel area, vertical distance and small bowel area rate in the pelvic radiation field in the supine, prone and prone position with device.

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD - Median (minimum - maximum)</th>
<th>Position with device (DP)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SBA (cm²)</strong></td>
<td>107.9 ± 46.2 87.8 ± 43.9</td>
<td>49.0 ± 36.6</td>
<td>DP-PP .000</td>
</tr>
<tr>
<td></td>
<td>105.3 (12.1-257.0) 85.7 (8.8-220.0)</td>
<td>41.2 (0-161.2)</td>
<td>DP-SP .000</td>
</tr>
<tr>
<td><strong>VD (cm)</strong></td>
<td>6.9 ± 2.8 8.0 ± 3.0</td>
<td>11.5 ± 3.8</td>
<td>DP-PP .000</td>
</tr>
<tr>
<td></td>
<td>6.6 (1.9-15.8) 7.2 (3.1-17.0)</td>
<td>12.0 (3.7-20.5)</td>
<td>DP-SP .000</td>
</tr>
<tr>
<td><strong>SBA/TA (%)</strong></td>
<td>36.6 ± 15.6 29.6 ± 14.5</td>
<td>16.2 ± 12.0</td>
<td>DP-PP .000</td>
</tr>
<tr>
<td></td>
<td>35.9 (5.3-82.9) 29.1 (3.3-72.2)</td>
<td>13.8 (0-50.2)</td>
<td>DP-SP .000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PP-SP .000</td>
</tr>
</tbody>
</table>

SBA: Small bowel area in treatment field; VD: Vertical distance between lower part of the small bowel and inferior border of the treatment field; TA: Treatment area. Student’s t-test.
Table 3. — *Correlation of pelvic surgery and vertical movement.*

<table>
<thead>
<tr>
<th>Pelvic Surgery</th>
<th>&lt; 5 cm Vertical movement n (%)</th>
<th>&gt; 5 cm Vertical movement n (%)</th>
<th>p (chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who had pelvic surgery</td>
<td>31 (63)</td>
<td>18 (37)</td>
<td>0.05</td>
</tr>
<tr>
<td>Patients who did not undergo pelvic surgery</td>
<td>17 (44)</td>
<td>22 (56)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. — *Comparison of acute enteric toxicity according to vertical intestinal movement.*

<table>
<thead>
<tr>
<th>Vertical movement distance</th>
<th>Grade 0-1 Acute enteric toxicity n (%)</th>
<th>Grade 2-3 Acute enteric toxicity n (%)</th>
<th>p (chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 cm</td>
<td>22 (46)</td>
<td>26 (54)</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt; 5 cm</td>
<td>31 (77)</td>
<td>9 (23)</td>
<td></td>
</tr>
</tbody>
</table>

Table 5. — *Comparison of acute enteric toxicity according to intestinal area ratio in the radiotherapy field.*

<table>
<thead>
<tr>
<th>Intestinal area ratio (SBA/TA)</th>
<th>Grade 0-1 Acute enteric toxicity n (%)</th>
<th>Grade 2-3 Acute enteric toxicity n (%)</th>
<th>p (chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20%</td>
<td>41 (69)</td>
<td>18 (31)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt; 20%</td>
<td>12 (41)</td>
<td>17 (69)</td>
<td></td>
</tr>
</tbody>
</table>

area did not get narrower compared to the prone position alone and supine position. In patients who had had previous pelvic surgery and in other patients, percentages of more than 5 cm vertical movement were 37% and 56%, respectively (p = 0.05) (Table 3).

Pelvic RT was generally well tolerated. Except for one, all patients completed their pelvic radiotherapy without requiring a break in treatment. The incidences of grade 1, grade 2 and grade 3 acute enteric toxicity were 18% (16 patients), 36% (32 patients) and 3% (3 patients), respectively.

In patients who had more than 5 cm intestinal vertical movement, grade 2-3 acute intestinal toxicity incidence was lower than in other patients (23% and 54%, respectively, p = 0.002). Similarly in patients who had more than 20% intestinal area in the pelvic radiation field grade 2-3 acute intestinal toxicity incidence was higher than for other patients (69% and 31%, respectively, p = 0.01) (Tables 4 and 5). The incidence of chronic intestinal toxicity was very low. Of 88 patients, two (2%) and one (1%), had grade 1 and grade 3 toxicity, respectively.

Discussion

Pelvic radiation therapy is often indicated in the treatment of patients with gynecological cancer. Although the goal of the radiotherapy is tumor control, this must be done with the minimum amount of toxicity to prevent worsening of the quality of life.

The small intestine is particularly sensitive to radiotherapy, because the intestinal epithelium has a rapid turnover. The diverse manifest of intestinal complications of radiation therapy may develop insidiously, are often progressive, and may be lethal. The incidence of late small bowel damage is one of the most important dose-limiting factors in radiation treatment of the pelvis. Most chronic injuries occur between 12 and 24 months after radiation [7]. Late small bowel complications that are generally irreversible are an indirect result of progressive scarring and blood vessel injury. It is complex and involves changes in most compartments of the intestinal wall. Prominent structural features include mucosal atrophy, intestinal fibrosis and vascular sclerosis. Following pelvic radiotherapy for gynecologic malignancy, incidence of severe late chronic radiation injury of the small intestine varies between 0.5 and 15% [8]. The incidence of small bowel damage is related to total radiation dose, dose per fraction, short treatment times and volume of irradiated tissue [9, 10].

The volume of the irradiated small bowel in the radiation portals for gynecologic carcinoma is considered to be an important factor with regard to the severity of acute and chronic morbidity [11, 12]. Prevention of these complications can be achieved by limiting the volume of small bowel treated.

One of the methods used to decrease the effects of radiation on normal tissues is to use a multiple field technique. Four-field radiotherapy has been utilized to reduce the complications resulting from two-field pelvic irradiation [13, 14]. This way the maximal effect is in the area where the beams cross which is targeted on the tumor, and the normal tissues get less radiation.

In 1986, Gallagher and associates described the “grid method” for the measurement of the irradiated small bowel volume for standardization. This method allowed a quantitative comparison of the efficacy of the different technical innovations. They used barium contrasted bowel loops on simulation radiographs and divided the bowel region into a grid of 1 cm x 1 cm squares. Consequently, they reported that a compression pillow with bladder distention in the prone position provided maximum sparing of small bowel radiation field and found a profound effect of the volume of irradiated small bowel on late toxicity [15].

The small bowel is a mobile structure and segments of small bowel can move in and out of the irradiated volume. Therefore, repositioning of normal tissues can be accomplished by mechanical rather than invasive surgical techniques. Some investigators have treated patients in the prone position to displace small bowel loops out of the pelvic fields. Caspars and Hop used small bowel contrast studies to evaluate prospectively the impact of positioning in small-bowel displacement from the pelvis. The volumes were calculated for the supine and the prone position. In comparison, they showed the prone position to be superior to the supine position in 78% of patients [16].

Treating a patient with a full bladder may push the small bowel up and out of the pelvis when pelvic radiotherapy is given. Green noted that in many patients distention of the bladder may be eased by displacing the small bowel from the pelvis [17].

Holst et al. described a small bowel displacement system (SBDS) that is fixed to the treatment table [18].
SBDS allowed a mean reduction of the small bowel within the field up to 57% compared to the quantity of small bowel visualized in the treatment field with prone positioning alone. Similarly, some investigators have reported that the small-bowel volume can be significantly reduced by a mean of 50-66% with the belly board device [19-22].

Huh et al. showed that by using the SBDS the mean distance of upward displacement of small bowel was 4.8 cm and average reduction of the mean percentage of the small bowel area was 59% compared to the prone position alone on PA films [4]. Similarly, in our study, corresponding figures were 3.7 cm and 45%, respectively.

Most radiotherapists are seriously worried about enhanced small bowel complications with postsurgery radiotherapy. Thus, in the pelvic radiotherapy field too much intestine may be included. Green et al. observed small bowel fixation in over 60% of patients who had pelvic surgery [17]. In our study, in patients who had previous pelvic surgery vertical intestinal movement was significantly limited compared to the other patients. Moreover, all four patients who did not have intestinal movement received radiotherapy postoperatively.

Huh et al. used a customized SBDS in the 3-D CRT to displace the small bowel maximally out of the pelvic radiation fields. In their series, ten consecutive patients were referred for pelvic radiotherapy for uterine cervical cancer. They showed that the median small bowel volume with SBBS was reduced by 56.4% compared to small bowel volume in the prone position alone. At the prescription dose, the median volume of the irradiated small bowel was significantly reduced by use of the SBDS (9.8% vs 1.2%) [21].

Kim et al. showed that these techniques can be used without causing serious set up errors. They investigated the inter-fractional setup accuracy of the customized SBDS and reported that the mean inter-fractional deviation of the isocenter, along the right-left, cranio-caudal, and posterior-anterior directions were 1.2 ± 1.6, 1.0 ± 3.0, and 0.9 ± 4.4 mm, respectively [23]. The aim of our trial was not to evaluate set-up errors. However we used immobilizing devices as the prone pillow and footplate and marked the top of the abdominal pillow and patients’ skin to prevent set-up errors. On weekly portal films, we did not determine any serious problems.

Historically, women with locally advanced cervical cancer were treated with radiotherapy alone. However, concurrent chemoradiation is obligatory in the management of locally advanced cervical cancer at present. This current trend is a poorly understood biological variable. Thus, bowel-exclusion techniques must be considered especially important, also in our study, in which 40 of 88 patients (46%) received concurrent chemotherapy. Nevertheless, grade 2-3 enteric toxicity was not significantly increased in patients treated with chemotherapy.

Various agents that confer protection against radiation have been developed, of which the most promising is amifostine (WR 2721). The few clinical trial data available on the use of amifostine in pelvic cancer patients suggest benefit in reducing lower GI tract toxicities [24]. However, the role of amifostine is still unclear for enteric toxicity.

In our study, the severity of the acute radiation effects closely correlated with the area of small bowel in the pelvic radiotherapy field. The chronic intestinal toxicity rate was not enough for statistical analysis and follow-up period was short to evaluate long-term toxicity. However, after incurring late toxicity of the small bowel, treatment is very difficult. For this reason, preventing intestinal toxicity is very important for treatment of patients with gynecological cancer. We think that the small bowel within the irradiation field can be reduced by using the abdominal pillow in pelvic radiotherapy. Therefore, this technique may help to prevent both acute and chronic enteric toxicity.

Conclusion

Radiation-induced intestinal injury is a difficult problem in pelvic irradiation. Therefore clinicians must consider that prevention of enteric toxicity is a part of the treatment of pelvic tumors. This study demonstrates that the small intestines can be displaced out of the radiation field by an abdominal pillow in the prone position. Thus acute toxicity may be reduced compared to conventional methods.

References


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Ovarian malignant immature teratoma associated with pregnancy - a case report

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Introduction

The diagnosis of an ovarian tumor during pregnancy is uncommon, occurring in approximately 0.1% of cases [1]. This frequency is tending to increase due to the fact that women are becoming pregnant at older ages. Malignant immature teratoma occurs in approximately 1/30,000 pregnancies. This cancer is associated with a low malignant potential, is radio- and chemo-sensitive, and is often diagnosed in young women.

Case Report

A healthy 36-year-old woman presented at 21 weeks of amenorrhea for her second-trimester prenatal ultrasonography. Ultrasonographic (US) examination showed an ongoing pregnancy and a voluminous ovarian mass localized on the left side of the uterus, measuring 175 mm in diameter, with a multilocular cystic structure.

A laparotomy performed at 22 weeks of amenorrhea revealed an isolated left ovarian tumor without any external vegetation, and a left ovariectomy was performed. Figure 1 shows a macroscopic view of the ovarian tumor, measuring 18 cm in diameter. Histologic examination revealed a malignant grade 2 immature teratoma, and the patient underwent three courses of chemotherapy with a good pregnancy outcome. A cesarean section was carried out at 39 weeks of amenorrhea, associated with a left salpingectomy on which the pathologist examination did not find any malignant cells. The newborn had a normal aspect, and the mother was considered to be in remission after two more courses of chemotherapy.

Discussion

The management of adnexal masses during pregnancy is difficult. The most frequently documented primary malignant neoplasms associated with pregnancy are breast cancer, cervix cancer, melanoma, lymphoma and ovarian cancer. An ovarian tumor is diagnosed in approximately 0.1% of pregnancies, although the proportion of malignancy remains weak ranging from 2 to 8.5% of cases. The mean age of pregnant women with an ovarian tumor is not different in comparison to the general population (32.3 years vs 31.1). The majority of adnexal masses are functional cysts that usually disappear by the end of the first trimester of pregnancy, or teratomas.

Clinical diagnosis is difficult because digestive symptoms are unspecific due to increased size of the uterus, uterine contractions, distension of the abdomen and hormonal impregnation. Few ovarian tumors are revealed with clinical symptoms and US examination plays a crucial role, leading to an early diagnosis principally during the first trimester of pregnancy. The risk for adnexal torsion (29% vs 7% in the general population) and tumoral rupture (14% vs 2-3%) are increased during pregnancy.

Surgical management is indicated in case of presence of symptoms, US findings including a tumor diameter above 7 cm, a solid component, increasing dimensions of the tumor, and persistence of the adnexal mass during the second and third trimester. Surgical treatment is considered dangerous for both the mother and fetus, leading to high risk of fetal loss and premature birth. Recommend-
tions concerning chemotherapy are to adapt the therapy to each patient, to avoid anti folic agents during the first trimester, and if possible any chemotherapy at that time. Radiotherapy is the only therapy forbidden during pregnancy due to the risk of fetal loss.

Conclusion

There is no argument to state that pregnancy worsens the prognosis of ovarian cancer, in contrast with breast cancer and melanoma, leading thus to restrict indications of pregnancy termination. Multidisciplinary assessment including a gynecologist, obstetrician, oncologist, pediatric and neo-natalologist is mandatory to determine the best therapeutic option for both mother and foetus in such cases.

References


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Squamous cell carcinoma of the vulva in a young woman with Crohn’s disease

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Division of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, NY (USA)

Summary

Background: Crohn’s disease is a chronic inflammatory disorder of the gastrointestinal tract. Because Crohn’s disease is transmural it may form fistulas to adjacent structures, including the perineum and vulva. Case: A 28-year-old white female with a history of Crohn’s disease presented with a non-healing vulvar fistula. Biopsy revealed squamous cell carcinoma. Conclusion: Young women may develop squamous cell carcinoma associated with fistulae of Crohn’s disease.

Key words: Squamous cell carcinoma; Vulva; Crohn’s disease.

Introduction

Crohn’s disease is chronic inflammatory disorder of the gastrointestinal tract. Because Crohn’s disease is transmural it may form fistulas to adjacent structures, including the perineum and vulva. We report a case of squamous cell carcinoma arising in a Crohn’s disease-associated fistula to the vulva.

Case Report

A 28-year-old white female was referred to our institution secondary to a vulvar biopsy consistent with invasive squamous cell carcinoma. The patient’s past medical history was significant for Crohn’s disease for which she had undergone resection of an anal fistula at 18 years of age followed by partial colectomy with ostomy and subsequent takedown with reanastomosis. Approximately two years prior to presentation, she reported developing two right-sided vulvar fistulas for which she received a six-week course of metronidazole and ciprofloxacin. She reported subsequent improvement in her symptoms for the following two years until she noticed a cyst-like structure on her right vulva at the site of a previous fistula that was becoming increasingly painful and swollen. After a six-week trial of metronidazole and ciprofloxacin without relief, a fistulagram and biopsy were performed. The fistulagram failed to show any abnormal communication. The biopsy results were reported as moderately differentiated, nonkeratinizing invasive squamous cell carcinoma.

The patient was referred to Roswell Park Cancer Institute. Upon exam, an ulcerated endophytic lesion approximately 3 cm in diameter was visualized. Upon further questioning, she denied any history of genital warts or smoking.

She admitted to a history of cervical dysplasia which was treated with a LEEP. She had received prednisone for her Crohn’s disease six years prior for six months.

She underwent a right hemivulvectomy and right inguinal lymph node dissection without complications. Pathological examination of the vulvectomy specimen revealed poorly differentiated squamous cell carcinoma measuring 3 cm in width and 0.4 cm out of 0.8 cm in depth. Angiolymphatic invasion was present. The surgical margins were free of tumor. Eleven of 11 lymph nodes were negative for malignancy. She had an uneventful postoperative course and was discharged home in stable condition on postoperative day number three.

Discussion

Squamous cell carcinoma of the vulva is rare among young patients [1]. Women with Crohn’s disease are at an increased risk of vulvar cancer. In their review of 1,227 patients with Crohn’s disease, Greenstein et al. reported two patients with squamous cell cancer of the vulva which represented a 14.2 times increase over the expected incidence [2]. One of those carcinomas was associated with perianal involvement of Crohn’s disease. Additionally, they observed three cases of squamous cell cancer of the anus, two of which arose in association with chronic perianal fistulas. Considering the association of fistula with the increased incidence of squamous cell cancer in Crohn’s disease the investigators concluded “that the association is more than incidental” and hypothesized that the lesions may result from chronic inflammation and intrinsic immunosuppression. The exact etiology of carcinoma arising in chronic fistulae is unsure. Church et al., in their review of four cases of fistula-associated carcinoma cases, proposed that the carcinomas develop due to chronic epithelial irritation with resultant hyperplasia and subsequent transformation to carcinoma [3].

Due to its rarity it is difficult to determine the incidence of squamous cell carcinoma arising in a Crohn’s disease fistula. In a survey conducted by Korelitz there were three reported cases of carcinoma occurring at the site of a fistula in 16,469 patients with Crohn’s disease [4]. In their review of over 1,000 patients with Crohn’s disease affecting the anus or rectum, Ky et al., noted a total of seven patients with carcinoma associated with anorectal fistulas, four with squamous cell carcinoma and three with adenocarcinoma [5].

A majority of the information regarding carcinoma arising in the fistulas of Crohn’s disease is in the form of...
case reports and small series of patients [3, 5-10]. In their report of seven patients with carcinoma arising in anorectal fistulas, Ky et al. reported that the average age of diagnosis was 47 years [5]. However, the two women diagnosed with squamous cell carcinoma were 30 and 31 years old. Similar findings were reported by Korelitz who observed that the average age of carcinoma found in an anorectal fistula of Crohn’s disease was 50 years old [7]. The three women diagnosed with squamous cell carcinoma were only 30, 31 and 38 years of age. Buchman et al. detailed the clinical course and diagnosis of squamous cell carcinoma associated with chronic perineal involvement of Crohn’s disease in women aged 28 and 35 [8]. These observations highlight the relatively young age at which females affected with Crohn’s disease fistulas and involvement of the perineum can develop squamous cell carcinoma.

A high index of suspicion must be maintained in women with Crohn’s disease with perineal involvement to avoid a delay in diagnosis. In discussing his nine patients with carcinoma arising in Crohn’s disease fistulas, Korelitz reported that in “no case was the carcinoma suspected on initial examination or, in some cases, even after multiple examinations” [7]. The diagnosis of carcinoma may be missed by attributing the symptoms to benign pathology. Most often the presenting complaint is pain [3, 7, 8]. One must also be suspicious of bleeding and discharge related to a fistula [3, 10].

By being aware of the possibility of squamous cell cancer developing in young women in association with a Crohn’s disease fistula, maintaining a high index of suspicion and a low threshold to biopsy worrisome lesions, it may be able to improve patients’ outcome via an earlier stage at diagnosis and prompt initiation of treatment.

References

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Ectopic breast cancer in the anterior chest wall: a case report and literature review

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Summary

Ectopic breast cancer is rare and when situated in the chest wall, it is even rarer. This report describes the case of an 86-year-old Brazilian woman with a palpable carcinoma, located in the right inframammary fold, and right axillary adenopathy. The patient was submitted to excision of the accessory breast and to right axillary lymphadenectomy. All 28 resected lymph nodes contained metastatic cells. Diagnosis and treatment of ectopic breast cancer should be carried out early in view of its aggressivity.

Key words: Breast; Cancer; Ectopic; Accessory; Supernumerary; Chest wall.

Introduction

Ectopic breast cancer is rare and in the majority of cases reported, has been located in axillary breast tissue and, less frequently, in the chest wall and vulva [1-11]. To the best of our knowledge, only 12 cases of ectopic breast cancer located in the chest wall have been reported on Medline between 1966 and 2007, six of which were described by Marshall et al. [2] in a review article. In view of the scarcity of reports on this subject, we would like to add one more case of ectopic breast carcinoma located on the chest wall of an 86-year-old patient, and to provide a literature review on the subject.

Case Report

An 86-year-old Brazilian woman, gravida 16, para 16, with an ectopic breast nodule located on the right inframammary fold, was admitted to the Mastology Department of the Getúlio Vargas Hospital of the Federal University of Piauí in April 2005, reporting a lesion that had appeared four months previously. The nodule became painful and grew progressively in size. It was associated with erythema, pruritus and a papillary flow that was serous in appearance. She reported having observed spontaneous milk secretion from the ectopic breast when she had breastfed her 16 children. At physical examination, the presence of a nodule of hardened consistency with imprecise borders was found, with a skin edema in the right inframammary fold (Figure 1). Hardened lymph nodes were detected in the ipsilateral axilla, which were clinically positive inframammary fold (Figure 1). Hardened lymph nodes were detected in the ipsilateral axilla, which were clinically positive for malignancy. There was no sign of infra- or supraclavicular lymphadenopathy and mammography of the topic breasts detected no abnormalities. Ultrasonography (US) of the ectopic breast revealed a solid, hypoechoigenic nodule measuring 2.5 x 1.2 x 1.1 cm with irregular contours and a posterior acoustic shadow. Histological examination of the biopsy sample showed a well-differentiated, infiltrating ductal carcinoma of the ectopic breast (Figure 2). Immunohistochemistry revealed positivity for estrogen and progesterone receptors. Radiography and computed chest tomography, transabdominal US, transvaginal US and bone scintigraphy detected no abnormalities; hence, the diagnosis was ectopic breast carcinoma, clinical Stage IIIb. The patient was submitted to resection of the ectopic breast and to right axillary lymphadenectomy. Anatomopathology of the sample showed invasive ductal carcinoma, the resected borders of which were unaffected; however, metastases to the 28 resected axillary lymph nodes were found. The patient and her family refused the recommended local-regional radiotherapy and endocrinotherapy with tamoxifen, and the patient died three months later, after suffering a stroke.

Discussion

Ectopic breast tissue is the result of a failure in the embryonic milk lines, two parallel ectodermal thickenings that extend from the axilla to the groin. Failure of any portion of these lines anywhere along the ridge to involute may result in polymastia or polythelia [2]. Histologically, the classification of ectopic breast consists of two types, supernumerary breasts and aberrant breast tissue [2, 3]. The supernumerary breast has an organized duct system connected to its overlying skin, whereas aberrant breast tissue is an island of breast tissue located close to the normal breast [2]. Other authors have described the supernumerary breast as having a nipple or areolar formation or both, with or without glandular breast tissue, unlike aberrant breast tissue, which consists of ectopic breast tissue without the nipple or areolar complex [3]. The present case consisted of a supernumerary breast, since the ectopic glandular breast had nipple and areolar formation.

The incidence of supernumerary breasts varies between 0.6 and 6% in women of various ethnic groups [2]. Supernumerary breasts not only undergo the same physiological processes as the normal breast but are also subject to the same diseases [1-12]. Nevertheless the incidence of carcinoma in an ectopic breast is somewhat rare.

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Incidentally, aberrant breasts have a greater tendency to malignant transformation compared to normal breast tissue; however, this is rare in supernumerary breasts [2]. The majority of tumors in ectopic breast tissue are located in the axilla (71%) compared to 29% in other sites [3]. A review carried out by Marshall et al. [2] showed that 58% of ectopic breast cancers are located in the axilla and 35.7% in the chest wall, 8.6% of these being in the submammary region. According to Nakao et al. [5], location in the inframammary region, as in the present case, is uncommon and represents less than 5.5% of the tumors located in the chest area. Therefore, breast carcinomas located in the chest wall are very rare and to the best of our knowledge, only 12 cases of breast cancer occurring in ectopic breast tissue in the chest wall have been reported on Medline between 1966 and 2007 [1, 2, 4, 6-9]. The size of the tumor varies from 0.8 to 7 cm and the age of these patients ranges from 39 to 81 years [1, 2, 4, 6-9]. At 86 years of age, the patient in the present case is the oldest reported in the literature.

The diagnosis of cancer in ectopic breast tissue should be suspected in all ectopic breast or abnormal tissue in the chest area, particularly if it is located in the mammary line and when abnormalities such as progressive growth, pain or inflammation are present [2]. In the cases reviewed, the patients only sought medical aid after detecting abnormalities in the ectopic breast tissue, the symptoms most commonly reported being localized pain and the appearance of progressively growing nodules [1, 2, 4, 6-9]. These two symptoms were also the motivating factor for the patient described in this case report to seek specialized medical care. Histological confirmation may be carried out using minimally invasive techniques such as fine needle aspiration or more aggressive procedures such as core biopsy or incisional biopsy [4]. Once diagnosis is established, clinical evaluation, and mammography and US of the topic breast should be carried out to confirm that the cancer is primary of the ectopic tissue and not metastasis from a tumor in one of the topic breasts.

Ectopic breast cancer should be treated in the same way and following the same criteria as topic breast cancer [2]. In the present case, axillary lymphadenectomy was performed due to the presence of palpable lymph nodes indicative of metastatic disease. There is no need to perform mastectomy of the homolateral breast, since, according to reports from other authors on the treatment of cancer in ectopic breast tissue, this does not alter the prognosis [2, 3]. Ectopic breast cancer has a poor prognosis compared to topic breast cancer because diagnosis generally occurs later, particularly in asymptomatic, aberrant ectopic tissue, since this is not submitted to screening [2]. Marshall et al. [2] found ipsilateral axillary lymph node metastases in 46% of patients with cancer arising in aberrant breast tissue. In the present case, the homolateral breast was normal; however, all the axillary lymph nodes removed were affected despite the relatively small size of the tumor, also suggesting a tendency for early metastasis in these tumors.

No specific literature reviews have been carried out on the survival of patients with ectopic breast cancer located in the chest wall, principally due to their rarity. Evans et al. [3] reviewed 42 cases of axillary ectopic breast carcinoma and showed that 28 patients (66.7%) survived longer than one year but only six patients (14.3%) were still alive and free of the disease after four years of follow-up. In the present case, the patient refused any additional treatment following surgery and died a few months later as a result of a cerebral vascular accident. Nevertheless, the disease appeared considerably aggressive and advanced at the time of diagnosis, which underlines the importance of detection and examination and even excision of ectopic breast tissue.
Ectopic breast cancer in the anterior chest wall: a case report and literature review

References


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Primary endometrial B-cell lymphoma: case report

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Summary

The female genital tract is usually involved with lymphoma as part of disseminated disease. Primary lymphoid neoplasms of the female genital tract are rare; the frequency was reported to be 2% among extranodal lymphomas in women. Most of the time, primary female genital tract lymphoma occurs in the ovary and cervix, whereas endometrial lymphoma is extremely rare. The case of an 89-year-old patient that presented with postmenopausal bleeding is reported. An endometrial polypoid formation was found on hysteroscopic examination and the biopsy revealed a diffuse large B-cell lymphoma. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were surgically performed. The histologic diagnosis was primary diffuse large B-cell lymphoma of the endometrium. Adjuvant therapy was not performed. Five months after initial diagnosis, the patient died. Only a few case reports of primary endometrial lymphoma have been published; therefore, information concerning etiologic factors, histologic type, treatment and prognosis is limited.

Key words: Endometrial lymphoma; Endometrial neoplasms; Lymphoma; Diffuse large B-cell lymphoma.

Introduction

Primary extranodal lymphoma is common and can occur in a wide variety of organs. However, primary lymphomas rarely involve the female genital tract, making lymphoma of the endometrium extremely rare [1, 2]. We report a case of primary lymphoma of the endometrium, diffuse large B-cell type.

Case Report

An 89-year-old female presented to our department with postmenopausal bleeding of a few days duration; she denied any other symptoms, including pelvic pain, weight loss or fever. Her past medical history included a stroke 17 years before; currently she had hypertension. Menarche occurred at 13 and menopause at 48 years of age, with no bleeding since then. She had had two spontaneous vaginal deliveries and no history of abortion. There was no case of malignancy in her family. Pelvic examination was normal, except for the presence of blood in the vagina. Transvaginal ultrasound (TVS) revealed an endometrial polyp with increased blood flow, suggestive of endometrial malignancy. The patient underwent hysteroscopic examination, which showed a polypoid formation with abnormal vascularisation. The biopsy of this mass was not sufficient for histologic diagnosis, which led to surgical hysteroscopy. Several biopsies were performed revealing the presence of a diffuse large B-cell lymphoma.

Once this diagnosis was made, the assistance of a hematologist was required for evaluation and treatment of the patient. There was no clinical evidence of systemic disease and a preoperative staging evaluation was undertaken. Complete blood count, iron studies, coagulation profiles and serum chemistry, including serum lactate dehydrogenase, were normal. Serum protein electrophoresis and serum b2-microglobulin were also normal. HIV and hepatitis screens were negative. Bone marrow biopsy was also negative. Chest radiograph, gallium scan and computed tomography (CT) scan of the neck, chest and abdomen showed no evidence of disease; the CT scan of pelvis showed only an enlarged endometrium.

The patient underwent exploratory laparotomy with total abdominal hysterectomy and bilateral salpingo-oophorectomy. Intraoperative findings were normal; there were no enlarged or palpable suspicious pelvic or paraaortic lymph nodes. There were no complications postoperatively. Adjuvant therapy was not administered. An International Prognostic Index (IPI) score of 1 was attributed to the patient. At first follow-up, three months after surgery, the patient remained free of systemic disease. Five months after surgery, the patient died as a consequence of bowel obstruction.

Histopathology

Macroscopically, an endometrial mass was found protruding into the cavity measuring 3.5 x 4.5 cm, friable with a yellow surface, 1.5 cm distance from the serosa; no other anomalies was noted on gross examination of the surgical specimen (Figure 1). Histologic examination revealed a tumor composed of sheets of pleomorphic cells, with large nuclei, thin chromatin and numerous nucleoli, which were arranged in both centroblastic and immunoblastic types (Figure 2). Tumor cells were disposed in a diffuse pattern and no nodes were observed. The neoplasm was well delimited and the surrounding endometrium was noted to be atrophic. The myometrium presented with superficial infiltration and large compression by tumor (Figure 3). Immunohistochemical studies revealed the B-cell nature of the neoplasm, showing positive staining for CD79A and CD20 with no reactivity for CD10, bc12 and bc6. Immunoreactivity for Ki67, representing the proliferative activity of the tumor, was present in about 50% of the cells. There were no neoplastic cells in the uterine cervix or adnexa. Histopathological diagnosis was primary diffuse large B-cell lymphoma of the

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endometrium. Pathological staging, according to the Ann Arbor staging system was Stage IE and according to FIGO it was Stage IB.

Discussion

Secondary involvement of the female genital tract by disseminated lymphoma is not unusual, but primary lymphoid neoplasms arising at this site are rare. The frequency of primary lymphomas of the female genital tract in Western countries was reported to be 2% among extranodal lymphomas in women [1, 2]. The ovary constitutes the most common primary location in the female genital tract [3]. Among uterine lymphomas, the cervix is the most involved site, whereas lymphoma of the endometrium is extremely rare [4, 5]. A review of the English literature shows a few case reports of primary endometrial B-cell lymphoma [1, 4-10] and only two cases of primary T-cell lymphoma of the endometrium [11, 12]. In a large recent series, reported by Lagoo and Robboy [10], 186 malignant lymphomas involving the female genital tract are described, six being primary diffuse large B-cell lymphomas of the uterine corpus. Harris and Scully [5] have published a study including 22 cases of primary lymphoma of the uterus, in which only two cases originated from the endometrium. In another study, reported by Vang et al. [6], in a series of 26 lymphomas involving the uterus, ten cases were presumed to be primary and only one did not involve the cervix. Additionally, Aozasa et al. [1] reported one case of primary lymphoma of the uterine corpus in a total of seven malignant lymphomas of the uterus.

The etiology of primary B-cell lymphoma of the endometrium is unknown. However, chronic inflammation, frequently with lymph follicle formation, has been associated with several types of extranodal B-cell lymphoma [13, 14]. The endometrial lymphoid tissue is a regionally specialized component of the immune system that plays a role in local immune surveillance, implantation, immunosuppression, cytokine-induced placental development in early pregnancy and regulation of endometrial epithelial proliferation [15, 16]. Possibly, unknown antigenic stimuli can induce a chronic B-cell response within the endometrial lymphoid tissue, leading to clonal B-cell proliferations, similar to what occurs with Helicobacter-induced chronic gastritis and gastric MALT lymphoma [4].

Because of important differences in therapy and management, other neoplasms, as well as benign proliferations that can simulate lymphoma, must be considered...
in the differential diagnosis of primary diffuse large B-cell lymphoma. These include small cell carcinoma, endometrial stromal sarcoma, granulocytic sarcoma, neuroectodermal tumor, melanoma and chronic endometritis [5, 17].

The number of case reports and case series are so limited that a standard treatment is difficult to define for primary uterine lymphoma. Treatment modalities reported in the literature include surgery alone, radiation alone, chemotherapy alone or a combination of these therapies [1, 5, 6, 18]. The management of this neoplasia is individualized and depends not only on the patient and the tumor itself, but also on factors like the experience of the institution and the available facilities and resources. However, the initial treatment of all patients with diffuse large B cell lymphoma should include a combination chemotherapy regimen [19].

In our case, adjuvant therapy was not performed given the fact that the tumor was completely excised, that there was no evidence of metastatic disease, and especially due to the fact that the tumor was completely excised, that there was no evidence of metastatic disease, and especially due to the fact that the tumor was completely excised.

The prognosis of uterine lymphoma is considered to be relatively favourable when the disease is in early stage and treated properly [1, 5], being best assigned using the IPI, which is a powerful predictor of outcome in all sub-types of non-Hodgkin’s lymphoma.

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Sclerosing stromal tumor of the ovary: a case report

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Summary
A case of a rarely occurring ovarian tumor, sclerosing stromal tumor of the ovary, in an 11-year-old girl treated laparoscopically is described.

Key words: Sclerosing stromal tumor; Ovary; Child.

Introduction
Sclerosing stromal tumor (SST) of the ovary is a rare benign neoplasm, originally described by Chalvardjian and Scully in 1973 [1]. Unlike other sex-cord stromal tumors of the ovary, which tend to occur in the fifth and sixth decades, SST of the ovary predominantly affects young women. Only two affected patients have been reported in children less than 14 years old [2, 3].

We present a case of SST of the ovary in a 11-year-old girl, third youngest patient reported in the literature to date.

Case Report
An 11-year-old postmenarchal girl first presented to her pediatrician with groin pain. On sonographic examination she was reported to have an uniloculated cystic mass of the left ovary, and was referred to our clinic for further evaluation. She had a history of sharp left groin pain which had woken her up that morning. She had no fever, malaise, weight loss, gastrointestinal or urinary symptoms. Her past medical history was unremarkable, and her family history did not show familial cancer. She denied any present or past medications. Physical examination revealed tenderness and rebound tenderness of the abdomen, with no palpable mass. The patient was Tanner III without evidence of virilization.

Ultrasonography demonstrated a left adnexal cyst measuring 65 x 37 x 40 mm with an 11 mm capsular thickness. Her uterus and right ovary were normal in sonographic appearance, but covered with peritoneal fluid, and the left ovary could not be demonstrated.

The patient underwent laparoscopy. The cul-de-sac was filled with haemorrhagic serous fluid. Her uterus, right ovary and both Fallopian tubes were unremarkable. There were no adhesions in the pelvis or masses in the liver, spleen, or peritoneum. The cyst originating from the left ovary was ruptured, and the cystic space was filled with blood clots. The cyst capsule was completely excised and sent for frozen section. Microscopic analysis was benign stromal tumor.

The excised cyst was composed of shiny white membranous tissue with scattered areas of hemorrhage. Microscopically the tumor showed a pseudolobular pattern in which cellular nodules were separated by less cellular areas of edematous connective tissue. There were areas of sclerosis within the nodules, prominent thin-walled vessels in some of the nodules, and a disorganized admixture of fibroblasts and rounded and vacuolated cells within the nodules (Figure 1). Mitoses were rare. No cytologic evidence of malignancy was seen.

The postsurgical recovery was uneventful, and the patient was discharged on the following day. She has been examined regularly for three years with no evidence of recurrence.

Discussion
SST of the ovary is a subtype of sex-cord stromal tumors, which has been reported to be benign and unilateral in nature [1]. However two cases of bilateral SST of the ovary have been reported [3, 4]. These ovarian tumors can be distinguished clinically by their early age of presentation. This report of an 11-year-old girl with SST follows two other cases describing a 10-year-old female with unilateral SST [2] and an 11-year-old with bilateral SST [3].

Most SSTs of the ovary are hormonally inactive, and they were originally considered to be nonfunctional tumors [1], but some investigators have described endocrine alterations caused by secretion of steroid hor-
mones [5, 6]. Being an emergent case, our patient was not investigated hormonally, nevertheless, she did not display any signs of virilization. Symptoms usually present with a pelvic tumor such as pelvic pain, a palpable pelvic mass, and menstrual irregularities were absent in our patient.

SSTs of the ovary are benign and can be successfully treated by surgical removal, and no local or distant recurrences have been reported [1]. Because ovarian malignancies are uncommon in the pediatric population, a cystectomy should be appropriately considered in any suspected ovarian lesion with particular effort to preserve future fertility. Biopsy of a normal appearing contralateral ovary would not be indicated because of the rarity of bilateral SSTs of the ovary.

References
Conservative management of a patient with endometrial carcinoma desiring fertility: how to inform?

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Summary
Conservative management of patients with endometrial cancer who desire fertility is becoming widespread in certain circumstances. A 36-year-old woman desiring fertility with early-stage endometroid type adenocarcinoma of the endometrium was treated with 160 mg/d megestrol acetate for six months. After confirmation of a normal endometrial biopsy she became pregnant spontaneously. Following an uneventful pregnancy a healthy baby at term was delivered by cesarean section. Definitive surgery was performed. The risks and benefits of this therapeutic approach are discussed and informing style of the patients emphasized.

Key words: Endometrial carcinoma, Conservative management, Patient information.

Introduction
Carcinoma of the endometrium is the most common female pelvic malignancy worldwide. Although primarily seen in postmenopausal women, disease may occur in childbearing age. It is well known that 3-5% of affected women are 40 years old or younger [1]. Another fact is that age at first pregnancy, especially in developing countries, is increasing due to the lifestyle of modern women. Thus the number of younger women with endometrial carcinoma desiring fertility preservation may be expected to increase. As a consequence, conservative management of endometrial cancer for a selected group of young women desiring fertility will be a challenging alternative to traditional surgical management in the future. However the optimal conservative management methodology has not been well formed by evidence in medicine yet. Many case reports and reviews addressing the subject comprise the indications for management. Although the medical treatment approach for young patients is very appealing, it should be remembered that the data are from small series or case reports, with short follow-up.

We present a case managed conservatively following the choice of an appropriately informed patient.

Case Report
A 36-year-old patient (gravida 1, para 1) was referred to our clinic following abnormal dilatation and curettage (D&C) with abnormal pathology. She was examined due to amenorrhea following regular menses. Gynecological examination revealed normal genital findings and transvaginal ultrasonography (US) demonstrated normal genital sonography except for endometrial fluid accumulation with a small echogenic mass inside. The endometrium was also noted as normal and regular in the sonographic documentation. Minimal endometrial tissue was obtained during the D&C procedure. Pathology, which was reviewed and confirmed by an expert gynecologic-pathologist, demonstrated endometroid-type adenocarcinoma or polyps showing atypical adenomatous hyperplasia. The woman was referred to us due to her desire to preserve further fertility.

She had an unremarkable medical and family history. On physical exam, the patient weighed 75 kg, and had a body mass index (BMI) of 26 kg/m2. Her general physical examination was unremarkable. No remarkable finding was observed on genital examination or transvaginal US during the initial evaluation. A Pap smear was within normal limits. Abdominopelvic magnetic resonance imaging (MRI) showed normal findings except for a minimally irregular endometrium with no signs of myometrial invasion. No cervical involvement was detected at MRI. CA-125 level were in normal range. Hysteroscopic endometrial evaluation and sampling were performed. Treatment options, risks, and success rates were explained and the patient preferred conservative management.

She was treated with megestrol acetate (Megace) with a daily dose of 160 mg for six months. The endometrial cavity was serially controlled by sonography during each visit. Two control hysteroscopies with endometrial sampling were performed after three and six months following initialization of medication. The endometrial cavity was observed to be regular during the controls. Hysteroscopy and pathologic results of endometrial samples were within normal ranges.

Ovulation induction was offered to the patient to obtain a pregnancy but she preferred spontaneous follow-up. She got pregnant after six months following cessation of medication. Following an uneventful pregnancy, a healthy baby at term was delivered by cesarean section. At the fourth postpartum month, the patient was examined and informed about risks and possible management options for the subsequent period. She opted for surgery at this point and total abdominal hysterectomy and bilateral salpingo-oophorectomy with bilateral pelvic lymph node sampling and partial omentectomy were performed. Pathologic examination of specimens showed proliferative endometrium and normal omentum, and seven lymph nodes obtained during sampling were normal.
Discussion

Conservative treatment has been increasingly chosen by most premenopausal women with endometrial carcinoma who have a strong desire to bear a child. This tendency is probably caused by a lack of nondirectional approaches of physicians under the guidance of successful consequences of several case reports and by patients’ irresistible desire to have a baby. The question is whether the patients are sufficiently and correctly informed. While informing a woman with endometrial carcinoma who has a strong desire for pregnancy, all clinical data must be sufficiently and correctly stressed in a way the patient can understand clearly.

Cell type, myometrial invasion and histologic grade are the main prognostic factors for patients who choose conservative fertility-preserving treatment. We offered conservative management to our patient because of the fact she was in early-stage and well differentiated endometroid cells were observed in the pathologic specimens.

Risk of pelvic and paraaortic lymph nodes and ovarian involvement and a consequence of such involvement in grade I tumors must be explained in detailed fashion. Creasman et al. showed that 2.8% of all grade I lesions have pelvic node involvement and 1.7% paraaortic node involvement [2]. Moreover, they showed 6% adnexal spread of tumors in clinical Stage I and occult in Stage II patients. It should be kept in mind that endometrial cancer is a surgically staged disease because only cell type and grade can be determined before hysterectomy. In a comparison of preoperative findings with surgical pathology, tumor histology was changed in 27% of patients, tumor grade was changed in 34% of patients, and the stage was changed in 51% of patients. Patients must be informed about possible errors in preoperative clinical staging.

Risk of probable coexisting ovarian and colorectal cancer and difficulties in early detection of such tumors should also be stressed. Crissman et al. [3] reported six of 32 (19%) patients had coexisting ovarian neoplasms. Mutations in the MSH2 and MLH1 genes increase the risk of endometrial carcinoma. These mutations are also associated with an increased risk of colorectal cancer [4]. Patients must be informed that for early detection of these tumors rigorous and expensive evaluations are required and diagnoses of these tumors may be delayed until symptoms appear.

Patients also need to be informed about evaluation methods in the pretreatment period and the period of treatment or follow-up such as CA-125 values, endometrial sampling, D&C, HS, US, CT and MRI, and the accuracy of these methods before conservative therapy. No study has addressed the role of CA-125 in conservative management. Powell et al. reported that sensitivity and specificity of a preoperative CA-125 cutoff level of 35 U/ml were 63% and 88%, respectively, with a positive predictive value of 61% and negative predictive value of 89% [5]. A steady correlation between an endometrial biopsy and D&C in the diagnosis of endometrial cancer has not been shown in the literature. Office endometrial biopsy may be unable to diagnose the disease. Even D&C may miss the focal endometrial carcinoma located at the tubal cornua. Bettocchi et al. [6] report that five of 15 cases of focal endometrial carcinoma located at the tubal cornua and four of 20 cases of complex hyperplasia were missed by curettage, and were subsequently found at hysterectomy. In another study, Stock et al. [7] found that less than one-half of the uterine cavity was curetted in 60% of cases and less than one-fourth in 16%. A recently published meta-analysis on radiologic staging in patients with endometrial cancer reported no significant difference in the overall performance of CT, US and MRI. However, contrast-enhanced MRI performed significantly better in the evaluation of myometrial invasion than non-enhanced MRI or US [8]. Endometrial carcinoma, especially in early stages, may be missed in diagnostic imaging studies and this probability must also be explained to the patient.

Choices of drugs that can be used in treatment, probable side-effects of these drugs, and lack of the data comparing dosages and the effects of drugs on disease and subsequent fertility need to be stressed. Medroxyprogesterone acetate (MPA) at a dose of 100-800 mg/day and Megace at a dose of 40-160 mg/day are the most commonly used regimens in treatment. An alternative and uncommonly used method is a combination of tamoxifen and progesterin to promote induction of progesterone receptors, and thus overcome the possible down-regulation of progesterone receptors, by continuous administration of progesterone alone. Although there is currently no consensus as to which progesterone to use, nor to the dose and length of treatment, it appears that 62-75% of women with clinical Stage I, well differentiated adenocarcinoma will respond well to progestational therapy within three to nine months of initiation of treatment [9]. Patients also should be informed about the possible cost and need for ovulation induction with drugs after regressions and lack of data about the effect of these drugs on the disease. Although the risks of ovulation induction drugs are unknown at this point, Benshushan et al. found no evidence that the use of ovulation induction agents, including clomiphene citrate, were associated with a higher risk of endometrial carcinoma [10].

In conclusion, the most important step after initial evaluation in the management of women with endometrial carcinoma who have a strong desire for pregnancy is giving the correct and enough information about the disease. Directional, insufficient, and incorrect counseling may often lead to medicolegal situations.

Although there are no standard recommendations for the selection of appropriate women, treatment protocols, or long-term surveillance for the conservative management of clinical Stage I endometrial adenocarcinoma endometroid-type histology, well differentiated tumor and strong patient motivation are clearly necessary.
References


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Life-saving hysterectomy in choriocarcinoma: presentation of two cases

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Summary

Background: Choriocarcinoma is a malignant tumor of the placenta. Life-saving hysterectomy was performed in two cases with choriocarcinoma who had profuse vaginal bleeding. Case 1: A 25-year-old, gravida 3, para 1, woman was referred to our emergency clinic with the diagnosis of choriocarcinoma and massive vaginal bleeding. She had been transfused seven units of blood at the hospital where she was first admitted. Pelvic examination demonstrated heavy vaginal bleeding and a uterus equivalent to the size of 14 weeks of gestation. Her β-hCG level was 560,000 mIU/ml. Despite four units of blood transfusion, she had a pulse rate of 130/min, arterial pressure of 90/60 mmHg and HCT of 19%. An emergency hysterectomy with vertical incision was performed. Case 2: A 54-year-old, gravida 3, para 3, woman was referred to our clinic with heavy bleeding with the diagnosis of choriocarcinoma. She was scanned to look for possible metastases and pulmonary metastasis was detected. Chemotherapy was planned but as sudden vaginal bleeding began she was referred to the Gynecology Department. At pelvic examination a soft uterus the size of 20 weeks of gestation was palpated. The β-hCG level was 554,700 mIU/ml. Due to hemodynamic instability and continuous vaginal bleeding an emergency hysterectomy was performed. Conclusion: Although chemotherapy is the cornerstone of treatment for choriocarcinoma, optimal treatment results may depend on the addition of surgery in selected circumstances. Hysterectomy is indicated in cases with life-threatening hemorrhage.

Key words: Hysterectomy; Choriocarcinoma; Massive hemorrhage.

Introduction

Choriocarcinoma is a malignant and aggressive tumor of the placenta. It belongs at the far end of the spectrum of gestational trophoblastic neoplasias (GTN) [1]. The cornerstone of treatment is chemotherapy but in cases when massive hemorrhage occurs, life-saving hysterectomy should be performed [2, 3]. We present two cases which were managed with hysterectomy due to massive hemorrhage.

Case Reports

Case 1: A 25-year-old gravida 3, para 1 woman was referred to our emergency clinic with the diagnosis of choriocarcinoma and massive vaginal bleeding. In her obstetrics history there had been pregnancy termination because of an anembryonic pregnancy six months before. She had been transfused seven units of blood at the hospital where she was first admitted. Pelvic examination revealed heavy vaginal bleeding and a uterus the size of 14 weeks of gestation. Human chorionic gonadotropin (hCG) level was 560,000 mIU/ml. Despite four units of blood transfusion, she had a pulse rate of 130/min, arterial pressure of 90/60 mmHg and HCT of 19%. An emergency hysterectomy with vertical incision was performed. Computed tomography (CT) scan of the abdomen, thorax and the brain was within normal limits. The patient was discharged from the hospital on the fourth postoperative day and referred to the Oncology Department because of high-risk metastatic GTN.

Case 2: A 54-year-old gravida 3, para 3, woman was referred to our clinic with heavy bleeding with the diagnosis of choriocarcinoma. She was scanned to look for possible metastases and pulmonary metastasis was detected. A chemotherapy regimen consisting of EMACO (etoposide, methotrexate, actinomycin, cyclophosphamide, and vincristine) was planned but as sudden vaginal bleeding began she was referred to the Gynecology Department. At pelvic examination a soft uterus the size of 20 weeks of gestation was palpated and the hCG level was 554,700 mIU/ml. Due to hemodynamic instability (HCT 17%, arterial pressure of 90/50 mmHg, pulse rate 130/min) and continuous vaginal bleeding an emergency hysterectomy with bilateral salpingo-oophorectomy was performed. After recovery the sixth postoperative day, she was referred to the Oncology Department for chemotherapy.

Discussion

Choriocarcinoma is a malignant and aggressive cancer of the placenta. The frequency is one in 30,000 pregnancies in the west and one in 11,000 in oriental communities [4]. It is characterized by early hematogenous spread to the lungs. It belongs at the far end of the spectrum of gestational trophoblastic diseases. Choriocarcinoma is a highly chemosensitive tumor. The cure rate, even for metastatic choriocarcinoma, is around 90-95% [5, 6]. The chemotherapy regimen includes EMACO. Although chemotherapy is the cornerstone of treatment [7, 8], the addition of surgery and irradiation in selected cases may be necessary for optimal treatment.

Hysterectomy may play a primary role in the management of non-metastatic or low-risk metastatic gestational trophoblastic disease. Hysterectomy provides several advantages in the management of choriocarcinoma. It may
reduce the side-effects and dosage of chemotherapy. Not only does it reduce the complications of chemotherapy, but it also increases the probability of cure. Hysterectomy makes it possible to resect the residual tumor or isolated metastasis completely. It is also essential to perform surgery in the management of chemo-resistant tumors [9]. Hysterectomy can be offered to patients over 40 years of age without fertility desire. Surgery is also indicated in cases of life-threatening hemorrhage. Severe uncontrollable vaginal or intra-abdominal bleeding from gestational trophoblastic disease may occasionally necessitate hysterectomy as an emergency procedure [10].

Pisal et al. [10] evaluated the value of hysterectomy in the management of gestational neoplastic disease. They performed hysterectomy in 40 patients out of 5,976 patients with the diagnosis of GTN between 1986-2000. Indications for hysterectomy included uncontrollable vaginal or intra-abdominal bleeding in 12 cases, and localized chemo-resistant disease or placental site trophoblastic tumor for the remaining patients. Also Flam [2] reported that in 92 patients treated for GTN at one institution, ten patients (11%) were subjected to invasive surgery, for the most part because of life threatening hemorrhage. In a recent paper, Tse et al. [3] reported their experience on 17 patients with the diagnosis of GTN attending their center with profuse bleeding over 20 years. Eleven patients had total abdominal hysterectomy with or without bilateral salpingo-oophorectomy (TAH ± BSO), two had arterial ligation, three had embolization, and one had suturing of a vaginal defect due to a metastatic nodule.

In our first case, sudden heavy vaginal bleeding occurred that could not be controlled with massive transfusion and tightly placed vaginal tampons. In her obstetrics history there had been pregnancy termination because of an amnionic pregnancy six months before. She had one healthy child so a hysterectomy was more accepted by the patient.

Even though our second case was 54 years old she was still menstruating with an irregular pattern. Although a demonstrable pregnancy was not detected massive vaginal bleeding started following a period of two months of amenorrhea. Hysterectomy for choriocarcinoma would be a difficult procedure. Involvement of the adjacent visceral organs and blood vessels, presence of arteriovenous malformations and a compromised hemodynamic status due to severe blood loss could complicate the procedure. Therefore the optimal situation providing experienced surgeons and anesthetists, and postoperative intensive care units should be mandatory. As mentioned above hysterectomy of the second patient could be performed with great difficulty due to a very large uterus (size of 20 weeks of gestation), widespread adhesions and obesity of the patient. In the postoperative period she was followed in the intensive care unit.

In cases over 40 years of age chemotherapy may be tried first to control the vaginal bleeding if possible. It reduces the vascularity and makes the surgery easier [11]. It should be kept in mind that severe vaginal bleeding may also occur during the first course of chemotherapy.

There are some other life-saving operations performed for choriocarcinoma [12]. Emergency laparotomy and resection of a bleeding tumor may be necessary in gastrointestinal bleeding or bleeding from liver or splenic metastases. Craniotomy may be required to relieve rising intracranial pressure due to brain metastasis or hemorrhage.

In conclusion, although the primary therapy of choriocarcinoma is chemotherapy and the cure rate, even for metastatic choriocarcinoma, is very high, hysterectomy should be applied in life-threatening situations such as profuse vaginal bleeding compromising the patient’s hemodynamic status.

References


Metastasis from breast carcinoma to endometrial polyp

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Summary

Metastasis of a breast carcinoma to an endometrial polyp is extremely rare, with only ten cases having been reported in the literature up to now. We present the case of a 60-year-old woman with invasive ductal carcinoma who complained of vaginal bleeding. She underwent hysteroscopy with biopsy. Microscopic examination revealed an endometrial polyp which contained foci of adenocarcinoma. The morphologic features of the tumor were identical to the original breast carcinoma.

Key words: Breast carcinoma; Metastasis; Endometrial polyp.

Introduction

Breast carcinoma frequently metastasizes to the ovaries; however, metastasis to the uterus is less common and to an endometrial polyp is extremely rare [1, 2]. A review of the literature revealed ten previously reported cases of breast carcinoma metastasizing to an endometrial polyp [2-10].

We report a case of metastatic invasive ductal carcinoma to an endometrial polyp and review the literature.

Case Report

A 60-year-old woman presented with generalized bone pain to Cerrahpasa School of Medicine Department of Endocrinology. At the initial evaluation she was found to have hypercalcemia with a serum calcium level of 13 mg/dl accompanied by multiple bone metastases detected by bone scan. Bilateral mammogram revealed primary cancer in the left breast. Incisional biopsy showed moderately differentiated invasive ductal carcinoma (Figure 1). Hormone receptor status was strongly positive for both estrogen and progesterone receptors. Computed tomography (CT) scan examination of the chest, abdomen and brain were all negative for tumor. Hypercalcemia resolved after appropriate treatment with isotonic NaCl perfusion, furosemide and steroids, as well as IV infusion of pamidronate 90 mg/q/3 weeks. She was also treated with palliative radiotherapy to the affected lumbar vertebrae, accompanied with severe back pain. Tamoxifen (20 mg daily) was started for hormone receptor-positive metastatic disease. Eight months following the initiation of tamoxifen, the patient complained of vaginal bleeding. Vaginal ultrasound and hysteroscopy revealed a polypoid mass appended to the uterine dome. The polypoid mass was removed and endometrial curettage was performed. The mass measured 6.5 x 3 x 2.5 cm. On the cut surface, numerous small cystic structures ranging from 1-2 mm to several centimeters in diameter were seen. Microscopic examination showed an endometrial polyp containing irregularly scattered glandular structures, many of which were cystically dilated, set in a fibrovascular stroma. There were also foci of adenocarcinoma forming abortive glandular structures, cribriform patterns and small nests in some areas within the polyp stroma (Figures 2 and 3).

The tumor cells had large vesicular nuclei with prominent nucleoli and a moderate amount of eosinophilic cytoplasm. The vascular spaces within the stroma were filled with tumor cells. The histopathologic features of the tumor were identical to the original breast carcinoma. Histology of the endometrial curetage apart from the endometrial polyp displayed atrophic endometrium with no tumor infiltration. At the time of this biopsy the patient had already developed multiple liver metastases and bilateral pleural effusion, accompanied by progression of the local disease in the breast. She was then treated with a combination chemotherapy regimen of cyclophosphamide, 5-fluourouracil and methotrexate (CMF) with no response. Due to progressive disease the chemotherapy was switched to anastrozole 1 mg daily. However, two months following anastrozole treatment, she died of progressive disease.

Discussion

Malignant tumors metastatic to the female genital tract usually originate from the breast, stomach and colon. The ovary and vagina are the most frequent metastatic sites for these tumors [1, 2]. In the uterus, the metastatic process most commonly involves the myometrium rather than endometrium. Endometrial deposits, though rare, are more likely to be symptomatic, presenting with vaginal bleeding which may be mistaken as a complication of the tamoxifen [2]. Thus, patients with breast carcinoma suffering from vaginal bleeding should be examined to exclude metastatic involvement of the endometrium. Metastasis to an endometrial polyp is extremely rare, and to the best of our knowledge, there are only ten cases of metastatic breast carcinoma involving endometrial polyps [2-10]. The details of these cases and of our case are shown in Table 1.

Invasive lobular carcinoma of the breast is most likely to metastasize to the female genital tract. The histologic types of the previously reported ten cases of breast carcinoma metastasizing to an endometrial polyp were lobular in five cases, ductal in four, and apocrine in one. In seven of these cases, the endometrial polyp appears to have been tamoxifen-associated. It was not stated in the other three reports whether the patients were taking tamoxifen [2-10].
Metastasis from breast carcinoma to endometrial polyp

Since distant metastases of breast carcinoma occur through arterial dissemination, the detection of uterine involvement is usually a reflection of advanced disease and widespread metastases as in our case. However, there are some exceptions in which only uterine metastasis is seen [11]. The interval time between initial diagnosis of breast carcinoma and the detection of an endometrial polyp metastasis has ranged from three to 72 months [2-10].

In conclusion, it is important to consider metastatic tumors in the evaluation of vaginal bleeding in patients with known breast carcinoma. Because of the possibility of involvement of endometrial polyps by metastatic carcinoma, pathologists should examine such polyps carefully and extensively.

References

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In conclusion, it is important to consider metastatic tumors in the evaluation of vaginal bleeding in patients with known breast carcinoma. Because of the possibility of involvement of endometrial polyps by metastatic carcinoma, pathologists should examine such polyps carefully and extensively.

Table 1. — Breast carcinomas metastasising to endometrial polyps: Review of the reports in the literature.

<table>
<thead>
<tr>
<th>Case</th>
<th>Author year of publication</th>
<th>Age (years)</th>
<th>Size of the endometrial polyp (cm)</th>
<th>Histologic type of breast carcinoma</th>
<th>Tamoxifen therapy</th>
<th>Time between primary tumor and endometrial polyp metastasis (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kumar et al. [2], 1983</td>
<td>55</td>
<td>NM</td>
<td>Invasive ductal</td>
<td>NM*</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Sullivan et al. [3], 1990</td>
<td>83</td>
<td>11.5</td>
<td>Invasive ductal</td>
<td>NM*</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>Corley et al. [4], 1992</td>
<td>58</td>
<td>NM*</td>
<td>NM*</td>
<td>+</td>
<td>NM*</td>
</tr>
<tr>
<td>4</td>
<td>Aranda et al. [5], 1993</td>
<td>76</td>
<td>9</td>
<td>Invasive lobular</td>
<td>NM*</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>Lambot et al. [6], 2001</td>
<td>70</td>
<td>1.5</td>
<td>Apocrine</td>
<td>+</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>Alvarez et al. [7], 2003</td>
<td>69</td>
<td>1.5</td>
<td>Invasive lobular</td>
<td>+</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>Houghton et al. [8], 2003</td>
<td>62</td>
<td>3</td>
<td>Invasive lobular</td>
<td>+</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>Houghton et al. [9], 2003</td>
<td>92</td>
<td>3</td>
<td>Invasive lobular</td>
<td>+</td>
<td>60</td>
</tr>
<tr>
<td>9</td>
<td>Acikalin et al. [9], 2005</td>
<td>58</td>
<td>5</td>
<td>Invasive ductal</td>
<td>+</td>
<td>48</td>
</tr>
<tr>
<td>10</td>
<td>Al-Brahim et al. [10], 2005</td>
<td>53</td>
<td>7</td>
<td>Invasive lobular</td>
<td>+</td>
<td>48</td>
</tr>
<tr>
<td>11</td>
<td>Current case</td>
<td>60</td>
<td>6.5</td>
<td>Invasive ductal</td>
<td>+</td>
<td>8</td>
</tr>
</tbody>
</table>

NM: Not mentioned.


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