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EUROPEAN JOURNAL OF GYNAECOLOGICAL ONCOLOGY (ISSN 0392-2936) publishes original peer reviewed works in the fields of female genital cancers and related subjects and also proceedings of gynecologic oncology society meetings all over the world. The Journal is covered by CURRENT CONTENTS, SCISEARCH, RESEARCH ALERT, INDEX MEDICUS, MEDLINE, EMBASE/Excerpta Medica, CURRENT ADVANCES IN CANCER RESEARCH, BIOSIS.
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A case of an ovary-preserving tumorectomy for immature teratoma in an adolescent is reported.
Tumour markers, ultrasonography, and ovarian cancer diagnosis

E.F.C. Murta

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Early diagnosis and/or prevention of ovarian cancer are still a problem. In a recent paper published in *Eur. J. Gynaecol. Oncol.*, 34 (6), 2013, we read Bozkurt et al.’s study [1]. They reported finding a significantly higher serum level of CA-125 and CA 15-3 \( (p = 0.000) \) in order to distinguish benign and malign ovarian neoplasms. The sensitivity and specificity were, respectively, 90.5% and 96.1% for CA 15-3; positive and negative predictive value (PPV, NPV) were, respectively, 80.6% and 90.5% for CA-125. The different test combinations between those tumour markers and CA 19-9, carcinoembryonic antigen, and alpha-fetoprotein did not have a contribution in the differential diagnostic between benign and malignant ovarian tumours.

Pelvic examination, ultrasonography (US), color-Doppler, and tumor-markers (TM) are indicated for diagnosis of ovarian cancer. Gene expression microarrays, proteomics, tumor microenvironment, and mathematical models are being tested. Nonetheless, the differentiation between benign and malignant ovarian neoplasm is a clinical challenge [2]. A study using association of US (with Doppler) and TM, analysing tumours stage and histological types (non-neoplastic findings, benign, and malignant neoplasia) showed that sensitivity, specificity, PPV, and NPV in malignant tumours are, respectively, 90.9, 84.3, 40, and 98.7%. Using those methods, 73% of malignant cases were diagnosed in Stages I or II [3].

The tumour stage and histological types of the cases analysed by Bozkurt et al. [1] were not cited. Their findings confirm other results in literature but the absence of these analyses is very important for interpretation of the data. We hope that the authors will address these points in the future.

References


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Reply from M. Bozkurt, A.E. Yumru1, İ. Aral

We have read with interest the comments made by the Author of the Letter to the Editor. The concerns raised regarding the stages of our ovarian cancer patients gives us the opportunity to highlight some important points. Sadly, ovarian cancer continues to be one of the leading health concerns worldwide.

In our discussed study, the sensitivity, specificity, PPV, and NPV of CA-125 with a cut-off 35 U/ml, were 78.9%, 86.9%, 63.8%, and 93.3%, respectively. The diagnostic odds ratio of CA-125 with a cut-off of 35 U/ml, was 25. With a cut-off 65 U/ml, the sensitivity, specificity, PPV, and NPV values were 65.7%, 95.3%, 81.6%, and 90.5%, respectively.

We have included 38 ovarian carcinomas in our research: 25 (65.78%) of serous type, four (10.52%) of mucinous type, eight (21.5%) of endometrioid type, and one (2.63%) of clear cell type epithelial ovarian carcinoma. Twenty-four of these 38 malign ovarian carcinomas were in advanced stage. CA-125 was above the normal range in ten (71%) of 14 early stage patients. It is interesting that all the early stage patients were in Stage 2.

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Thus, the sensitivity, specificity, PPV, NPV, and diagnostic accuracy values of CA-125 cannot be studied in Stage 1 patients. Although it is rare to encounter ovarian cancer patient at admission to the obstetric and gynecology clinic in
the early stage, we have considered the lack of Stage 1 patients as a limitation in our research. CA-125 levels are reported above the normal range in 20 (83.3%) of 24 (18 patients in Stage 3, six patients in Stage 4) advanced stage ovarian cancer patients. With CA-125 and CA15-3 combined, four more patients were diagnosed with malign adnexal masses (34 of 38 patients: 89.4%).

Due to the fact that CA-125 level remains constant in blood flow at the early stages of the disease and it is also affected by various pathologies, many tumor markers have been studied extensively and the most promising one is found to be the human epididymis protein 4 (HE4).

Risk of Ovarian Malignancy Algorithm (ROMA) algorithm is formed by the combination of CA-125 and HE4. ROMA uses the results of HE4 and CA125 to generate a predictive index (PI) for ovarian carcinoma.

Evaluating all tumor markers, none of them seem to be ideal for diagnosis of ovarian cancer yet although HE4 research is promising. As a result, the combination of patient age, family history, vaginal examination findings, imaging tools like Doppler sonography and magnetic resonance imaging, tumor markers, risk of malignancy index (RMI), and the use of the ROMA algorithm are the most appropriate approaches in the distinction between benign and malign adnexal masses. Perhaps the most important point worth mentioning here is that the most ideal approach for an accurate diagnosis is the combination of diagnostic and imaging modalities.

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Single port access (SPA) robot-assisted laparoscopic posterior pelvic exenteration for patients with advanced and recurrent ovarian cancer: Farghaly’s technique

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Introduction
Pelvic exenteration is the most extensive surgery performed for treatment of advanced and recurrent gynecological cancers. It was first reported in 1948 [1]. It has been performed for recurrent gynecologic malignancies limited to the pelvis, specifically for recurrent cervical cancer. The procedure involves en bloc resection of the uterus, cervix, vagina, adnexa, lower urinary tract (anterior pelvic exenteration), and rectosigmoid colon (posterior pelvic exenteration). Urinary conduit and an end colostomy are created at the end of these procedures. These procedures come with significant risks, morbidity and impact on quality of life. The related mortality in these procedures is approximately 3–5%, and morbidity could approach 60% [2-13]. Posterior exenteration has been described for treatment of cancers of the cervix, uterus, ovary, and rectum [14-17]. The complexity of the surgery has been a deterrent for performing it, but this has changed with the adoption of minimally invasive methods of exenteration. However, there are a few case reports of minimally invasive techniques being used [18–20].

Materials and Methods
Patients and Surgical Characteristics:
Patients with advanced and recurrent ovarian cancer would undergo preoperative lab work, imaging studies (e.g., chest X-ray and abdominal and pelvic cross-sectional and PET imaging. Positron emission tomography (PET) scan is valuable in the diagnosis of advanced and recurrent ovarian cancer. Those patients who present with malignant deposits on the rectum and confirmed with magnetic resonance imaging (MRI), computed tomography (CT), and proctoscopy were selected for this surgical technique.

Instruments
Da Vinci® si advanced 3D HD Surgical System was used. It has a magnified 3D high-definition vision system with small wristed instruments that bend and rotate more efficiently than the human wrist. Five-lumen port which provides access for two single-site instruments: the 8.5 mm 3DHD endoscope, a 5/10 mm accessory port and insufflation adaptor, is used. Curved five-mm cannula was used to optimize triangulation toward the target anatomy and provide an unobstructed view of the surgical field, separate the instrument arms outside the body wall, maximizing range of motion, and minimizing potential internal and external crowding. A five-mm semi-rigid instruments were used to go through curved cannula. Also, a blunt five-mm trocar, and a five-mm 30-degree laparoscope were used. In addition, mono and bipolar cautery, the Harmonic TM ACE, PK dissecting forceps, suture cut needle driver, intuitive surgical’s hot shears monopolar curved scissors, and curved retractors were used. The instruments and camera cross within the single-site port and the center technology of the system allow avoidance of cannula collisions, arm interferences and port-site movement. The system software automatically detects and re-associates surgeon’s hands with the instrument tips to create intuitive movement through crossed cannulas. Three trocars, standard five-mm grasping instruments with 70-degree freedom, and a five-mm 30-degree laparoscope with a flexible tip were used. For ligation and dissection, the Ligasure Advanced TM was used to promote greater spacing and control of instruments. EEA stapler for the proximal bowel and a V-care uterine manipulator for tissue manipulation were also used.

Technique
All patients underwent bowel preparation, and a single dose of prophylactic antibiotics preoperatively, with additional antibiotics administered postoperatively when required. Administration of subcutaneous heparin was routinely used.

Once the patient was anesthetized, she was placed in a modified Lyoid-Davis position in yellow fine stirrups and her arms tucked at her side. The patient was then placed in the steep trendelenberg position and the da Vinci system was docked between her legs. After prepping and draping the patient, a standard V-care uterine manipulator was placed in the vagina, and a foley catheter was inserted into the urinary bladder. The Applied Medical Gelpoint was placed and was utilized for both the transperitoneal and the extraperitoneal approaches. The surgeon was positioned to the left of the patient, and the assistant was placed to
the left of the patient and the surgeon’s left. The assistant periodically placed an endoscopic suction device directly through the port. A 2.0-cm vertical incision was made through the umbilicus. The skin, subcutaneous fat, and fascia were opened along the same oblique axis. The anterior-lateral abdominal muscles were divided. Twelve mm Hg of carbon dioxide gas is insufflated through a separate cannula on the single port device. The laparoscope (10-mm, 0-degree) was placed into the most cephalad channel. Rigid straight dissection forceps were introduced into the caudal trocar, and the Harmonic scalpel into the lateral trocar. Tissue dissection was performed utilizing monopolar cautery. In cases of advanced ovarian cancer, a radical hysterectomy, including removal of the ovaries, tubes, and para-aortic and pelvic lymphadenectomy and ultraradical cytoreductive surgery were performed. Cancerous tissues and loco-regional metastases were debulked to residual tumor less than two mm in diameter. In cases of recurrent ovarian cancer, only ultraradical cytoreductive surgery for cancerous tissues was performed as above. Following that, the inferior mesenteric pedicle was identified and ligated. The sigmoid colon was divided with the endo-GIA stapler at the level of the pelvic brim after creating a mesenteric window. The mesenteric blood supply of the sigmoid colon was divided using the Harmonic scalpel. The retrorectal space was developed followed by dissection of the mesorectum along anococcygeal ligament to the level of the posterior levator hiatus. The proximal rectum was divided at a level with adequate proximal surgical margin. Laterally, pararectal spaces on both sides were entered. The pararectal spaces were dissected to expose the levator ani on the lateral aspects. The ureters were visualized, dissected, and freed up to urinary the bladder. The next step, the urinary bladder was dissected of the vaginal wall and was exposed. Then, an incision was made around the vagina, perineal body, and around the anus. Colpotomy was performed anteriorly; extending posterolaterally. The rectum was transacted distal to the tumor involvement. This cut was extended anteriorly to join the colpotomy, and the surgical specimen was retrieved through the vagina. The proximal colon was brought out through the anal canal and a coloanal anastomosis was performed from below. A temporary proximal loop transverse colostomy was performed to protect the anastomosis in right upper quadrant. Pelvic drain was introduced through the single port, and the port was removed under vision. The vagina was closed with 2-0 vicryl. The fascia was closed using 0 vicryl suture and the skin was closed with running 4-0 monocryl subcuticular stitch. The perineal wound was then closed with Tisseel, virus-inactivated, 2-component fibrin sealant that contains thrombin and fibrinogen made from pooled human plasma. The advantage of this component is to reduce bruising, swelling, drainage, and hematoma formation. Estimated operative time was 210 minutes and average blood loss of 230 ml. Postoperative management included positive pressure ventilation, continuous enteral nutrition from the first postoperative day, and epidural analgesia. The pelvic drain was kept for 24-48 hours depending on the drainage. Hospital stay was about four to five days.

Discussion
Pelvic exenteration has been performed for recurrent gynecologic malignancies limited to the pelvis. It was first described by Brunschwig in 1948, and the procedure has undergone changes in modifications and indications [21-22]. Advances in laparoscopic evaluation, and laparoscopic assisted exenterations have been described [23-25]. Obesity and an aging may influence surgical and survival outcomes of pelvic exenteration [26-27]. Patients usually selected to undergo the procedure have considerable local symptoms including tenesmus, constipation, pain, and foul-smelling discharge. In addition, technologies such as PET scan, laparoscopic evaluation, and fine needle aspiration have enabled surgeons to accurately assess the extent of disease preoperatively, and refining candidates for exenteration. Moreover, robot-assisted laparoscopic surgery for patients with advanced and recurrent ovarian cancer has been shown to be safe and effective alternative to laparoscopic and laparotomy surgery. It has the advantage of three-dimensional vision, ergonomic, intuitive control, and wristed instrument that approximates the motion of the human hand. It can decrease the incidence of intraoperative complications and postoperative wound complications without significantly increasing operative time or blood
loss [28]. The advantage of using the robotic system is that it assists the surgeon to dissect tissues in a narrow pelvic floor. There is also improved visualization with the binocular optics generating 3-D stereoscopic vision. The Harmonic scalpel allows for control of the pelvic sidewall vessels and transection of the ligamentous attachments circumferentially around the extirpated pelvic structures. The articulating wristed robotic instrument allows for fine sewing. The SPA has been shown to be safe and effective approach in several surgical specialties, leading to decreasing postoperative pain, better cosmesis and decreased hospital stay, and offering minimal scar [29]. The most important step in the procedure is the identification of the presacral plane to enable en bloc mesorectal excision and anterior dissection of the urinary bladder from the uterus and upper vagina. In addition, the low colpotomy enables visualization of the distal rectum once the posterior vaginal cuff is cut, allowing stapler insertion and transection. In general, posterior pelvic exenteration is an effective technique to obtain an optimal result in patients with advanced-stage disease with extensive involvement of the pelvic organs [30-34]. It is worth noting that the anterior resections of rectum are being performed by the Natural Orifice Transluminal Endoscopic Surgery [35], and Natural Orifice Specimen Extraction [36] techniques. Farghaly’s technique uses a similar technique for posterior pelvic exenteration in patients with advanced and recurrent ovarian cancer. The proximal colon after transection was anastomosed to the anal canal. Thus, the patient had no laparotomy incision. The oncological clearance is adequate, and the postoperative recovery is faster. In the absence of scar, further adjuvant treatment could be offered early.

Conclusion

Farghaly’s technique of single port access robot-assisted laparoscopic surgery for posterior pelvic exenteration in women with advanced and recurrent ovarian cancer is feasible and has the advantage of decreasing morbidity, short hospital stay, and is cost effective.

Acknowledgment

The topic of this manuscript was presented at the 40th American Association of Gynecological Laparoscopists Annual Meeting on Minimally Invasive Gynecology, Hollywood, Florida (USA) in November 2011.

References


Cervical atypical glandular cells and false negative HPV testing: a dramatic reality of the wrong test at the right place

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Summary

Background: Due to cervical cancer screening the number of squamous cancer have declined. The number of adenocarcinomas (ADCs) does appear to be rising. ADCs are often missed and human papillomavirus (HPV) testing could be helpful in detecting these abnormalities earlier.

Case: A 36-year-old woman, who had a normal smear three years earlier, had a pap smear with atypical glandular cells. The L1 HPV test showed that there was no HPV infection. Other HPV tests which looked at E6 and E7 showed an infection with HPV 16. Due to unknown reasons, no action was taken regarding the atypical glandular cells. Two years later the patient was diagnosed with a FIGO Stage IVb ADC of the cervix. The L1 HPV test was still negative and the E6/E7 HPV test was still positive. Despite several multiple treatment modalities she succumbed of her disease two years later leaving behind a young family.

Conclusion: HPV test looking only at L1 can give false negative results if the virus is integrated in the human genome.

Key words: Human papillomavirus; HPV; Adenocarcinoma; L1; E6; E7; Integration; False negative; Cervical cancer; Prophylactic vaccination; Screening; Cross-protection; HPV testing.

Original Articles

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tion of virus) and very low in cancer (only limited number of HPV copies who transformed the initial basal cell). Because HPV tests have a fixed sensitivity cutoff, the same amount of measurable HPV takes more time to accumulate in cancer (viral load doubling every 289 days) compared to transient infections (viral load doubling every three days), resulting in older (larger) cancers upon detection. HPV tests that only focus on L1 favor detection of transient infections while HPV tests targeting E6 and E7 can both measure transient and persistent infections [7]. When during viral DNA integration L1 is lost, this could lead to false negative HPV results in test targeting only the L1 region.

This article is written to highlight the value of HPV testing in general and to point out the value of E6 and E7 HPV testing in case of integration. It is important to detect the integrated HPV because those are the lesions, which are mostly likely to progress to an invasive cancer.

Case Report
This case is a description of a 36-year-old woman, G2P2, who had a normal smear in September 2002 and again in March 2004. Three years later she had a repeated smear that showed atypical glandular cells (AGC). The L1 HPV test showed no signs of a HPV infection. The E6/E7 HPV test on the other hand showed an infection with HPV 16. The viral load for HPV 16 E6 was ten copies per cell, while the viral load for HPV 16 E7 was 13 copies per cell. Due to unknown reasons, no further action was undertaken regarding the AGC. Two years later she had a repeated smear that still showed AGC. The L1 HPV test was still negative and the E6/E7 HPV test was still positive. The viral load increased both for E6 and E7 and was at this time, respectively, 24 in 2,755 copies per cell. The increase in HPV 16 E7 load was 0.0031 HPV 16 E7 copies per cell per day. Independent HPV 16 E2 PCR was also negative for all three PAP smears. In 2009, retesting of the liquid based cytology leftover from the 2004 normal smear also already showed the presence of HPV 16 E6 (one copy/cell) and E7 (seven copies/cell). A biopsy taken of the cervix showed an invasive ADC and subsequent staging revealed positive lymph nodes in the groin. The lesion was negative for HPV L1 on immunostaining. The FIGO Stage was therefore IVb. Despite multiple treatment modalities, the patient succumbed two years later, leaving behind a young family.

Discussion
This case clearly illustrates that HPV L1 based tests can miss cervical cancer, although E6/E7 based test could detect HPV many years earlier, leading to a delayed detection and treatment of the cancer. Invasive cervical cancers (ICC) can be divided in SCC (75%-90%), ADC (10%-25%) and a rest group containing adenosquamous cell carcinoma and rare types like melanoma, sarcoma, lymphoma, neuroendocrine tumors, and cancers of unspecified histology [3,8,9]. SCC occurs mainly at the ectocervix, while ADC will appear at the endocervix with a normal ectocervix. The latter probably responsible for the often false negative smear. ADC in situ (AIS) is multifocal in 15% of women [10]. Misdiagnoses between ADC of the endocervix and of the endometrium occur [4,5]. Misdiagnosis leads to mismanagement because surgery, chemotherapy, and radiotherapy differ for the two tumor types. The use of HPV is often helpful in the distinction between the tumor types. However there are some types of ADC, which are known to be HPV negative [11].

The top five HPV types for squamous cancer are the same as the top five for ADC [4,5,12]. The top five HPV types are HPV 16, HPV 18, HPV 31, HPV 33, and HPV 45. The distribution of the HPV types for the two histological cancer types are however different. HPV 16 infection results in predominantly squamous cervical neoplasia, while HPV 18 and HPV 45 have greater tendency to induce glandular cervical neoplasia [12]. ICC caused by HPV 16, 18, and 45 tended to be at an earlier age (average of 47 years) than ICC associated with other HPV types (average age 56 years) [4,5].

Together HPV 16, 18, and 45 account for approximately 90% of ADC and 70% of SCC worldwide [3-5, 8, 13]. This has major implication for primary prevention. There are two commercially available HPV vaccines Gardasil and Cervarix both are targeted on the high-risk types 16 and 18. Gardasil also targets the low risk types 6 and 11, and has a cross protection against high risk type HPV 31 [14]. Cervarix on the other hand has cross protection not only against high-risk type HPV 31 but also against the high-risk types HPV 33, HPV 45, and HPV 51 [14-16]. Due to this broadened cross protection there is an increase of prevention between ten to 15% against cancer. Translating the efficacy, in which the percentage of cancer could be prevented, would mean that roughly 70% of the SCC and more than 90% of the ADC could be prevented. Especially the impact on ADC is important because those are the cancers, which are often missed by the classical cytological screening.

AGC are reported in 0.4% of all cervical smears [17-21]. Regardless of HPV status, cytological results of AGC require further investigations. Because these cytological abnormalities are associated with significant risk of an underlying precancerous (9%-38%) or malignant neoplastic processes (3%-17%). The ASCCP clinical follow-up guideline of 2001 and subsequently 2006 are quite clear they recommend colposcopic evaluations and endocervical sampling on all patients with AGC Pap results, regardless of age [17-21].

Primary HPV testing will increase the detection of adenocarcinomas, because cytology is frequently normal while HPV testing is positive in these cases. HPV testing can however also become false negative. In low-grade lesions the percentage of integration is very low, while there is a high percentage of integration of HPV into the host genome in high-grade lesions and invasive cancers. The integration frequency is different for the different HPV types. The integration in cancer for HPV 18 is 92%-100%, HPV 45 is 83%, HPV 16 is 55%-80%, HPV 33 is 37%, and HPV 31 is 14%
sequences amplified by the SPF10 primers [25]. There is however never a loss of E6 and E7. Current HPV test are based on primers for either L1 or E6/E7 or all three regions. If a HPV test is solely based on the L1 region, one will miss about 15% of the integrated HPV [26]. As current case, these patients can become L1 negative. Together with the fact that cytology will miss almost half of the abnormalities, one will have the wrong test at the right place. The sensitivity of an arbitrary HPV testing is at least 30% better then cytology in cervical cancer screening. One should therefore opt for HPV cervical cancer screening. Lesions that progress from low grade, to high grade, to ICC are more likely to have HPV integration. In order not to miss these cancers a HPV test based on the E6/E7 region should be used, instead of L1. This will further increase the sensitivity by at least 10%. The latter is especially important for cervical ADCs because there are frequently false negative on cytology.

The role of viral load in cervical cancer screening is gaining more and more interest. The viral load threshold cannot be used to distinguish between a clinically relevant (leading to CIN3+) and an irrelevant (transient) HPV infection. The viral load course (for a specific HPV type) can (or is) the sum of transient infections (limited in time) and linearly progressing infections leading to CIN3+. There can be one or more infections at the same time. In a single infection, there is a transient prophase preceding the linear increase, meaning that a given threshold can be reached three times during the natural course of an HPV infection leading to CIN3+. The first time in the beginning of the reproductive transient prophase, the second time when the transient infection is clearing, and a third time when the linear increase underneath reaches the threshold level again.

The viral load in the transient (LSIL) (pro) phase can be very high, because it represents the summit of the reproductive phase of the virus infection. This very high level of viral load can in most cases never be reached in many of the CIN3+ lesions, because the size of the lesion is limited by the law of universal growth, and because each of the tumor cells which are derived from one clonal cell is limited by the number of HPV copies present in this cell. An example, the measured viral load of a CIN3+ lesion comprising of Hela cells (+/-50 HPV 18 copies/cell) would have a lower load (per CIN3+ cell) than a Caski tumor with the same amount of cells (+/-600 HPV copies/ Caski cell).

The load per scrape cannot always be reduced (calculated) to the load per cell. Also load per scrape and the load per cell does not correct for the number of HPV copies present per cell, whereas assessing the type specific viral load over time does by eliminating it from the equation.

It is not the viral load threshold in se that is primordial in cervical cancer detection, but how fast the type specific (E6/E7) load increases or decreases over time [2]. The road to cervical cancer lies on well predestined line (HPV type specific E6/E7 load =1e-5e0.0068 number of days) the lower the analytical sensitivity of the test (HPV), the sooner the process of doubling basal cells carrying the cervical cancer marker (type specific HPV E6/E7) can be detected. This implies that type specific HPV slope measuring can detect a malignant process much sooner, and in time will lead to a higher clinical sensitivity. As in many other types of cancers, improving the sensitivity of measuring the malignant process will impact the clinical sensitivity and inevitably the outcome for the patient. A disadvantage of the hc2 is that it introduces a HPV viral load threshold, through a predefined cytology threshold, thereby limiting the action to be undertaken: waiting until a certain threshold is reached denies preventive action.

In conclusion cervical cancer screening should be based on HPV testing with detection in E6/E7 instead in L1, to avoid missing lesions with integrated HPV. The right test in the right place will detect almost all cervical cancers in an early and curable stage.

References


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Survival and toxicity of radical radiotherapy (with or without brachytherapy) for FIGO Stage I and II cervical cancer: a mono-institutional analysis

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Summary

Purpose of investigation: To add to the existing outcome data regarding radical radiotherapy (RT) for FIGO Stage I and II cervical cancer in a mono-institutional series and to evaluate the cost-benefit ratio of the addition of brachytherapy (BRA) to external-beam radiotherapy (EBRT). Materials and Methods: The authors report on 240 patients (pts) with FIGO Stage I and II cervical cancer, consecutively treated with radical RT from 1990 through 2009 at the Istituto del Radio O. Alberti (EBRT alone, 32, EBRT and BRA, 189, BRA alone, 19). BRA was delivered with low dose rate (LDR, 133.64%) until 2003 and then with high dose rate (HDR, 75.36%). RT was associated with concomitant chemotherapy (CHT), mainly weekly cisplatin 40 mg/m², in 87 pts, mostly after 2000. The Chi-square test was used to compare the different variables, the Log-Rank test to compare the actuarial survival values, and the Cox-model for the multivariate analysis. Results: Five-year actuarial overall survival (OS) equaled 65%, disease specific survival (DSS) 77%. Regardless of disease stage, better DSS was evident in pts treated with EBRT and BRA compared with those treated with EBRT alone (82% and 58% respectively, \( p = 0.005 \); pts treated with concomitant CHT (dose intensity \( \geq 50\% \)) and higher RT doses (RT cumulative EQD\(_{2} \geq 75\ Gy \) ) obtained better DSS. Complete response (CR) rate approached 88.4% (206/233 evaluable pts) and more than half of the subsequent failures (21/36) were in distant sites. Older patients and those given BRA had better OS and DSS, while BRA dose rate did not result related with these outcomes. Chronic G3/G4 toxicity involved more frequently the intestinal/rectal tract than other organs at risk. Rectal and vaginal serious chronic sequelae developed mainly in pts treated with EBRT and BRA and suggest the need for more advanced treatment techniques. Conclusions: the present mono-institutional analysis confirms the efficacy of radical RT for the treatment of cervical cancer and provides support to the role of BRA to obtain better outcomes. An effort to reduce long term toxicity of the treatment is needed.

Key words: Cervical cancer; Radical radiotherapy; Brachytherapy.

Introduction

Cervical cancer represents the third most frequent cancer site among women. For early-stage disease, survival outcomes of surgery and radiotherapy (RT) are known to be similar. Locally advanced carcinoma of the cervix should be treated with a combination of external-beam radiotherapy (EBRT) and intracavitary RT (brachytherapy-BRA). Since 1999, concurrent chemotherapy (CHT) with radiation has been the standard of care in the treatment of cervical cancer. [1-7]

BRA is a kind of conformal dose escalation and plays an essential role for its ability to deliver very high doses to the tumour, decreasing the risk of residual cancer and of pelvic relapse. [8-9] Low-dose-rate (LDR) BRA has been in use for the treatment of cervical cancer for nearly a century, although the method has been greatly refined, while high-dose-rate (HDR) BRA has been in use for over 30 years. HDR and LDR BRA seem to be equivalent treatments in terms of survival outcomes. [10-14]

In this study the authors retrospectively analyzed the survival outcomes and the treatment-related toxicity for women with cervical cancer treated with radical RT at the present Institution. The authors’ aim is to establish a historical benchmark database to assist in identifying possible pathways to improve results taking advantage of the technical and clinical advancements in dose planning and delivery, both for BRA and for EBRT.

Materials and Methods

Between 1990 and 2009, 247 patients (pts) affected by cervical cancer (FIGO Stage I and II, any N) were treated with radical-exclusive RT (+/- concomitant CHT) at the “Istituto del Radio O. Alberti” – Radiation Oncology Department of the Brescia University; seven of them were excluded for the lack of any information after treatment, leaving 240 pts available for the analysis. All the data were retrospectively collected from the clinical records; if no information was available, patient’s vital status was defined through the municipality of residence or directly by telephone interview; as far as the evaluation of chronic sequelae and the maintenance of tumour control are concerned, pts examined only once after treatment were judged

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“lost at follow up”. In the absence of further information, pts alive at least eight years after treatment were judged “alive without disease”. The median effective follow up was 1,695 days (average 2,048). Clinical response to the treatment was assessed at least six months after the end of treatment, using diagnostic imaging (ultrasonography (US), computed tomography (CT) or magnetic resonance imaging (MRI) +/- biopsy in case of doubtful persistence of disease) and/or clinical examination.

Pts and disease features are shown in Tables 1 and 2. The authors analysed distinctly the disease features of the first and the second decade considered because in the last years the present Institution modified the diagnostic protocols used for staging, according to the improvement of diagnostic imaging techniques, and to the their increasing availability. Staging included clinical examination alone in nine pts, CT in 79 pts, MR (+/-CT) in 139 pts, and CT positron emission tomography (CT-PET) (+/-MR) in 13 pts: MR and CT-PET were mostly used after 2000, while CT was the main procedure used until 1999. Along with an increased use of more accurate imaging techniques, a higher proportion of patients with advanced clinical stage was also registered after the year 2000: the new techniques allowed to detect more efficiently any parametrial invasion or nodal involvement, adding information about pelvic and para-aortic nodes and the metabolic activity of the suspected disease sites (Tables 3-5).

Thirty-two pts were treated with EBRT alone because cervical anatomical characteristics did not enable a correct implant for BRA boost or for poor general conditions: the dose to the pelvis was 45-50 Gy, while the tumour was boosted to higher doses reaching a total dose of 66 Gy or more in 56.3% of cases. Nineteen pts were treated with BRA alone (14 LDR BRA, five HDR BRA boost).
Concomitant CHT was administered only to 87 pts: the major-
dose received with BRA (using point-B as reference point).

The pelvis (including the tumour and the obturator, internal
iliac, external iliac, common iliac, and pre-sacral lymph nodes,
with cranial limit between L4 and L5) was irradiated mainly
with cranial limit between L4 and L5) was irradiated mainly
with four-box-field technique (206 pts); the two-fields tech-
nique (AP-PA) was used for six pts; for nine pts the EBRT tech-
ique was not specified in the clinical records. Until 1997 a

Table 6. — Point A EQD2 for the pts of the entire series. Of the pts treated with BRA alone (19 pts), 14 were given 70 Gy
EQD2, one was given 59.5 Gy EQD2, three were given 48 Gy EQD2, and one was given 43 Gy EQD2.

<table>
<thead>
<tr>
<th>EQD2</th>
<th>&lt; 60 Gy</th>
<th>60-69 Gy</th>
<th>70-74 Gy</th>
<th>75-79 Gy</th>
<th>≥ 80 Gy</th>
<th>TOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRA LDR</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>40 (30.1%)</td>
<td>24 (18%)</td>
<td>69 (51.9%)</td>
<td>133 (100%)</td>
</tr>
<tr>
<td>BRA HDR</td>
<td>5 (6.7%)</td>
<td>2 (2.7%)</td>
<td>3 (4%)</td>
<td>14 (18.7%)</td>
<td>51 (68%)</td>
<td>75 (100%)</td>
</tr>
<tr>
<td>NO BRA (EBRT alone)</td>
<td>4 (12.5%)</td>
<td>20 (62.5%)</td>
<td>8 (25%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>32 (100%)</td>
</tr>
<tr>
<td>TOT</td>
<td>9 (3.8%)</td>
<td>22 (9.2%)</td>
<td>51 (21.3%)</td>
<td>38 (15.8%)</td>
<td>120 (50%)</td>
<td>240 (100%)</td>
</tr>
</tbody>
</table>

Table 7. — Clinical response (p = 0.6).

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>All Cases</th>
<th>EBRT + BRA</th>
<th>EBRT alone</th>
<th>BRA alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>206/233 (88.4%)</td>
<td>172/186 (92.5%)</td>
<td>17/30 (56.7%)</td>
<td>17/17 (100%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>21/233 (9.1%)</td>
<td>13/186 (7%)</td>
<td>8/30 (26.6%)</td>
<td>0/17 (-)</td>
</tr>
<tr>
<td>Non response</td>
<td>2/233 (0.8%)</td>
<td>1/186 (0.5%)</td>
<td>1/30 (3.4%)</td>
<td>0/17 (-)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>4/233 (1.7%)</td>
<td>0/186 (-)</td>
<td>4/30 (13.3%)</td>
<td>0/17 (-)</td>
</tr>
</tbody>
</table>

Results

The clinical response to treatment is shown in Table 7 (the
table does not consider the seven pts without clinical infor-
mation after treatment); the median EQD2 was 82 Gy for pts
who reached CR (average value 77.7 Gy, range 40-98 Gy) and
71 Gy for those with partial response, non response or disease
progression (average value 71 Gy, range 54-85 Gy). Overall
survival (OS) at five and ten years was respectively, 65% and
51% while disease specific survival (DSS) was 77% at five
years and 73% at ten years: disease related deaths occurred in
fact mainly within three years after the end of treatment.

In the present series, prognosis seems to be more related
to the type of treatment received than to the stage of dis-
eease: with some limit, related to the non-homogeneity of
the sample, better results were reached in women treated
both with EBRT and BRA compared with those treated
with EBRT alone (five years DSS 80% vs. 58%, p = 0.00),
regardless of the stage of disease (Figure 1). Women treated
with high radiotherapy doses obtained better outcomes, also
if they were affected by more advanced disease: five years
DSS was 83.5% for pts treated with EQD2 ≥75 Gy and
66% for pts treated with EQD2 <75 Gy, without CHT, 60% for pts treated
with CHT+RT ≥75 Gy and 59% for pts treated with RT <75 Gy
without CHT (p= 0.047) (Figure 2).
Among pts treated with BRA (+/- EBRT), no significant differences in OS and DSS rates were found according to the different dose rates; a CR was achieved in 89.5% of pts treated with LDR-BRA and in 93.3% of pts treated with HDR-BRA ($p = 0.18$).

Older pts had better outcomes than younger ones regardless of the stage of disease, of histological features or treatment received (data not shown); women younger than 60 years had worse outcomes than older ones (five-year DSS 81% vs. 68%, $p = 0.083$); this difference was more evident for women younger than 45 years (five-year DSS 78.5% vs. 58.2%, $p = 0.04$) (Figure 3).

At multivariate survival analysis, only combined treatment (EBRT + BRA) was confirmed to be a significant variable determining better DSS ($p = 0.00$) (Table 8).

The majority of pts did not develop any chronic toxicity; the majority of G4 chronic sequelae, mainly arose within three years after treatment, involved the intestine or rectum (13 cases), as mucosal ulcerations/fistula or bowel occlusions implying temporary or definitive bowel diversion; three patients underwent pieostomy for bladder perforation, one patient developed pelvic fibrosis. Among G3 sequelae, hemorrhagic proctitis requiring laser-coagulation or transfusion for anaemia was experienced in 20 pts, two

Table 8. — **Multivariate analysis of disease specific survival.**

<table>
<thead>
<tr>
<th></th>
<th>p-value</th>
<th>Exp (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60 yrs</td>
<td>0.06</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 60 yrs</td>
<td>0.581</td>
<td>0.581</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBRT + BRA</td>
<td>0.00</td>
<td>1</td>
</tr>
<tr>
<td>BRA alone</td>
<td></td>
<td>1.841</td>
</tr>
<tr>
<td>EBRT alone</td>
<td></td>
<td>2.805</td>
</tr>
</tbody>
</table>

Figure 1 – DSS for the different treatment groups (EBRT alone vs. BRA +/- EBRT).

Figure 2 – DSS according to the treatment received.

Figure 3 – DSS and patients age ($p = 0.04$).
Table 9. — Different kinds of toxicities may coexist in the same patient.

<table>
<thead>
<tr>
<th>Hematopoetic system</th>
<th>Rectum/intestine</th>
<th>Urinary trait</th>
<th>Skin</th>
<th>Pelvis</th>
<th>Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>222</td>
<td>125</td>
<td>178</td>
<td>221</td>
<td>114</td>
</tr>
<tr>
<td>G1</td>
<td>1</td>
<td>39</td>
<td>27</td>
<td>51</td>
<td>1</td>
</tr>
<tr>
<td>G2</td>
<td>0</td>
<td>26</td>
<td>13</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>G3</td>
<td>0</td>
<td>20</td>
<td>2</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>G4</td>
<td>0</td>
<td>13</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gx</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>240</td>
<td>240</td>
<td>240</td>
<td>240</td>
<td>240</td>
</tr>
</tbody>
</table>

Table 10. — Rectal toxicity and radiotherapy dose ($p = 0.02$).

<table>
<thead>
<tr>
<th>Rectal-enteric toxicity</th>
<th>≤ 75 Gy EQD2 (82 pts)</th>
<th>≥ 75 Gy EQD2 (158 pts)</th>
<th>Tot</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0</td>
<td>50/82 (61%)</td>
<td>75/158 (47.5%)</td>
<td>125/240 (52.1%)</td>
</tr>
<tr>
<td>G1-G2</td>
<td>16/82 (19.5%)</td>
<td>49/158 (31%)</td>
<td>65/240 (27.1%)</td>
</tr>
<tr>
<td>G3-G4</td>
<td>7/82 (8.6%)</td>
<td>26/158 (16.4%)</td>
<td>33/240 (13.7%)</td>
</tr>
<tr>
<td>GX</td>
<td>9/82 (11%)</td>
<td>8/158 (5.1%)</td>
<td>17/240 (17.1%)</td>
</tr>
</tbody>
</table>

pts had hemorrhagic cystitis requiring hospitalization, seven pts developed vaginal narrowing that enabled physical examination, one patient experienced a pubic fracture due to radio-osteonecrosis two years after treatment. Regarding less severe sequelae (G1-G2), intermittent hemorrhagic proctitis was the more common disorder along with increased bowel frequency, urinary urgency, and vaginal substens (G2) or hypotrophy (G1) (Table 9).

Rectal-enteric chronic toxicity developed mainly in pts treated with higher RT doses (Table 10) and in pts treated both with EBRT and BRA: 28.6% of pts treated with the combined treatment experienced G1-G2 toxicity vs. 15.8% of pts treated with BRA alone and 25% of pts treated with EBRT alone. G3-G4 toxicity developed in 16.4% of pts treated with EBRT+BRA and in 6.3% of pts who received EBRT alone (no G3-G4 rectal sequelae were registered in pts treated only with BRA ($p = 0.031$)). BRA delivered with HDR seemed to be associated with a higher frequency of G3-G4 rectal sequelae if compared to LDR (22.7% vs. 10.5%, $p = 0.004$).

All the vaginal stenosis and 92% of the vaginal substenosis developed in pts treated both with EBRT and BRA, while the frequency of vaginal hypotrophy of pts who received the combined treatment overlaps that of pts treated with BRA alone or with EBRT alone ($p = 0.002$); no differences were found between HDR and LDR. Analyzing distinctly the two decades, we registered more chronic urinary and enteric-rectal G4 toxicities in pts treated between 1990 and 1999: 66.7% of G4 urinary sequelae vs. 33.3% ($p = 0.006$) and 53.8% of G4 enteric-rectal sequelae vs. 46.2% ($p = 0.016$); G3 urinary sequelae (two cases) developed in pts treated before 2000, while G3 enteric-rectal sequelae developed mainly after 2000 (35% in the first decade vs. 65% in the second decade, $p = 0.016$). Also as far as pelvic toxicity is concerned, the authors registered less toxicities after 2000: 43% of pts did not develop any toxicity in the first treatment period vs. 50.3% in the second one; vaginal stenosis (G3) and substens (G2) arose mainly in pts treated before 2000 (G3, 4.3% vs. 2%; G2, 22.6% vs. 19.7%) while mucosal vaginal hypotrophy (G1) was the main side effect registered after 2000 (17.2% in the first decade vs. 23.8% in the second decade) ($p = 0.05$). The authors found no significant statistical correlation between the development of serious chronic sequelae and the association with concomitant CHT.

### Discussion

As for other retrospective studies, the present analysis presents some limitation: the non-homogeneous features of the sample, the different staging procedures, and the variability of treatment (in terms of planning, dose-prescription, and delivery techniques); another limitation is the lack of homogeneous follow up procedures, since the selection of suitable exams plays a crucial role to evaluate the tumour response and the effectiveness of treatment. Nevertheless the data demonstrated satisfying results in terms of DSS and local control: the use of BRA boost to EBRT is fundamental, since pts who received the combined treatment (EBRT + BRA) had better outcomes than the others. The authors recorded few local relapses and found that distant metastasis were the more common manifestation of recurrence, especially in the first period analyzed; this fact is probably due to the increasing use, in the second decade, of imaging techniques (CT, MRI, CT-PET) that allowed to better define the disease extension, reserving more aggressive treatments to more advanced diseases. Although clinical examination still represents the main staging procedure for cervical cancer evaluation, it is now mandatory to make use of adequate and standardized staging procedures, including MRI to better define soft tissue characteristics and CT/CT-PET to evaluate lymph-nodes status and/or disease systemic extension [15-17].

In this univariate analysis the authors demonstrated that higher RT doses ($≥ 75$ Gy EQD2) allowed to obtain better outcomes (DSS) irrespective of stage disease: the use of BRA was essential to deliver such high doses to the tumour. At multivariate analysis only the combined-treatment modality “EBRT+BRA” seems to influence significantly the DSS, while the effect of higher total cumulative doses ($≥ 75$ Gy) do not maintain statistical significance, very likely because of the confounding effect derived from the concentration of all the cases treated with higher EQD2 among those treated with “EBRT+BRA”. Furthermore, the OS curves of pts treated with less than 75 Gy EQD2 (+/- CHT) roughly overlaps that of DSS: this suggests that per-
haps other factors could contribute to a worse outcome (e.g. deterioration of performance status justifying the choice of a less aggressive treatment). As already known from the literature data [10-14], in this series LDR BRA and HDR BRA demonstrated the same efficacy; however, in the authors’ experience, the use of a BRA boost (especially when delivered with HDR), was associated with a higher number of severe rectal-enteric chronic sequelae and a significant percentage of vaginal stenosis and substenosis. Also G3-G4 rectal-enteric toxicity was found to be correlated to RT-doses (≥ 75 Gy EQD2). Since high radiation-doses are indispensable to obtain tumour regression [18], adjacent organs at risk may receive high doses, thus increasing the probability that severe late toxicity will occur. The authors found an higher number of severe urinary and rectal-enteric late sequelae in pts treated before 2000 as opposed to those treated more recently; however, the incidence of G1/G2 toxicities (involving mostly the rectum and the vagina) that, though mild, can worsen pts quality of life remains a problem also in the more recent years. This mono-institutional analysis, in accordance with the literature [1-9, 19-24], confirms the efficacy of exclusive radical radio-chemotherapy for cervical cancer and underscores the important role of BRA boost both for early stages and for the locally advanced ones, to improve local control and survival. Since women affected by cervical cancer have a reasonably good prognosis, the reduction of late toxicity is an important endpoint to achieve to offer them a better quality of life: the percentage of serious chronic sequelae should be further reduced by new EBRT techniques (such as pelvic IMRT) and new BRA planning procedures. [25-27] The possible benefits deriving from the adoption of these technical improvements should be validated against the benchmark data obtained from the analysis of large retrospective series like the present one.

References


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Adjuvant radiotherapy for endometrial cancer - a comparative review of radiotherapy technique with acute toxicity

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Summary
Objectives: The addition of pelvic radiotherapy to brachytherapy (EBRT-BT) in early-stage endometrial cancer is controversial and may cause unnecessary toxicity. The incidence of acute toxicity of EBRT-BT will have an impact on clinical decision and patient compliance but is currently poorly understood. This study compares the acute toxicities of EBRT-BT versus BT alone. Materials and Methods: Seventy-nine patients with FIGO Stage IA-II endometrial cancer who underwent adjuvant radiotherapy, (EBRT-BT or BT alone) from 2001 to 2011 were included in the study. Medical records of these patients were reviewed retrospectively and toxicity graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Patients were followed up for at least three months post-treatment to assess resolution of toxicity. Results: The mean age of the study group was 60.6 years. Median follow-up was four years. Forty patients received EBRT-BT. There was a 37% increase in Grade 1-3 diarrhea with the addition of pelvic radiotherapy (OR 18.67, p < 0.0005) and a 34% increase in lethargy (p < 0.0005). There was also an increased occurrence of genitourinary and skin toxicities. Two patients in the EBRT-BT group required hospitalisation for severe diarrhea and three patients were unable to complete the treatment. All acute toxicities had resolved by three months post treatment. Conclusion: EBRT-BT causes significantly more acute toxicities compared to BT alone. Patients should be informed of this during counselling.

Keywords: Endometrial cancer; Brachytherapy; Radiotherapy; Toxicity.

Introduction
Radiotherapy is the most common form of adjuvant therapy used in the clinical management of endometrial cancer after surgery. The GOG-99, PORTEC 1 & 2, and the ASTEC trials [1-3] were large trials which evaluated the role of adjuvant therapy in reducing loco-regional recurrence for moderate to high-risk early-stage endometrial cancer. However, the mode of radiotherapy used differed in all the studies.

External beam radiotherapy (EBRT) delivered to the pelvis or brachytherapy (BT) have been shown to be equivalent in early-stage endometrial adenocarcinoma in the recent PORTEC 2 trial. However, EBRT is still indicated for certain subgroups [4-5] of patients who would benefit from sterilisation of microscopic disease in the tumour bed and draining lymphatics. This is the case for patients [6] who did not undergo a pelvic lymph node dissection, or those who were found to have positive lymph nodes after pelvic lymph node dissection. Certain histological subtypes [7] have also been shown to be more aggressive with higher local recurrence rates. In such patients, delivering EBRT followed by BT (EBRT-BT) may be beneficial if the treatment is well tolerated.

Sorbe et al. [8] demonstrated that EBRT-BT decreased locoregional relapse rates at five years from 5% to 1.5% compared with BT alone. In light of these findings, the acute toxicity of this treatment has become clinically relevant. Toxicities may have an impact on treatment compliance, requiring symptomatic treatment when necessary.

Acute toxicities may also be worsened by the addition of chemotherapy and is likely to lead to increased risk of late complications. [9] Most studies have however focussed on the long term toxicity of EBRT in the pelvis.

The quality of life assessment of the patients in the PORTEC 2 trial showed that EBRT caused more gastrointestinal disturbances when compared with BT and was therefore relatively poorly tolerated. While it may seem intuitive that EBRT-BT would have worse side effects compared with BT alone, there appears to be a lack of data on its severity in patients and how well-tolerated the treatment is.

The aim of this retrospective study is to assess and compare the severity and incidence of acute toxicities experienced by patients who underwent EBRT-BT and those who received BT only.

Materials and Methods
Patient selection and eligibility criteria
Seventy-nine patients who were treated with curative intent for endometrial cancer at the present centre between 2001 and 2011 were included in the study. The information was retrieved from medical records and entries made by the radiation oncologists and nurses during weekly consults while on radiotherapy. During these consults, radiation oncologists routinely graded and recorded toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 and these were recorded in the centre’s computerised Local Area Network Therapy Information System (LANTIS). Patients were asked a fixed set of questions during these consults regarding the toxicities they experienced.

Permission to retrieve the records of the patients was obtained

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from the medical ethics committee of the hospital. (Domain Specific Reference B/09/576).

Patients with early stage endometrial cancer who had undergone surgery followed by radiotherapy were included and classified according to low-risk, early-stage disease (FIGO IA or IB and low grade pathology [G1, G2]) and intermediate-risk to high-risk, early-stage disease (FIGO IA or IB with high grade pathology [G3], FIGO IIA). Other factors used in decision making were: presence of lymphovascular invasion, presence of pelvic lymph node dissection, and age. All patients were discussed at a multidisciplinary tumour board with a gynaecologist, pathologist, and an oncologist. Decision regarding use of BT and EBRT - BT was discussed. Prior to the use of FIGO 2009, majority of patients was staged using the FIGO 1988 staging system and these patients were restaged according to FIGO 2009 for this study. Surgery consisted of total abdominal hysterectomy and bilateral salpingo-oophorectomy; clinically suspicious pelvic and/or para-aortic lymph nodes were removed and pelvic lymph node dissection was performed according to surgeon preference. International Federation of Gynaecology and Obstetrics 2009 staging was assigned on the basis of the surgical and pathological findings.

Exclusion criteria were: 1) patients with missing records, 2) patients who had refused surgery and had only received primary radiotherapy (EBRT-BT or BT), 3) patients who had autoimmune diseases (eg. systemic lupus erythematosus, ulcerative colitis), 4) patients who received concurrent chemotherapy and radiotherapy, and 5) patients who had an Eastern Cooperative Oncology Group (ECOG) score of more than 2.

Procedures

EBRT was delivered to the whole pelvis in a total dose of 45-50.4 Gy in 1.8 Gray daily fractions treating from Monday to Friday, five days a week in 25-28 fractions with 10 MV photons. The clinical target volume for EBRT consisted of the proximal half of the vagina, the parametrial tissues, the internal and proximal external iliac lymph node region, and the caudal part of the common iliac lymph node chain (up to the L5-S1 vertebrae junction)(Figure 1). Radiation dose was prescribed to the planning target volume and specified at the isocentre, with homogeneity requirements according to recommendations by the International Commission on Radiation Units and Measurements (ICRU-50). For all patients, computerised treatment planning was used. The beam arrangement consisted of a four-field...
plan with an anterior-posterior beam arrangement and two lateral beams. Shielding was achieved with multi-leaf collimators.

BT was delivered to the upper half of the vagina using a vaginal cylinder applicator (Figure 2). A high dose rate (HDR) iridium source was used to deliver the treatment via a remote afterloader. If the patient had received EBRT, two to three fractions of five to six Gray per fraction prescribed to a 0.5 cm depth of vaginal mucosa was delivered two fractions per week. Patients receiving BT alone were treated with a total of four to five fractions of the same dose per fraction delivered two to three times a week. Selection of fractionation and dose was a clinical decision and depended on the patient’s histology, margin positivity, and the type of surgery performed. Fractionation schedules included five Gray per fraction for five fractions, six Gray per fraction for five fractions and 8.5 Gray per fraction for four fractions. Doses to the bladder and rectum reference points (according to ICRU-38 criteria) as well as at the vaginal mucosal surface were documented.

Follow-up
Patients were seen on a weekly basis by the radiation oncologists throughout the course of radiotherapy. They were assessed for acute toxicities and medication providing symptomatic relief was administered if indicated. Patients who tolerated the treatment poorly were hospitalised for observation. At the completion of treatment, patients were reviewed at one week, four weeks, and at three months post-treatment for resolution of acute side effects. A pelvic examination was performed at every visit.

The primary endpoint of this study was to assess the incidence of acute toxicity in patients who received EBRT-BT and compare this with those who received BT alone. The secondary endpoint was the severity of acute side effects experienced.

The results were analysed using chi square test or Fischer’s exact test where applicable. The $p$-value was set at < 0.05 for significance.

Logistic regression analysis was used to analyse the risk factors associated with each toxicity. The authors reported the odds ratios and their corresponding 95% confidence Intervals as estimates of effect size. Data analysis was done in Stata V11 and level of significance set at five percent.

**Results**

**Study population and compliance**

The authors enrolled 79 patients from the years 2001 to 2011 with Stage IA to II endometrial cancer using the ear-
Some patients experienced severe toxicity requiring hospitalisation for rehydration (grade 3 diarrhea). One patient in the EBRT-BT group experienced grade 2 lethargy and required a caregiver at home. Three (7.5%) patients in the EBRT-BT group did not complete the treatment prescribed due to toxicity. By the first follow-up at three months post-treatment, all the symptoms experienced during the radiotherapy had resolved.

**Disease recurrence**

There were two recurrences in this study group. Both were of intermediate risk and did not undergo pelvic lymph node dissection. They received EBRT-BT and subsequently recurred with distant metastases.

**Discussion**

In this study, the authors demonstrated that endometrial cancer patients treated with a combination of postoperative EBRT-BT experienced greater acute toxicities as up to 40% of patients had increased nausea and vomiting, diarrhea, and lethargy compared to BT alone. This resulted in a few patients not completing the treatment prescribed.

Studies in cervical cancer and prostate cancer have shown that up to 45% of patients experienced grade 2-3 gastrointestinal toxicities while receiving pelvic EBRT [10-14]. The follow-up study on the PORTEC 2 trial on toxicity of treatment also found significant gastrointestinal toxicity which affected quality of life in the patients receiving EBRT alone. [15]

The present results are meaningful at the cusp of a fundamental shift in the delivery of adjuvant radiotherapy for endometrial cancer. While the results of the PORTEC 2 trial showed that BT alone may be sufficient for adjuvant therapy for early stage endometrial cancer, the combined modality approach has been shown to reduce pelvic recurrences by up to 93% [8] in medium risk patients. The acute toxicity and tolerability of EBRT-BT is important as it will impact clinical decision-making.

Patients with unstaged endometrial cancer present a difficult dilemma in that BT alone is inadequate treatment for women with unrecognized nodal disease. Adjuvant pelvic irradiation is commonly offered in clinical practice when a pelvic lymph node dissection has not been performed [16]. This was reflected in the present study as almost all the patients in the EBRT-BT group did not have a pelvic lymph node dissection. Pelvic lymph node dissections, however, have not been shown to improve overall survival or disease free survival [17-19] while increasing systemic morbidity from surgery, lymphoedema, and lymphocyst formation [17-19]. EBRT-BT and its tolerability will need to be further evaluated before it can be used in all medium risk patients. This study contributes to the evaluation of adjuvant therapies in the treatment of endometrial cancer.

This study required its authors to restage the patients according to the FIGO 2009 staging criteria. Also, they excluded histologies other than endometrioid carcinoma from

### Table 2. — Significance levels between the EBRT-BT and BT groups for each toxicity.

<table>
<thead>
<tr>
<th>Toxicty</th>
<th>p-value</th>
<th>Odds ratio</th>
<th>Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>&lt;0.0005</td>
<td>18.67</td>
<td>2.35 - 148.42</td>
</tr>
<tr>
<td>Lethargy</td>
<td>&lt;0.0005</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>0.486</td>
<td>1.56</td>
<td>0.44 -0.52</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>0.193*</td>
<td>3.38</td>
<td>0.68 -16.63</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>0.023*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dysuria</td>
<td>0.310*</td>
<td>2.57</td>
<td>0.51 -13.04</td>
</tr>
</tbody>
</table>

*Fischer’s exact test used.
the analysis as chemotherapy was frequently used concurrently with the radiotherapy for adjuvant treatment of more aggressive histologies. This would worsen the acute toxicity experienced by the patient.

The limitations of this study are its small sample size and its retrospective study design. Unlike the PORTEC 2 trial which was a prospective study and used questionnaires to assess the patients after radiotherapy, this study used notes entered by the doctors caring for the patient during the treatment and their assessment of the severity of toxicity using the CTC grading. This helped focus on the clinically relevant toxicities experienced by the patient. Bias was also limited as most of the entries were made by the radiation oncologist on duty who was usually not the physician who performed the BT.

In this study, the authors also noticed an increase in the incidence of urinary symptoms with increasing age and ECOG status. Current studies of concurrent chemotherapy and radiotherapy in cervical cancer [20-21] show increased toxicity and treatment breaks in patients above 60 years of age with up to 44% of patients in this group requiring treatment breaks due to grade 3-4 symptoms. While the present study group did not experience such severe toxicity, a larger sample size in the authors’ future studies could give a clearer picture regarding the relationship with age.

Treatment toxicity has a great impact on the patient both physically and psychologically and every effort should be made to decrease its frequency.

Advances in treatment delivery have allowed radiotherapy to pelvic organs to be delivered more precisely [22] (eg. intensity modulated radiotherapy) resulting in better tolerated treatment [23-24]. This is especially significant as studies have shown that the gastrointestinal toxicity experienced from external beam irradiation of the pelvic organs is directly related to the volume of small bowel irradiated [25-26]. Lactobacillus supplements and amifostine [27] have also shown some promise in preliminary trials in decreasing diarrhea symptoms and radiation colitis [28].

Future research should focus on vaginal BT with concurrent targeted therapies or chemotherapy, especially for intermediate to high risk endometrial cancer to eliminate the need for external beam radiotherapy in these patients. More studies are needed before intensity modulated radiotherapy is used routinely for pelvic radiotherapy.

Conclusion

EBRT-BT causes significantly more acute toxicities compared to BT alone. With the option of vaginal BT alone, postoperative patients with endometrial cancer should be carefully evaluated regarding indications for EBRT-BT and better informed of risk-benefit considerations.

References


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Maspin expression in endometrial hyperplasia and carcinoma, and its relation with angiogenesis

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Summary

Aim: The purpose of this study was to evaluate the maspin expression in endometrial hyperplasia and cancer, and also to investigate its relation with angiogenesis. Materials and Methods: A total of 19 women with complex atypical hyperplasia, 44 patients with simple hyperplasia without atypia, and 67 patients with endometrial carcinoma were included. Maspin expression was assessed by immunohistochemistry (IHC), and tested for possible significant relation with age, FIGO stage, histologic type, grade, depth of myometrial invasion (MI), lymphovascular space involvement (LVSI), lymph node metastasis, and overall survival (OS). Angiogenesis was determined by vascular endothelial growth factor (VEGF) staining. Results: Maspin expression was detected in only three patients with endometrial hyperplasia (5%). In patients with endometrial cancer, cytoplasmic and nuclear maspin expressions were detected in 36 (53.7%) and 18 (26.9%) patients, respectively. No significant relation was noted between staining localizations and prognostic variables. The five-year OS rate for patients with cytoplasmic staining was 91%, compared to 87% for patients without staining (p = 0.31). These values for nuclear expression were 100% and 87%, respectively (p = 0.16). The cytoplasmic and nuclear maspin expressions were found to be significantly correlated with VEGF (r = 0.278, p = 0.02 and r = 0.295, p = 0.01, respectively). Discussion: This is the first study to demonstrate the relation between maspin expression and angiogenesis in endometrial cancer. Although no survival difference was noted for cytoplasmic or nuclear maspin expressions, a tendency was detected for nuclear staining. Further series will clarify the exact prognostic role of maspin expression in gynecological malignancies including endometrial cancer.

Key words: Maspin; Endometrial cancer; Endometrial hyperplasia; Angiogenesis; Survival.

Introduction

Maspin is a member of serpin gene family which inhibits serine protease. It was first isolated in normal mammary epithelium by subtractive hybridization. Reduced tumor formation and metastasis were observed in the presence of maspin suggesting tumor suppressor characteristics of this unique gene [1]. In the subsequent series, it was detected that maspin inhibits breast cancer cell motility, invasion, and metastasis [2, 4]. It is located at 18q21.3 along with other serpin superfamily and encodes 375-amino acid protein with a molecular weight of 42 kDa [5]. Maspin is bound to the active site of the serine protease by the reactive center loop which is situated near the carboxy terminus. At promoter region, several important transcription factor binding sites such as Ets, Ap1, HRE, and p53 were demonstrated [6]. Although the expression of serpin family proteins is limited to the cytoplasmic compartment of the cell, maspin was found to be extracellular, cell-membrane associated, intranuclear, and within the cytoplasmic compartment [7, 8]. The prognostic value of maspin expression has been widely studied in non-gynecological cancers. Although it was found to be protective in breast and prostate cancers; in pancreatic cancer, maspin was reported to be over-expressed in progression from pre-invasive lesions to invasive disease [1, 4, 9]. Only a few series examined the role of this important gene in gynecological cancers [10-16]. There are only two reports on maspin expression in endometrial cancers [15, 16]. However, hyperplastic tissues were not evaluated in those series, and the effect of maspin expression on overall survival was not investigated. Therefore the authors decided to detect the rate of expression and prognostic importance of maspin in samples of both endometrial hyperplasias and cancers.

Angiogenesis is essential for tumor growth and metastatic spread by supplying metabolic requirements for the growing tumor and providing a vascular pathway for hematogenous spread to distant sites [17, 18]. Although many important promoters of angiogenesis have been reported, the most heavily studied one is vascular endothelial growth factor (VEGF), which induces capillary tube formation, and increases vascular permeability [19].

The purpose of this study was to evaluate the maspin expression in endometrial hyperplasia and cancer, and also to analyze the relation with prognostic variables and survival. In addition, the correlation between maspin expression and angiogenic factor VEGF was also investigated to observe its effect on tumoral angiogenesis.

Materials and Methods

The patients with endometrial hyperplasia and cancer treated at Gazi University Hospital were included in this study. The patients with invasive cancer were subjected to the initial surgical staging procedure including peritoneal cytology, total abdominal
hysterectomy, bilateral salpingo-oophorectomy, and complete pelvic-paraaortic lymphadenectomy. Ten patients with IA, IB; grade 1-2 tumors did not undergo lymphadenectomy. Staging was performed according to the FIGO 1988 recommendations. Data were obtained from patients’ charts, pathology records, special gynecologic oncology files, or from direct contact with the patients and personal physicians. When necessary, personal communication was used to verify patient’s status. Maspin expression was assessed by IHC and tested for possible significant relation with age, FIGO stage, histologic type, grade, depth of myometrial invasion (MI), lymphovascular space involvement (LVSI), lymph node metastasis, and overall survival (OS). Angiogenesis was determined by using VEGF and compared with the results of maspin staining to detect any correlation. The co-author pathologist (O.E.) reviewed the paraffin blocks, and the paraffin block with the maximum tumor tissue was chosen for IHC in each case.

**Immunohistochemistry**

Formalin-fixed, paraffin-embedded tissues were used for IHC. Four-micrometer-thick sections from tissue blocks were stained with Maspin (Ab-1, EAW24), and VEGF (VEGF Ab-7, Clone VG1) by using the standard streptavidin–biotin indirect method. Primary antibodies were performed for two hours at room temperature after blocking endogenous peroxides and proteins. AEC (3-amino-9-ethylcarbazole) was used as a chromogen. Breast carcinoma (for VEGF), and prostate carcinoma (for Maspin) were used as positive control. Negative controls were incubated with PBS instead of the primary antibody. Nuclear and cytoplasmic stainings were evaluated separately, and percentage of positive cells and staining intensity were recorded. The percentage of cells was rated as follows: 0 point, negative; 1 point, < 10%; 2 points, 10-20%; and 3 points, > 20%. Staining intensity was scored as 0 (negative), 1+ (weak), 2+ (moderate), and 3+ (strong). The final score was calculated by adding these two scoring systems, and categorized into three groups: mild (score, 1-2), moderate (score, 3-4), and strong (score, 5-6). Cytoplasmic staining was considered positive for VEGF. The staining score was determined according to the intensity of staining (0: no staining, +1: weak staining, +2: moderate staining, +3: strong staining), and the percentage of cells staining (0: no staining, +1: positive staining in < 25% of glandular epithelial or tumor cells, 2: positive staining in 26%-50% of the glandular epithelial or tumor cells, 3: positive staining in > 50% of the glandular epithelial or tumor cells). The final index score was calculated by addition to results of these two methods. Scores between 0 and 2 were accepted as negative, scores of 3 and 4 were regarded as weakly positive, and scores of 5 and 6 were regarded as strongly positive. Two different scoring systems were used for maspin and VEGF expressions as suggested in the previous publications [10-19].

**Statistical analysis**

SPSS for windows (Statistical Package for the Social Sciences) was used for statistical analyses. Categorical variables were compared by Chi-square and Fisher’s exact tests, and the analyses of continuous variables were performed using Student’s t, Mann-Whitney U, one way ANOVA, and Kruskal-Wallis tests where appropriate. The bivariate Spearman correlation coefficient was used to detect any significant relation. Survival estimates were obtained via the Kaplan-Meier method, and tested for significance by log-rank test. OS rate of the patients was calculated from the date of initial surgery to the date of death or last follow-up. All p values were the results of two-sided tests, and they were considered significant if < 0.05.

**Results**

A total of 19 women with complex atypical hyperplasia, 44 patients with simple hyperplasia without atypia, and 67 patients with endometrial carcinoma were included. Maspin...
expression was detected in one patient with complex atypical hyperplasia, and it was found to be positive in two patients with simple hyperplasia without atypia. Cytoplasmic staining was 2% with a mild intensity for all of these patients. Nuclear staining was not positive for any of the women with endometrial hyperplasia. Overall, 67 patients with endometrial cancer were subject of this study. The mean age of these patients at the time of diagnosis was 58.2 ± 11.1 years (range, 28-76). The clinical and histopathological characteristics of the patients are documented in Table 1. Of these patients, 42 (62.7%) had Stage I disease, nine (13.4%) had Stage II, 13 (19.4%) had Stage III, and the remaining three (4.5%) patients had Stage IV tumors. The most common histology was endometrioid type endometrial cancer (88.1%). The distribution of patients according to the grades was as follows: grade 1, 25 (37.3%); grade 2, 24 (35.8%); and grade 3, 18 patients (26.9%). Myometrial invasion was negative for seven patients (10.4%), < 1/2 for 36 (53.7%), and ≥ 1/2 for 24 (35.8%) patients. LVSI was detected in 19.4% of the patients (13/67), and the lymph node metastasis was found to be positive in 11 patients (16.4%).

In patients with endometrial cancer, cytoplasmic and nuclear maspin expressions were detected in 36 (53.7%) and 18 (26.9%) patients, respectively. All the patients with nuclear staining had also cytoplasmic maspin expression. Both the cytoplasmic and nuclear staining characteristics were analyzed for possible relation with age, stage, histologic type, grade, depth of MI, LVSI, and lymphatic metastasis, but none of these comparisons revealed significant correlation between staining localizations and prognostic variables (Table 1). The number of patients and the percentages of positive cells according to the cytoplasmic staining were as follows: <10% in 29 patients; 10-20% in five; and > 20% in two patients. These values for nuclear staining were < 10% in 16 patients and 10-20% in two patients. Cytoplasmic staining intensity was +1 for 12 patients, +2 for 17, and +3 for seven patients, and the nuclear staining intensity was +1 for eight patients, +2 for eight, and +3 for two patients (Table 2). The mean score for cytoplasmic staining was 1.67 ± 1.73. Ten patients (14.9%) had mild staining (score 1-2), 22 (32.9%) had moderate (score, 3-4), and four (5.9%) had strong staining characteristics (score, 5-6). When the mean scores were compared with respect to prognostic variables, no significant variance was noted for any of them. The mean nuclear score was 0.7 ± 1.3 (range, 0-5), and it was not significantly different when analyzed with respect to the prognosticators.

The mean follow-up period was 54.2 ± 37.3 months. The five-year OS rate for patients with cytoplasmic staining was 91%, compared to 87% for patients without staining (p = 0.31, Figure 1). These values for nuclear expression were 100% and 87%, respectively (p = 0.16, Figure 2). When the
patients stratified into two groups according to the scores of cytoplasmic maspin expression as negative-mild and moderate-strong, the five-year OS rates were 88% and 92%, respectively ($p = 0.27$, Figure 3).

The sections of two patients could not be stained with VEGF, and the mean score for VEGF staining was $4.2 \pm 1.6$ (range, 0-6). Fourteen patients were negative (22%), 21 (32%) were weakly positive, and 30 (46%) were strongly positive for VEGF staining. The cytoplasmic and nuclear maspin expressions were found to be significantly correlated with VEGF ($r = 0.278$, $p = 0.02$ and $r = 0.295$, $p = 0.01$, respectively). The mean VEGF score for patients with cytoplasmic staining was $3.8 \pm 1.7$ vs $4.6 \pm 1.4$ for patients with negative staining ($p = 0.04$). These values for nuclear stainings were $3.5 \pm 1.7$ and $4.4 \pm 1.5$, respectively ($p = 0.03$).

**Discussion**

Targeted therapies will be a part of standard care of cancer patients in near future. Therefore, it is mandatory to identify the critical cellular and molecular pathways. Maspin is one of the most spectacular candidate having tumor suppressive and anti-angiogenic properties [1-4]. In the published literature contradictory findings were reported in the series especially including non-gynecological cancers. Although it was found to be silenced in breast, prostate, and thyroid cancers [1, 20, 21]; in pancreatic, lung, and gastric cancers it was demonstrated that the maspin expression was increased in malignant cells compared to their normal cells of origin [4, 22, 23]. In addition, the elevated levels of maspin expression was found to be related with improved prognosis [24, 25].

Despite the substantial number of studies investigating the value of maspin expression in breast cancers, only a few trials have investigated its’ importance in gynecological cancers mainly including the patients with ovarian cancer [10-16]. Sood et al. were the first to analyze the role of maspin expression in ovarian cancer tissues and cell lines [10]. They observed that cytoplasmic staining was more predominant in invasive cancers when compared with benign and low-malignant potential tumors, and it was associated with high tumor grade, presence of ascites, and suboptimal cytoreduction. Nuclear expression was related with improved outcome, whereas cytoplasmic localization was related with poor survival. Another striking result of their study was that in vitro invasive potential of the maspin-transfected cell lines was 44-68% lower than the control group. Also, Gynecologic Oncology Group investigated the prognostic value of this important gene by immunoblot analysis including 68 women with advanced stage ovarian cancer, and they showed 72% expression rate with a significant relation with progression free and overall survivals [11]. Solomon et al. analyzed 118 patients with high grade advanced stage epithelial serous ovarian carcinoma [12]. Overall, 81.4% of the patients expressed maspin. It was only localized to the nuclear compartment in 21.2% of the cases, and 60.2% of the patients had cytoplasmic staining with or without nuclear expression. The median survival values for negative, cytoplasmic, and nuclear staining groups were 1146, 637, and 1,803 days, respectively, with a significant variance ($p < 0.001$). Maspin localization was also a significant predictor of survival in multivariate analysis. On the contrary, Surowiak et al. observed that cytoplasmic expression was related with cisplatin sensitivity in their series including 43 patients with epithelial type ovarian cancers, and these patients had significantly longer progression free and OS rates [13]. Only one study evaluated the maspin expression in the setting of progression from in situ to invasive cervical carcinoma including 18 women with cervical intraepithelial neoplasia-grade 3 (CIN), 7 patients with microinvasive disease, and 11 cases with invasive squamous cell cancers [14]. A significant decrease in maspin scores was reported between CIN 3 vs invasive cancer, and microinvasive vs invasive cancers. Also the maspin scores were lower in tumor emboli, and they speculated that maspin immunopositivity may be related with metastatic potential. No survival analysis was performed in that study.

There are a few reports on maspin expression in endometrial cancer. In the study of Murai et al. the samples of 41 patients with endometrioid type adenocarcinoma and 30 women with uterine leiomyoma were stained immunohistochemically [15]. It was completely negative in patients with uterine leiomyoma, whereas 66% of the cases with cancer had maspin expression. No significant relation was noted between the maspin immunoreactivity and the clinicopathological variables including stage, grade, lymph node involvement, distant metastasis, and recurrence. No survival data was given in that study. Interestingly, they showed a significant correlation between aberrant maspin expression and squamous differentiation. Li et al. evaluated the expression of maspin gene by reverse transcriptase polymerase chain reaction including 34 endometrial cancer and 28 normal endometrium samples [16]. They reported that maspin expression was significantly higher in Stage I and Stage III patients when compared to normal endometrium ($p < 0.01$ for both comparisons). No significant variance was noted between Stage I and III diseases. In the current study, 19 cases with complex atypical hyperplasia, 44 women with simple hyperplasia without
atyia, and 67 patients with endometrial carcinoma were analyzed for maspin expression. Although only a few cases were positively stained in the group of patients with endometrial hyperplasia, 53.7% of the patients with endometrial cancer had maspin expression. Neither cytoplasmic nor nuclear staining were found to be significantly related with the clinicopathological prognosticators. The percentages of the cells stained with maspin was not as high as the reported rates for ovarian cancer patients [11, 12]. Similar to the present findings, in the study of Murai et al., only 24% of the patients had maspin expression in more than 20% of the cells [15].

In some of the published series on gynecological cancers, the importance of subcellular localization of maspin was reported. Both the Sood et al. and Solomon et al. showed that nuclear localization was associated with favorable survival in contrast to cytoplasmic staining which was associated with poor outcome [10, 12]. This feature was also supported in the series evaluating non-gynecological cancers [26-31]. Therefore, Hirai et al. speculated that nuclear maspin is the active form suppressing tumoral growth, whereas cytoplasmic component has no effect on the carcinogenesis [26]. In the current study, no significant survival difference was found neither for cytoplasmic nor nuclear stainings. However a tendency was noted for patients with nuclear staining with a 13% survival difference between positive (100%) and negative cases (87%).

Maspin was demonstrated to be an inhibitor of angiogenesis [12, 32, 34]. Zhang et al. performed in vivo and in vitro tests to explore the relation between maspin and angiogenesis [32]. They observed that maspin blocked the mitogenesis, tube formation, and migration of cultured endothelial cells towards basic fibroblast growth factor and vascular endothelial growth factor in vitro. In a xenograft mouse model it blocked tumor growth and decreased the microvessel density. Neovascularization of the rat cornea was also blocked by maspin in vivo. In gastric and colon cancers, microvessel density was found to be lower in patients with maspin expression [33, 34]. In the gynecological cancer setting, only Solomon et al. investigated the relation between maspin expression and angiogenesis in their large series including 118 cases with epithelial serous ovarian carcinoma [12]. They reported that both the VEGF expression and microvessel density were lower in patients with nuclear maspin expression. Although the microvessel density was lower in patients with cytoplasmic maspin expression, VEGF expression was paradoxically higher in these cases. In the present study, the VEGF expression was found to be correlated with both the cytoplasmic and nuclear maspin stainings. The mean scores of VEGF were significantly lower in cases having cytoplasmic or nuclear maspin expression.

In conclusion, this is one of the largest study investigating the existence of maspin expression in patients with endometrial hyperplasia and endometrial cancer. Although it was detected in only 5% of the patients with endometrial hyperplasia (3/63), 53.7% of the patients with endometrial cancer had maspin expression. However, no significant correlation was noted between the expression of maspin and clinicopathological prognosticators as reported by Murai et al. In addition, the current study is the first to demonstrate the relation between maspin expression and angiogenesis in endometrial cancer. Although no survival difference was noted for cytoplasmic or nuclear maspin expressions, a tendency was detected for nuclear staining similar to the literature. Further series will clarify the exact prognostic role of maspin expression in gynecological malignancies including endometrial cancer.

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Radiosensitization of cervical cancer cells with epigenetic drugs hydralazine and valproate

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Summary

Purpose: To evaluate the radiosensitizing effects of the DNA methylation inhibitor hydralazine in combination with valproic acid, a histone deacetylase inhibitor, in cervical cancer cells. Materials and Methods: Cell viability assays were performed in the SiHa cervical cancer cell line treated with hydralazine and valproic acid for five days with and without cisplatin. Cell irradiation was performed using teletherapy (1.25 MV). Results: Neither hydralazine, valproic acid nor cisplatin as single agents increased the cytotoxicity from radiation, however, the combination of hydralazine with valproic acid at ten µM and one mM, respectively, did induce radiosensitization (p = 0.046). Interestingly, this effect was further increased with the triple combination of hydralazine, valproic acid, and cisplatin (p = 0.041), where cell viability decreased more than 50% as compared to radiation alone. Conclusions: The present results demonstrate that epigenetic drugs increase the efficacy of cisplatin chemoradiation in cervical cancer cells.

Key words: Cervical cancer cells; Radiosensitization; Epigenetic drugs; Hydralazine; Valproate.

Introduction

Cervical cancer is the third most commonly diagnosed cancer worldwide and the fourth leading cause of cancer death in females, accounting in 2008 for 9% (529,800) of the total new cancer cases, and 8% (275,100) of the total cancer deaths among females [1]. Pelvic external beam radiation therapy and intracavitary brachytherapy (BCT) continue to be the cornerstone in the primary treatment of locally advanced cervical cancer (FIGO Stages IB2-IVA). In the last decade, the results of radiation treatment were significantly improved with the addition of cisplatin-based chemotherapy concurrent to radiation. This regimen became the standard of care for IB2-IVA patients and was rapidly adopted in clinical practice [2, 3]. Most recently, the addition of gemcitabine to cisplatin-chemoradiation plus two adjuvant courses of cisplatin-gemcitabine increased 9% further the three-year absolute survival [4], however, it appears that toxicity of this regimen may limit further improvements using combinations of classical cytotoxics as radiosensitizers, thereby the need to investigate molecular-targeted agents to be used in combination with radiation, as well as, in the adjuvant setting. Among molecular-targeted approaches, epigenetic drugs are promising in cervical cancer due to the fact that as many other tumor types, this malignancy has a vast number of epigenetic alterations including the known interaction between human papilloma virus (HPV) oncoproteins with epigenetic machinery players such as DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) [5]. Interestingly, DNMTs and HDACs inhibitors are known to have radiosensitizing properties in head and neck cancer cell lines [6], however, these effects remain to be evaluated in cervical cancer.

The combination of hydralazine, an antihypertensive agent repositioned as DNA methylation inhibitor [7], with valproic acid, a HDAC inhibitor shows inhibitory growth effect in vitro and in vivo, chemosensitization, synergistic effect on global gene expression [8, 9], up-regulation of class-I human leukocyte antigen expression, and antigen specific cytotoxicity by T-lymphocytes in cervical cancer cells [10]. These data lead the present authors to evaluate whether the combination of hydralazine with valproic acid could show radiosensitizing activity in cervical cancer.

Materials and Methods

Cervical cancer cell line SiHa, was cultured at 37°C in a humidified atmosphere containing 5% CO2 in DMEM supplemented with 10% (v/v) fetal calf serum.

Cell irradiation was performed using teletherapy, in a 15 x 15 cm2 field size at 80 cm source-to-surface distance (SSD) for viability assays. The absorbed doses evaluated were one, three, and five Gy.

To assess cell viability, cells were seeded into 24-well microtiter plates at a cell density of 2.5 x 104 and cultured in complete medium. The next day, cells were treated for five days with hydralazine, valproic acid, or both. Cisplatin was added at day 5 only for 24 hours. Medium with drugs was changed every other day. At day 6 cell viability was measured by conventional crystal violet assay. Briefly, after aspiration of culture medium, surviving cells were fixed and stained with 0.5% crystal violet in 95% ethanol for five minutes and washed with tap water several times. Then one percent sodium dodecyl sulfate (SDS) solution was added to each well to elute the blue dye, and the absorbance of the eluted samples was measured at 595 nm spectrophotometrically, for quantitative evaluation.

Assays were performed twice in triplicates.

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cate. The cytotoxic effect of each treatment was expressed as a percentage of cell viability relative to untreated control cells.

Results

To determine the experimental conditions to test the radiosensitizing properties of hydralazine and valproic acid upon cervical cancer cells, untreated SiHa cells were exposed to one, three, and five Gy of radiation dose. After 24 hours of the radiation exposition, the percentage of cell viability was determined. Figure 1A shows the viability dose curve to radiation. It can be seen that 24 hours after the exposition to one Gy there is an approximate 20% decrease in cell viability, hence this dose was set for further assays.

Likewise, a cisplatin viability dose curve was built to assess the cytotoxic effect of cisplatin. Figure 1B shows that viability decreased as a function of the cisplatin dose evaluated at ten, 20, and 30 µM at 24, 48, and 72 hours. The IC10 for cisplatin for SiHa was 5.98 µM.

To determine whether there was a synergistic effect of epigenetic agents with radiation, and radiation plus cisplatin, SiHa cells were treated with hydralazine (at two different doses), valproic acid and the combination of these two. As shown in Figure 2, hydralazine at any dose, valproic acid or cisplatin did not increase cytotoxicity from radiation. On the other hand, the combination of hydralazine with valproic acid (at ten µM and one mM, respectively) did induce radiosensitization ($p = 0.046$). Interestingly, this effect was further increased with the triple combination of hydralazine, valproic acid, and cisplatin ($p = 0.041$), where cell viability decreases more than 50% as compared to radiation alone.

Discussion

The results of this study show that in SiHa cells, the combination of both epigenetic agents hydralazine and valproic acid increased radiation sensitivity, as shown by the increased cytotoxic effect in comparison with radiation alone. This radiosensitizing effect was further increased with the triple combination of hydralazine, valproic acid, and cisplatin, however, none of these agents showed statistically significant radiosensitization by their own.

Despite the radiosensitizing effects of epigenetic agents, mostly HDACs inhibitors are well documented in literature [11, 12], their clinical efficacy is yet to be evaluated. The authors recently reported the results of a small exploratory study in FIGO Stage IIIB cervical cancer patients who received hydralazine and valproic acid added to standard chemoradiation using weekly cisplatin. An interesting increase in clinical response rate was observed suggesting that epigenetic therapy indeed may increase the efficacy of chemoradiation [13]. Nonetheless, the radiosensitizing effects of this combination had not been tested in cell culture.

Valproic acid on its own has shown radiosensitization properties in a number of cancer cell lines and these effects corre-
late with its ability to increase histone acetylation and the inhibition of DNA double-strand break repair [14-16]. It has also been demonstrated that valproic acid may also induce radiosensitization independent of its transcriptional nuclear effects via acetylation of p53 protein [17-19]. In this regard, it has been demonstrated that valproic acid induces p53 acetylation not only in vitro but also in the primary tumors of patients receiving the combination of hydralazine and valproate [9].

DNA methylation inhibitors, on the other hand, have been less tested as radiosensitizers. One of these studies shows that zebularine can enhance tumor cell radiosensitivity in vitro and in vivo and suggests that this effect may involve an inhibition of DNA repair [20]. 5-Aza-2’-deoxycytidine has also radiosensitization effect in colon, breast [21] and head neck cancer cell lines [6]. In concordance with the findings of this study, the combination of a DNA demethylating agent and a HDAC inhibitor either 5-Aza-2’-deoxycytidine plus TSA LBHS589, or MGCD0103 [6] or 5-Aza-2’-deoxycytidine plus butyrate [21] are more effective than that of single agent treatment.

The present results are limited by the fact that only one cervical cancer cell line was tested and that no molecular analyses were performed; however, the combination of hydralazine and valproate has shown in previous clinical trials to induce DNA demethylation and histone hyperacetylation, as well as, to synergize gene expression [8, 9, 22, 23].

In conclusion, the results of this study and published data on hydralazine and valproic acid in cervical cancer support the continuing testing of this epigenetic combination for the treatment of locally advanced cervical cancer.

Acknowledgments

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Appendectomy with cytoreductive surgery for ovarian and type 2 endometrial carcinoma

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Summary
There is considerable variation within and between cancer centers in the practice of appendectomy as part of cytoreductive surgery for ovarian carcinoma and in the surgical staging of endometrial carcinoma. The purpose of this study was to determine the prevalence and the type of appendiceal pathology, the morbidity associated with appendectomy in gynaecologic cancer surgery. 

Materials and Methods: This is a retrospective review of all cytoreductive surgery for ovarian carcinoma and surgical staging for endometrial carcinoma with appendectomy over a four year period. Results: Two hundred and fifty-one patients (38 patients for endometrial carcinoma surgery and 213 patients for ovarian cytoreduction) had an appendectomy performed. Metastases to the appendix was present in 46 (23.2%) of primary ovarian carcinoma and one (2.6%) primary endometrial carcinosarcoma. The appendix was more likely to be involved in advanced stage ovarian cancer with positive peritoneal washings, omental deposits, grade 3 differentiation, and papillary serous histology. Sixteen (6.4%) co-incidental primary appendiceal tumours were detected. No postoperative morbidity specific to appendectomy was identified. One case of ovarian carcinoma was upstaged from IC to IIA by the appendiceal metastases. There was no upstaging of disease in the endometrial carcinoma group. Discussion: Appendectomy is an integral part of ovarian cytoreductive surgery but the authors found it did not upstage the disease in a clinically significant manner. The incidence of co-incidental appendiceal primary tumours was high in this series and may add value to the procedure in preventing further surgeries. The absence of procedure related morbidity is reassuring. The authors recommend appendectomy for all ovarian staging surgery and its consideration in type 2 endometrial cancer.

Key words: Cytoreductive surgery; Ovarian cancer; Endometrial cancer; Appendectomy; Gynaecological malignancy; Staging; Appendiceal tumours.

Introduction
Appendectomy is a common procedure in cytoreduction of ovarian epithelial cancers. Papillary serous and clear cell cancers originating in the endometrium (type 2 cancers) also have a propensity to spread in the peritoneal cavity. Surgical practices in cytoreduction of ovarian cancer vary from universal appendectomy to selective removal as part of the gross cytoreductive effort in Stage IIIC disease or only in apparent Stage I disease. [1-3] There is no defined standard of practice in intraperitoneal extirpation for staging of endometrial cancer. Occult intraperitoneal metastasis has been reported in patients with endometrial cancer grossly confined to the uterus. [4] Dilek et al. [5] reported 3.9% incidence of appendiceal metastasis with endometrioid carcinoma.

The geographical proximity of appendix to the right adnexa and shared coelomic epithelial covering may enhance the likelihood of its involvement by metastasis from ovarian or endometrial cancers. Synchronous primary malignant and benign tumours of appendix can be detected. The authors’ practice has been to excise the appendix and infracolic-omentum in all ovarian epithelial cancers and less consistently endometrial cancers other than grade 1 or 2 endometrioid adenocarcinoma that appear to be confined to the uterus. They undertook this review of appendectomy to evaluate their practice by measuring the prevalence of appendiceal pathology and the morbidity associated with the procedure in the surgical management of ovarian and endometrial cancers.

Materials and Methods
This retrospective review of all appendectomies performed at surgical staging laparotomy for endometrial type 2 and ovarian carcinoma was conducted in a tertiary gynaecology oncology centre over a four year period (2008-2011). This centre receives an average 87 new referrals for ovarian cancer and 80 new referrals for endometrial cancer annually. All surgical procedures were performed by three experienced gynaecologic oncologists.

The authors identified all cases of appendectomy with confirmed ovarian or uterine malignancy from the gynaecology cancer database. Information on histopathology was obtained from the tumour board multidisciplinary outcomes and laboratory database. Supplementary information was extracted from the patients’ medical records.

This study has been approved by the Division of Gynaecologic Oncology, St James’s Hospital, St James’s Hospital Ethics Committee, prior to commencement of the project.

A positive histology of the appendix was defined as histology other than normal and included malignant primary and metastatic cancer and benign appendiceal tumours. Primary appendiceal tumours were classified using the WHO histological classification of tumour of the appendix. Appendiceal metastases included tumours at all locations.

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Statistical analysis
All data was processed using Microsoft Excel 2010, SPSS 18 (PASW Statistics 18). Significance values were calculated using Pearson's Chi Square Test or x² test.

Results
Two hundred and fifty-one patients had an appendectomy performed at ovarian or endometrial cancer surgery over the four year period (January 1st 2008 to December 31st 2011). During this time, there were a total of 242 ovarian debulking and 233 endometrial staging surgeries. Two hundred and thirteen patients (84.9%) initially presented with a pelvic mass suggestive of ovarian carcinoma. Thirty-one of these had radiologically guided cytology or histological diagnosis and had chemotherapy prior to surgery. Six patients who had surgery for ovarian cancer were deemed at final histopathological diagnosis to have primary peritoneal cancer and four of these had metastasis to appendix. Five patients had primary appendiceal carcinoma with large volume metastasis to pelvis. Four patients with primary endometrial/ovarian cancer had occult primary malignant appendiceal tumours. All other malignant appendiceal lesions were considered to be metastatic. Seven patients had benign primary appendiceal tumours. Thirty-eight patients had surgery for a preoperative histological diagnosis of endometrial malignancy. Figure 1 shows the groupings.

The patients’ median age was 65.0 (45-83) years for endometrial cancer and 58.0 (22-87) years for ovarian cancer. Nulliparity was 11(28.9%) for the endometrial and 38 (17.8%) in the ovarian cancer group. Body-mass index was 27.8 (20-34) for endometrial and 27.3 (20.4-44.9) for ovarian cancer group. Median Karnofsky score at diagnosis was 80% (range 60-100%) in the endometrial group and 70% (range 50-100%) in the ovarian cancer group.

Figure 2 compares the outcomes of those with and without appendiceal metastases in the ovarian cancer group of 198 patients. Forty-six (23%) had appendiceal metastases. Twenty (43.4%) had obvious tumour deposits in the appendix on gross pathological examination. One patient with disease apparently confined to ovary at laparotomy had appendix as the sole site of histopathological extra ovarian disease but her peritoneal cytology was positive. Her cancer was papillary serous grade 2 within a cyst in her left ovary. Her pelvic and para-aortic lymph nodes were negative. Her disease was upstaged on the basis of appendiceal metastasis from Stage IC to IIIA. She received adjuvant chemotherapy. A comparison of ovarian cancer patients with and without appendiceal metastases showed those with appendiceal metastases were more likely to have apparent advanced Stage III/IV disease (97.7% vs 28.9%, p < 0.001), omental disease (91.8% vs 15.7%, p < 0.001), papillary serous histology (76% vs 46.1%, p < 0.001), grade 3 differentiation (84.7% vs 36.1%, p < 0.000) and positive peritoneal cytology.
Appendectomy with cytoreductive surgery for ovarian and type 2 endometrial carcinoma

Figure 2. — Histological characteristics of the ovarian cytoreduction group; those with positive appendiceal metastases compared with the group with negative or benign appendix histology.

Endometrial carcinoma group with malignant appendix histology n=1

Stage 3c Carcinosarcoma (MMMT) with positive omentum, peritoneal

Endometrial carcinoma group with negative and benign appendix histology n=37

No residual - 2(5.4%)
Stage 1-22(59.5%)
Stage 2-2(5.54%)
Stage 3-9(24.3%)

Type 1- Endometrioid 15(40.5%)
Type 2- Papillary serous 11(29.7%)
Papillary serous & endometrioid- 4(10.8%)

Grade 1-3(8.1%)
Grade 2-7(18.9%)
Grade 3-12 (32.4%)
Not mentioned -

6(16.2%)
4(10.8%)
9(24.3%)

Figure 3. — Histopathological characteristics of the endometrial carcinoma group.
ogy (87% vs 27.6%, p < 0.001). Out of the 31 patients who received neo-adjuvant chemotherapy, appendiceal metastases were present in eight (25.8%).

Figure 3 shows the histopathological characteristics for the endometrial carcinoma group. One patient had metastasis to appendix that was grossly visible at surgery. Her final histology was carcinosarcoma of uterus. A further eleven patients with advanced Stage III/IV disease had no involvement of appendix.

Table 1 shows the individual cases of primary malignancy of appendix. All cases arose in patients presenting with complex pelvic mass deemed likely to be primary ovarian preoperatively. The appendix appeared macroscopically abnormal in only two cases. One, a goblet cell carcinoid had a fusiform expansion of the distal appendix. Another, a signet ring cancer had a shrunken fibrosed appearance. Frozen section was not performed.

The benign tumours of the appendix were hyperplastic polyp (3), mucinous cystadenoma (2), and benign mucocoele (2). Other benign appendiceal lesions were acute appendicitis (6), necrotizing granulomata (1), endometriosis (3), intussusception (1), lymphoid hyperplasia (1), and focal dysplasia (1).

There were no perioperative / postoperative adverse events attributed to the appendectomy in all 251 patients.

Discussion

A questionnaire based European review of clinical practice of cytoreductive surgery for ovarian carcinoma by Cibula et al. [1] revealed substantial differences in the spectrum and complexity of procedures performed for advanced ovarian cancer. Half of the centres reviewed would conduct an appendectomy in advanced ovarian cancer. A third would remove the appendix only if it was macroscopically involved. As appendectomy is not routinely performed in most gynaecology oncology centers in Europe, the present authors undertook this review to evaluate their own practice of appendectomy in the surgical staging of all ovarian neoplasms and type 2 endometrial cancer. Overall 32.7% (82) of 251 patients undergoing surgical staging for ovarian and endometrial cancer in this series had some appendiceal pathology. Forty-seven patients had metastases to the appendix and 20 patients with benign appendiceal pathology. Nine patients had malignant primary appendiceal tumours.

Our ovarian cancer patients had metastasis to appendix in 23% which is lower the 37% to 43% reported by other authors Ayhan et al. [6], Fontanelli et al. [2], Rose et al. [3]. All but one of the patients in this series had gross metastases within the peritoneum and/or omentum. Appendiceal metastases were more likely with grossly evident Stage III/IV disease, positive peritoneal cytology, and with the papillary serous (PSC) type histology. This association confirms the authors’ impression that PSC is more likely to involve the peritoneal cavity more extensively than the clear cell, mucinous or endometrioid sub-types. Appendiceal metastases may represent transcoelomic spread or synchronous malignant evolution of other parts of the coelomic epithelium [7]. The close proximity of the appendix to the adnexa makes it a likely repository for transcoelomic spread. The authors consider removal of the appendix is an integral part of the cytoreductive effort. Usually a simple surgical procedure, extreme fibrosis or large volume metastasis can make appendectomy challenging and caecotomy can result but repair of this is well within the remit of Gynaecological Oncologists.
Only one patient out of 108 with apparent Stage I/II ovarian disease had occult appendiceal metastasis that upstaged her. The low rates of sole occult appendiceal metastases is confirmed by other authors. Fontanelli et al. [2], Ramirez et al. [8], and Bese et al. [9] reported none in their series of 57, 160, and 90 patients respectively. Ayhan et al. [6] reported a rate of 4.9% in 106 patients. Only Ayhan et al. [6] has previously reported upstaging of the disease based on appendiceal metastases alone and our case adds a second to this category. That upstaging may not have been clinically relevant in our case because her positive peritoneal cytology would have raised her to Stage IC and chemotherapy would have been administered in any case. However, complete excision of microscopic disease may be beneficial. The absence of complications related to the appendectomy in this and all other series (Ayhan et al. [6]; Fontanelli et al. [2]; Rose et al. [3], Ramirez et al. [8]) is particularly reassuring when the appendiceal pathology per se did not dictate additional treatments.

One of 35 borderline ovarian tumours involved the appendix. As expected the borderline tumours in our series were predominantly mucinous (85.7%) and the single case with appendiceal metastasis was mucinous. A further three cases had mucinous cystadenoma or myxoma of appendix with secondary involvement of ovary and the appendiceal primaries were occult in all these cases. The appendix and ovarian surface share a propensity for mucinous neoplasia. [10]. Failure to identify and remove the appendiceal mucinous tumour might put the patient at risk of tumour recurrence or subsequent pseudomyxoma peritonei. Timofeev et al. [11] found a low prevalence of appendiceal pathology with cystadenoma of ovary and recommended appendectomy for borderline or invasive mucinous tumours of ovary. However, exclusion of borderline change in a large mucinous cystadenoma of ovary is not easy on frozen section sampling. The occult nature of the appendiceal lesions is concerning. The authors concur with Dietrich et al. [12] that routine appendectomy is reasonable when a mucinous ovarian tumour is suspected. When there is a suspicion of primary appendiceal cancer frozen section should be undertaken so that appropriate colonic staging with right hemicolectomy can be progressed if needed.

The authors’ policy of routine appendectomy identified 16 (6.4%) coincidental primary appendiceal tumours, both benign (2.7%) and malignant (3.6%). All were occult and the rate of detection may reflect the thoroughness of their histopathologists. Tumours of the appendix are infrequent and are usually found during a “routine” appendectomy. In a study of 71,000 specimens taken at appendectomy, Collins et al. [13] found 958 malignant and 3,271 benign tumours, giving an overall incidence of 4.6% for benign tumours and 1.35% for the malignant tumours. The significance of small carcinoid tumours is unknown. Lesions less than one centimetre and possibly up to two centimetres are unlikely to metastasize from the appendix. Metastasis from small bowel carcinoid may occur earlier. Primary appendiceal cancer often presents as pelvic adnexal masses. A review of goblet cell carcinoid like and signet ring tumours by Hristov et al. [14] revealed a majority presenting as ovarian lesions and appendix thickened but fibrosed and not expanded. Goblet cell carcinoid (adenocarcinoid) tumour of the appendix is rare and carries a risk of concomitant and metachronous colorectal cancer [15], so follow-up with endoscopy is recommended. The authors’ general surgery colleagues did not undertake further staging surgery in any of these cases. The only case of signet ring cell carcinoma of the appendix with metastases to the pelvis was deemed unfit for further surgery. The diagnosis of benign appendiceal lesions ranged from acute and chronic inflammation, lymphoid hyperplasia in a cohort of patients with adnexal or uterine pathology is interesting. The inflammation may be a response to the neoplastic process in the pelvis or truly co-incident but giving rise to symptoms that lead to diagnosis of the pelvic neoplasm.

Current gynaecologic oncology guidelines make no clear recommendations on appendectomy and omentectomy in type 2 endometrial cancers. In this group, intraperitoneal staging yielded positive omental metastases in 10.8% and positive peritoneal washings in 16.2%, and appendiceal metastases in 2.6% of 38 patients. The single patient with appendiceal metastasis had omental disease as well. Dilek et al. [5] reviewed appendectomy and omentectomy in 51 patients with clinical Stage I endometrioid adenocarcinoma and found that 3.9% metastases to appendix and six percent metastasis to the omentum. Saygili et al. [16] also found a similar rate with six percent omental metastasis and two percent appendiceal metastasis in apparent early Stage I endometrioid adenocarcinoma. To the authors’ knowledge, this is the first review on appendectomy with type 2 endometrial carcinoma. It is known that type 2 endometrial histology has a propensity for earlier extra uterine spread. Adjuvant chemotherapy is of limited value in such cases and disease remission may rely most on optimal surgical debulking. As such, the present authors would recommend that an appendectomy should be included in the primary surgery effort for patients with type 2 endometrial cancers. Appendectomy does not add to the morbidity of the surgery and can be safely undertaken with minimal access surgery as well.

The continued practice of appendectomy in all ovarian neoplasms and type 2 endometrial cancers is reasonable and safe.

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Contraception after breast cancer: a retrospective review of the practice among French Gynecologists in the 2000’s

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Summary

Purpose of investigation: To describe the French practices regarding contraception after breast cancer in the 2000’s. Materials and Methods: A total of 2,500 forms were sent to gynecologists practicing in France. Inclusion criteria were premenopausal patients who had a history of breast cancer and who had been prescribed contraception after diagnosis. Between June 1, 2002 and January 1, 2003, 197 evaluable responses were retrieved. Results: The median age of the sample was 38.5 years. The most commonly used form of contraception was an intrauterine device (n = 144, 73.1%). Hormonal contraception was prescribed for 42 patients (21.3%), and other methods were used in 29 patients (14.7%) (Condoms n = 14, tubal sterilization n = 7, and others n = 8). Recurrence occurred in 27 patients (13%); 2.9% in the progestin group, 16.3% in the IUD group, and 14.8% with the other methods). Conclusions: It is necessary to evaluate current contraception practices after breast cancer to evaluate the efficacy and safety of contraception in these patients.

Key words: Breast cancer; Contraception; Progestagens; Progestins; Levonorgestrel IUD-intra uterine device.

Introduction

Breast cancer among young women is a major public issue. Of women who are diagnosed with breast cancer, 25% to 30% are premenopausal, and a majority of those patients will undergo chemotherapy. In most case control studies in the literature, pregnancy after breast cancer does not seem to affect malignancy prognosis [1-5]. Nevertheless, when desired, it must be carefully planned in the setting of active counseling by a multidisciplinary team [6-7]. For patients who do not wish to become pregnant, pregnancy should be actively avoided, particularly during tamoxifen treatment, as this medication is known for its teratogenic effects [8]. Moreover, chemotherapy-induced amenorrhea might be associated with an unpredictable resumption of menses, which may result in an unwanted pregnancy. Thus, efficacious, safe and well-tolerated contraception remains of substantial interest in this population. Classical options, solely based on guidelines, include intrauterine devices (IUD), or local methods. Little is known regarding the use of progestins-estrogen or progestatin only contraception. The aim of this survey was to describe the French practice regarding contraception after breast cancer in the early 2000’s. The rate of relapse in this population was also assessed.

Materials and Methods

The authors conducted a retrospective study between June 1, 2002 and January 1, 2003. A total of 2,500 forms were sent once to members of the following three French gynecologist organizations: GERM (Groupe d’Etude et de Réflexion sur les Mastopathies), FNCGM (Fédération Nationale des Collèges de Gynécologie Médicale), and SFG (Société Française de Gynécologie). Patients were included during routine gynecologic consultation. Inclusion criteria were a previous history of premenopausal breast cancer and subsequent contraceptive prescription during the six months period of the study.

Physicians were asked to return forms anonymously after retrieving data on patients who matched the inclusion criteria from their own medical records. No financial or material compensation was granted from returning forms. Breast cancer treatments were delivered primarily in French institutions. Demographic data, patient characteristics, tumor characteristics, and relapses were collected into Excel spreadsheets.

Because of the long follow-up period, some patients may have used several contraception methods. Thus, the time interval of use for each contraceptive method was recorded. To assess relapses based on contraception methods, patients were classified according to the contraceptive they had used for the longest period of time. Given the design of the study, patients who died during the time interval between prescription of contraception and the date of study were not included. In addition, due to its descriptive nature, no statistical testing was performed.

Results

A total of 204 responses were obtained. Seven patients were excluded (no contraception n = 5, missing data n = 1, and menopause n = 1). Results were obtained for 197 patients. Patient characteristics, tumor characteristics, and the treatment modalities utilized are summarized in Table 1.

The median age at cancer diagnosis was 38.5 years, and the median follow up period was 43 months. A high majority of patients had a history of a previous pregnancy
(86.3%) and had one or more children (83.8%). When staged, tumor size was mostly small (T1: 45.8%). Pathologic characteristics showed rather invasive (89.4%), node negative (48.9%), and hormone receptor positive (56.7%) tumors. Treatments included chemotherapy (68%) and endocrine therapy (43.8%).

The most commonly used contraceptive was an IUD (total n = 144, levonorgestrel releasing IUD n = 14). Hormonal contraception was prescribed in 42 cases (progestins n = 40 or combined oral contraceptive n = 2), 18 of whom had hormone receptor positive tumors. Other methods (e.g., tubal sterilization, condoms, other local contraception, and GnRH agonists) were used in 29 patients (Table 2).

The authors categorized the sample into three groups: IUD, progestins, and other methods. A trend towards a longer follow up was seen in the progestin’s group (median follow up: 55 months vs. 43 months (IUD) and 31 months (other methods), respectively, with a lowest rate of grade 3 (11.4% vs. 31.1 and 25.9%, respectively) and node positive tumors (5.7% vs. 22.2 and 18.5%, respectively). After a median follow up of 43 months, 27 patients (13.7%) underwent relapses (ipsilateral (n = 10), contralateral (n = 2), distant (n = 11) or non stageable (n = 4) recurrence). The rates of relapse were 2.9% in the progestin group, 16.3% in the IUD group, and 14.8% with the other methods (Table 3).

Discussion

To the authors’ knowledge, this study is one of the first to date to evaluate the current contraceptive practices after a diagnosis of breast cancer [9]. There is currently little data concerning this area of research in the existing literature. In a survey of 20 cancers survivors (90% of whom had breast cancer), Patel et al. [10] found that 55% of the women (n = 11) were using some type of contraception, with abstinence
Contraception after breast cancer: a retrospective review of the practice among French Gynecologists in the 2000’s

as the preferred method (n = 6, 54.6 %). In the present survey, the most commonly used contraception was IUD, as is often recommended by expert panels [11]. The IUD represents an effective, low cost, and long term contraceptive method that can be used without problems with compliance. In women with breast cancer, its additional lack of theoretical interaction with hormonal and oncologic pathways designates it as the gold standard for contraception. However, its use may be limited by inability to tolerate the device and abnormal bleeding patterns due to unfavorable myometrial or endometrial conditions. It may also aggravate bleeding disorders during menstrual recovery from chemotherapy-induced amenorrhea. Some authors have suggested that the levonorgestrel IUD be used [12], particularly during concomitant tamoxifen therapy. As a SERM (selective estrogen receptor modulator), tamoxifen acts as an agonist on the genital tract, and its use is associated with endometrial pathologies ranging from endometrial hyperplasia and polyps to endometrial malignancy. The use of the levonorgestrel IUD in the setting of the prevention of endometrial pathology remains to be defined. After breast cancer, one case control study compared 79 breast cancer patients using LNG IUD to a control group who did not use LNG IUD (n = 120); there was no significant difference in the recurrence rate between the groups (21.5 and 16.6%, respectively, HR 1.86; CI [0.86-4.00] [13]. However, the retrospective design of this study and the low number of patients does not provide sufficient evidence to recommend LNG IUD after breast cancer routinely. Canadian Gynecologists’ societies [14] consider progestin-only contraception (including levonorgestrel IUD) as a viable option for breast cancer survivors. However, the drug is classified as unacceptable according to the WHO guidelines [11] in women with a diagnosis of breast cancer. Some patients might be unwilling to have such a device placed, while others may have contraindications to an intrauterine device.

Though its safety after breast cancer has not been demonstrated, the second most commonly used contraception was progestin, mostly as oral high dose progestagens. These results highlight specific habits with respect to contraception [15, 16]. French gynecologists have been using progestins for a long time to treat a wide range of “female disorders”, from menstrual and menopausal transition bleeding to mastodynia and benign breast disease. Though most of them are not labeled for use in this setting, they are also widely used as contraceptives. Their current use, based on data from a Parisian hospital service, has increased with the advent of the uniquely French specialty of medical gynecology. They are an efficient and well-tolerated contraceptive with mostly weak metabolic or cardiovascular adverse effects when compared to estrogen-containing contraceptives. As a result, consumption of progestins in

| Table 3. — Relapses according to patients characteristics and contraception type. |
|---------------------------------|--------|--------|--------|--------|        |
| 197 135 | % Relapse 22 | Progestins 35 | Relapse 1 | Others 27 | Relapse 4 |
| Relapse rate (%) | 16.3% | 2.9% | 14.8% |
| Median follow up (months) | 43 | 55 | 31 |
| Mean age at treatment | 42.9 | 44.7 | 42.9 |
| Histological type |
| in situ | 14 | 10.4% | 4 | 3 | 8.6% | 2 | 7.4% | 1 |
| invasive | 121 | 89.6% | 18 | 32 | 91.4% | 1 | 25 | 92.6% | 3 |
| Tumor size |
| T0 | 5 | 3.7% | 1 | 1 | 2.9% |
| T1 | 57 | 42.2% | 1 | 19 | 54.3% | 13 | 48.1% |
| T2 | 25 | 18.5% | 8 | 22.9% | 9 | 33.3% | 1 |
| T3 | 7 | 5.2% | 2 |
| T4 | 3 | 2.2% |
| NP | 38 | 18 | 7 | 20.0% | 1 | 5 | 18.5% | 3 |
| Grade (invasive disease only) |
| 1 | 17 | 12.6% | 4 | 7 | 20.0% | 3 | 11.1% |
| 2 | 47 | 34.8% | 4 | 12 | 34.3% | 12 | 44.4% | 2 |
| 3 | 42 | 31.1% | 7 | 4 | 11.4% | 1 | 7 | 25.9% |
| N.S. | 15 | 11.1% | 7 | 9 | 25.7% | 3 | 11.1% | 2 |
| Nodal status(invasive disease only) |
| Node positive | 30 | 22.2% | 3 | 2 | 5.7% | 5 | 18.5% | 1 |
| Node negative | 58 | 43.0% | 9 | 14 | 40.0% | 15 | 55.6% | 1 |
| NP | 33 | 24.4% | 10 | 16 | 45.7% | 1 | 5 | 18.5% | 2 |
| Hormonal receptor |
| negative | 34 | 25.2% | 10 | 5 | 14.3% | 1 |
| positive | 68 | 50.4% | 7 | 15 | 42.9% | 18 | 66.7% | 3 |
| NP | 19 | 14.1% | 5 | 12 | 34.3% | 7 | 25.9% | 1 |

Note: when several contraception were reported for one patient, she was classified according to the method used the longest period. Combined oral contraception is not reported in this Table because the two patients had taken another contraception method any longer.
France is estimated at least ten-fold higher than in other European countries or in the US, and one quarter of French premenopausal women would have used progestagens at some point [16]. Therefore, these results clearly do not represent the prescription patterns of other countries. Moreover, this survey was conducted in the early 2000’s, just before the WHI study [17], which incriminated the medroxyprogesterone acetate (MPA) portion of hormonal replacement therapy in increasing the risk of breast cancer. Until that time, progestagens had long been considered to protect the mammary gland from breast cancer [18], and studies on progestasive contraception and the risk of breast cancer provided reassuring data [19-24]. It is well known that different progestagens may act differently on the mammary gland, and the deleterious results of MPA have not been confirmed with French oral progestagens [25]. However, it seems impossible that such a large number of progestagens should currently be prescribed after breast cancer.

Several other methods, including local methods, were used as contraception. Their lack of interaction with the mammary gland is noteworthy; however, their efficacy has not been explored in this context. Moreover, one must also consider the frequent alterations in sexuality seen in breast cancer survivors (sexual discomfort, fear of sexual intercourse, etc.) [26, 27]. Local methods may not represent a suitable method for couples encountering such difficulties. In the present sample, tubal sterilization was rare, but could represent an option for patients who achieved their parental project, as the hysteroscopic sterilization method, Essure®, is now available as a less invasive method than tubal sterilization.

Although the results of this study are interesting, several limitations must be highlighted. First, the low rate of responses raises concerns about the representativeness of the gynecologists surveyed. Second, the retrospective design of the study introduces many biases. The studied population might have been selected for unintentionally, as women undergoing ambulatory follow up are less likely to have metastatic breast cancer and may represent a healthier population. As the median follow up was 43 months, it can be assumed that high-risk patients who relapsed early failed to be screened. This is consistent with the weak proportion of node-positive diseases and the high rate of hormone responsive tumors, reflecting a category of low-risk patients when compared with tumor characteristics generally encountered in young breast cancer patients [28]. In the present study, the authors found no difference in the relapse rates based on contraception use. However, the study was not designed to assess relapse rates. It must be noted that a trend towards a lower frequency of recurrence was noted in the progestin group, although the median follow-up in this group was longer than in the other groups. Although not significant, the difference in node positive and grade 3 disease (lower in the progestins groups) may be relevant and probably widely overrules prognosis than contraceptive use differences. Patients who relapsed after progestins may also have been underreported due to medical/legal fears. The prescription of such drugs is indeed classically contraindicated after breast cancer. The latter hypothesis seems improbable because of the anonymous nature of the form. Another hypothesis is that progestins might effectively decrease breast cancer recurrence. The survey the authors conducted does not allow to draw any conclusions concerning the protective effect of progestagens after breast cancer. Considerable concerns have recently been raised about the impact of the progestins on the breast, and it is unlikely that randomized controlled trials will occur. In this context, our work, which does not support a deleterious effect of progestagens in this setting, although biased by multiple factors, may be the only study of its kind for a long time.

With the increase in both breast cancer incidence and cure rate, survivors are becoming much more numerous, leading to a growing burden of post-breast cancer care. Supportive care and counseling in gynecology and fertility are a major concern for these women, and contraception is an important part of this issue. To date, it is unclear whether the contraception has an effect on the evolution of breast cancer. Further data would be needed to evaluate the efficacy and safety of contraception in breast cancer patients. In this setting, contraception is a personal choice that should be discussed with the patient based on her sexuality, her desire, and her compliance. Therefore, it seems improbable that a randomized controlled trial would be conducted. Prospective longitudinal studies of contraceptive use in premenopausal women after breast cancer should be done.

Acknowledgements

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References


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Borderline ovarian tumors: outcomes of fertility sparing surgery

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Eskisehir Osmangazi University School of Medicine, Eskisehir (Turkey)

Summary
Aim: Borderline ovarian tumors (BOT) account for ten to 20 percent of all epithelial ovarian carcinomas and often occur in reproductive ages. The aim of this study was to evaluate the clinical and reproductive outcomes of patients who were diagnosed with BOT and underwent fertility sparing surgery. Materials and Methods: Patients younger than 40 years who underwent fertility sparing surgery for BOT from 2004 to 2012 were reviewed retrospectively and were evaluated according to the reproductive and clinical outcomes. Results: Twenty-eight patients younger than 40 years with BOT underwent fertility sparing surgery. Median follow up time was 42 ± 28.1 months. During the follow up period, two patients (7.1%) developed recurrence at 35 and 36 months, respectively. Five (17.9%) out of 28 patients became pregnant during the follow up period. Conclusion: Fertility sparing surgery should be the first choice for the treatment of BOT in patients who wish to preserve fertility.

Key words: Borderline ovarian tumors; Fertility sparing surgery; Pregnancy.

Introduction
Borderline ovarian tumors (BOT) account for ten to 20 percent of all epithelial ovarian carcinomas and often occur in reproductive age. This group of tumors are a distinct diagnostic category of ovarian tumors, which have a favorable prognosis compared with the invasive epithelial ovarian tumors. Due to the fact that one-third of the cases with borderline tumors are under the age 40, preserving of childbearing capacity and ovarian hormonal function is more important despite the proper staging procedures, including hysterectomy and bilateral salpingo-oophorectomy [1]. The treatment has to be personalized according to the fertility request of the patients. Although fertility sparing treatment modalities such as cystectomy or unilateral salpingo-oophorectomy are usually performed for maintenance of ovarian function [2, 3], preservation of uterus with ovarian cryopreservation is also an option for preserving childbearing capacity [4]. Fertility sparing surgery (FSS) is feasible in both early and advanced stages of disease [5]. The aim of this study was to evaluate the clinical and reproductive outcomes of patients who underwent FSS in the present institute.

Materials and Methods
Fifty-five patients diagnosed with BOT from 2004 to 2012 were retrospectively reviewed from the hospital records and patient charts. Patients who were younger than 40 years and underwent FSS with pathologically confirmed BOT on the definitive report were included in the study. Preservation of ovarian function and uterus was defined as FSS. Patients who were diagnosed as menopausal after surgery, who had an insufficient follow up data, were excluded from the study. Patients’ age, obstetric history, menstrual cycle, complaint, mode of surgery, type of surgical procedure, and type of BOT histology were reviewed. The laparotomies were achieved with midline incision. Regardless of the mode of surgery, peritoneal washings and inspection of the abdominal cavity were performed at the time of surgery. During the follow up period, patients were assessed with pelvic examination, CA-125 testing and ultrasonography every three months for the first two years, every six months up to five years and then annually. The proper follow up continued during pregnancy and thereafter.

Results
Twenty-eight patients younger than 40 years with BOT underwent fertility sparing surgical procedures. The median age of the patients was 29.07 ± 5.41 years. Fifteen (53.5%) of the patients were nulliparous and all of the patients had regular menstrual cycles. The most common complaint was pelvic pain (39.3%). Demographic characteristics of the patients are presented in Table 1. The mean of preoperative CA-125 value was 52.07 ± 101.24 IU/ml. Four (14.2%) patients underwent laparoscopy and the remaining underwent laparotomy. Cystectomy, cystectomy, and lymphadenectomy, unilateral salpingo-oophorectomy (USO), and USO+ lymphadenectomy were performed in eight (28.5%), five (17.9%), 13 (46.4%), and in two (7.1%) of the patients, respectively (Table 2). Omentectomy was performed in seven (25%) of the patients who also underwent lymphadenectomy. Histologic subtype of the tumor was serous in 20 (71.4%) of the patients and mucinous in eight (28.6%) of the patients. A total of 28 patients were evaluated in early stage disease, 20 (71.4%) of which were in Stage IA and the remaining eight (28.6%) were in Stage IC. None of the patients had adjuvant chemotherapy after surgery. Median follow up time was 42 ± 28.1 months. Dur-
and pregnancy continued uneventfully. Eight (28.6%) patients were pregnant at the time of surgery and bilateral salpingo-oophorectomy. Among 28 patients, four recurrences were treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy. The recurrences developed after cystectomy and lymphadenectomy. The other four recurrences developed after cystectomy and the other four vaginally. After deliveries, the follow up period, two (7.1%) of the patients developed recurrence at 35 and 36 months after the surgery. One of the recurrences developed after cystectomy and the other recurrences were treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy. Among 28 patients, only one (3.6%) patient was pregnant at the time of surgery and pregnancy continued uneventfully. Eight (28.6%) patients attempted to conceive and five (17.9%) of them became pregnant spontaneously during the follow up period and delivered healthy newborns at term. One of them conceived four times in total, three of which resulted in abortion. During the pregnancy, none of the patients had adverse outcomes. One of the patients delivered by cesarean section and the other four vaginally. After deliveries, the follow up continued uneventfully and no recurrences were diagnosed.

Table 1. — Patients' demographic characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Standard deviation (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.07</td>
<td>± 5.41</td>
</tr>
<tr>
<td>Gravida (n)</td>
<td>1.17</td>
<td>± 1.56</td>
</tr>
<tr>
<td>Parity (n)</td>
<td>0.92</td>
<td>± 1.18</td>
</tr>
<tr>
<td>Abortion (n)</td>
<td>0.21</td>
<td>± 0.56</td>
</tr>
</tbody>
</table>

Table 2. — Types of surgeries performed.

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>n (28)</th>
<th>% (100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystectomy</td>
<td>8</td>
<td>28.6</td>
</tr>
<tr>
<td>Cystectomy + lymphadenectomy</td>
<td>5</td>
<td>17.9</td>
</tr>
<tr>
<td>Unilateral salpingo-oophorectomy</td>
<td>13</td>
<td>46.4</td>
</tr>
<tr>
<td>Unilateral salpingo-oophorectomy + lymphadenectomy</td>
<td>2</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Discussion

Since BOT was first described, treatment options became more conservative with the knowledge of rare recurrence rates and excellent prognosis. In the present study the authors exposed that reproductive outcomes after FSS for BOT are promising and the recurrence rate is comparable with the previously published data [2, 3]. Various studies have suggested the oncologic safety of FSS in patients with early-stage BOT [2, 3], also feasibility of FSS in advanced stages of disease was reported [5]. In the present study, all of the patients were evaluated in early stages of disease which varied between Stage IA to IC.

As the importance of surgical staging was previously shown for patients who undergo FSS, the procedure is suggested as a complete surgical staging, except for total abdominal hysterectomy and bilateral salpingo-oophorectomy. Furthermore, systematic lymphadenectomy is not recommended for comprehensive staging surgery, unless in the presence of lymph node positivity [6]. Regardless of the mode of surgery, either laparoscopy or laparotomy, peritoneal washings and exploration of the abdominal cavity were performed in the present study. In seven (25%) out of 28 patients in this study, lymphadenectomy was performed but lymph node positivity was not determined.

Preserving of uterus with ovarian cryopreservation was reported to be feasible in 53% of patients in which the procedure was planned before surgery [4]. Ovarian cryopreservation may be an option for patients with bilateral BOT.

The rate of spontaneous fertility was reported to be about 50% after FSS [7]. The rates of pregnancy are promising and the complication rates are not disappointing after conservative treatment [2, 8]. Neither the rates nor the ongoing pregnancy are influenced by the disease, hence FSS is worthy for patients who wish to preserve fertility.

In a multicenter study, the recurrence rate was reported 30% for cases who underwent cystectomy [9]. Also, in the presented cases, both recurrences occurred after cystectomy and they accounted for 15.4% of the patients who underwent cystectomy. Cyst rupture, type of surgical procedure, stage, and peritoneal implants were reported to be independent prognostic factors for recurrence in several studies [9-11].

In a French multicenter study, Fauvet et al. recommended salpingo-oophorectomy rather than cystectomy for borderline ovarian tumors in pregnancy [12]. In this study, one of the patients who underwent salpingo-oophorectomy for BOT was pregnant and the pregnancy continued uneventfully without any adverse outcomes.

Romeo et al. revealed the association between the shorter time of recurrence and incomplete surgery [6]. After completion of childbearing, prophylactic removal of remaining ovaries in which most of the recurrences develop, may be recommended [13]. The time of surgery may be delayed until the diagnosis of recurrences or after menopause in younger patients [2]. To date, there is no published data evaluating the efficiency of prophylactic oopherectomy for BOT in the literature and further studies are needed.

Conclusion

FSS should be the first choice for the treatment of BOT in patients who wish to preserve fertility, but the higher recurrence rates, especially in cystectomy, should be kept in mind.

References

Borderline ovarian tumors: outcomes of fertility sparing surgery


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Management of breast lobular carcinoma in situ: radio-pathological correlation, clinical implications, and follow-up

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Summary

Purpose of investigation: to show management of patients with breast lobular carcinoma in situ (LCIS). Materials and Methods: This study is the retrospective review of 65 patients, between 1996 and 2012, with isolated LCIS of the breast, evaluated through clinical examination, ultrasound, and mammography at the first examination and follow-up. Results: In 53 patients (81.54%), clinical examination was negative. In 14/65 (21.54%) cases, ultrasound was positive and led to biopsy. The clusters of tiny calcifications were the predominant mammographic pattern (45 cases, 69.23%). Forty-six patients (70.77%) underwent surgical biopsy after guided stereotactic palpation of metallic marker (hook-wire), 12 (18.46%) by stereotactic vacuum biopsy (SVB), 5 (7.69%) by core needle biopsy (CNB) under ultrasound guidance, two (3.08%) patients CNB with clinically palpable nodules. Fourteen (21.54%) women underwent a quadrantectomy or total mastectomy, five relapses occurred, respectively, three LCIS and two infiltrating ductal carcinomas (IDC). Follow-up ranged from 12 to 144 months. Conclusion: LCIS is a risk factor for invasive carcinoma and should be managed with careful follow-up, but if there is a discrepancy between pathology and imaging, surgical excision is mandatory.

Key words: Lobular carcinoma in situ (LCIS); Breast cancer; Follow-up; Lobular intraepithelial neoplasia (LIN); Management.

Introduction

The management of lobular carcinoma in situ (LCIS) remains controversial: its definition is controversial, as well as biology, clinical significance, natural history and the best management in the short and long term after diagnosis.

The true incidence of LCIS in the general population is unknown, but it ranges from 0.8% to 5% of all breast cancers [1]. The LCIS is often multifocal (50% - 80%), multicentric (60-90%) and bilateral (23%-59%) [2-3].

The diagnosis is often incidental as there are no specific clinical and mammographic signs for this lesion [4-6]. Lobular neoplasia broadly defines the spectrum of changes within the lobule, ranging from atypical lobular hyperplasia (ALH) to LCIS. LCIS and ALH are associated with an increased risk of invasive breast cancer, both ipsilateral and contralateral, and more than 50% of these diagnoses occur 15 years after the first diagnosis of LCIS [7]. However, this risk of malignancy in the literature also achieves 37% [8-10].

The purpose of this manuscript was:

1. to examine the clinical, sonographic, and mammographic correlations of LCIS, the signs that have aroused suspicion and led to the diagnostic biopsy;
2. to evaluate the follow-up of patients with diagnosis of isolated LCIS at biopsy, not associated with malignant breast disease or previous breast cancer.

Materials and Methods

The authors evaluated 65 patients aged between 22 and 76 years (mean age 50 years) with a diagnosis of LCIS detected on biopsy, recruited at the “Breast Unit of the Institute of Radiological Sciences “C. Bompiani”, University of Sassari, between 1996 and 2012. The present Institutional Review Board approved the study.

Initially, the authors enrolled 162 patients, but selected only cases with the following recruitment criteria:

– Knowledge of the clinical and radiological findings relevant to the diagnosis of LCIS;
– Histological diagnosis of LCIS in the absence of other malignancies;
– Absence of previous malignancy (ipsilateral and contralateral breast diagnosed with LCIS);
– Knowledge of the course of follow-up for a minimum of 12 months.

In detail, 97 patients were excluded for the following reasons:

– 19 had history of previous malignancy;
– 45 did not undergo follow-up in our Institute and it was not possible to know their follow-up results;
– Clinical and/or radiological finding were not present for 25 patients because they were studied in other facilities before biopsy;
– Eight patients had other malignancies at specimens.

Among all patients, 36 (55.38%) were premenopausal and 29 (44.62%) postmenopausal. Family history of breast cancer was present in 28 patients (43.07%), 18 patients took the contraceptive pill for a period exceeding two years (27.69%), nine (13.85%) had performed estrogen replacement therapy for a period exceeding two years, 33 (50.77%) had their first full-term pregnancy before 35 years, and ten (15.38%) have had one abortion.

The patients were studied by clinical examination, ultrasonography (with high frequency probes: 7-15 MHz) and mammogra-
tours in 11 cases: six (9.23%) without calcifications, and 69.23% (Table 3).

were the predominant mammographic pattern (45 cases, with calcifications. The clusters of tiny calcifications lesions without calcifications; architectural distortions, nodules with clear margins (fibroadenoma); star
biopsy were: minute clustered calcifications, nodular le-

Results

In most patients (53 cases, 81.54%) the clinical examination was negative. Two patients (3.08%) had nipple discharge, serous type. In three patients (4.61%), the clinical examination revealed areas of thickening, corresponding to two cases of structural distortion and a case of irregular nodular lesion without calcifications at mammography. In two patients (3.08%), clinical examination showed a single isolated nodule. Five patients (7.69%) had diffuse nodular texture in both breasts (Table 1).

In 14/65 (21.54%) cases, ultrasound was positive and led to biopsy (Table 2); percutaneous core biopsy under ultrasound guidance in just five patients was done; the others underwent surgical biopsy (48 patients) or percutaneous guided stereotactic vacuum biopsy (12 patients). The mammographic findings that have suggested the biopsy were: minute clustered calcifications, nodular lesions with irregular contours with or without calcifications, nodules with clear margins (fibroadenoma); star lesions without calcifications; architectural distortions with calcifications. The clusters of tiny calcifications were the predominant mammographic pattern (45 cases, 69.23%) (Table 3).

LCIS was present in nodular lesions with irregular contours in 11 cases: six (9.23%) without calcifications, and five (7.69%) with calcifications. In one case (1.54%) the lesion was represented by a nodular lesion with clear limits, that histologically resulted to be a fibroadenoma with a LCIS in its contest. Similarly, in one case (1.54%) the cancer was contained in a star lesion without calcifications. Four patients (6.15%) had an area of architectural distortion of the breast, with clustered calcifications inside.

Fifty-one patients (78.46%) who presented with a mammographic finding were negative at ultrasound examination. Two (3.07%) nodular lesions with irregular contours on mammogram, one with and one without calcifications, appeared as hypoechoic nodules with polilobulated margins at ultrasound. In three other cases of irregular breast lump at mammography (two with and one without calcifications), ultrasound showed a hypoechoic area with poorly defined margins. Three cases, at mammography, of irregular nodular lesion with calcifications and two cases of structural distortion with calcifications showed to be a dishomogeneous hypoechoic area at ultrasound examination. The case of fibroadenoma appeared as a hypoechoic three-cm nodule with regular shape and sharp boundaries.

Histologic examination was performed on surgical biopsy after guided stereotactic placement of metallic marker (hook-wire) in 46 patients (34 clustered calcifications, nine nodular lesions with irregular contours, one star lesion without calcifications, two structural distortions with calcifications), two patients with clinically palpable nodules (one hypoechoic nodule with regular contours and one hypoechoic nodule with polilobulated contours), percutaneous stereotactic vacuum biopsy in 12 patients (ten clustered calcifications, two architectural distortions with calcifications), percutaneous core biopsy under ultrasound guidance in five patients (one hypoechoic area with poorly defined boundaries, three dishomogeneous hypoechoic areas, and one hypoechoic nodule with polilobulated contours).

After the first biopsy diagnosis, the authors performed four quadrantectomies, respectively, for a unifocal LCIS and for three multifocal LCIS. Histological examination of the surgical specimens confirmed the first diagnosis in three cases, but in one case (LIN III) the excised quadrant contained an infiltrating lobular carcinoma (ILC) (Table 4). In ten cases the authors performed immediately complete

<table>
<thead>
<tr>
<th>Mammographic findings</th>
<th>N. patients</th>
<th>%</th>
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<tbody>
<tr>
<td>Negative</td>
<td>3</td>
<td>4.62</td>
</tr>
<tr>
<td>Calcifications</td>
<td>45</td>
<td>69.23</td>
</tr>
<tr>
<td>Irregular nodular lesions without calcifications</td>
<td>6</td>
<td>9.23</td>
</tr>
<tr>
<td>Irregular nodular lesions with calcifications</td>
<td>5</td>
<td>7.69</td>
</tr>
<tr>
<td>Nodular lesion with clear margins (fibroadenoma)</td>
<td>1</td>
<td>1.54</td>
</tr>
<tr>
<td>Star lesions without calcifications</td>
<td>1</td>
<td>1.54</td>
</tr>
<tr>
<td>Architectural distortion with calcifications</td>
<td>4</td>
<td>6.15</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>100 %</td>
</tr>
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Table 1 — Clinical examination.

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<tr>
<td>Nipple secretion</td>
<td>2</td>
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<tr>
<td>Areas of thickening</td>
<td>3</td>
<td>4.61</td>
</tr>
<tr>
<td>Single nodule</td>
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<tr>
<td>Diffuse nodular texture</td>
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<tr>
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<td>100 %</td>
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Table 2 — Ultrasound findings.

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<tbody>
<tr>
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<tr>
<td>Hypoechoic nodule with regulars margins</td>
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<tr>
<td>Hypoechoic nodule with polilobulated margins</td>
<td>2</td>
<td>3.07</td>
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<tr>
<td>Hypoechoic area with poorly defined margins</td>
<td>4</td>
<td>6.15</td>
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<tr>
<td>Dishomogenous hypoechoic area</td>
<td>7</td>
<td>10.76</td>
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<tr>
<td>Total</td>
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<td>100 %</td>
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mastectomy due to the presence of multicentric LCIS, and in one case of these histologic examination, they found the presence of ductal carcinoma in situ (DCIS) with comedo and cribriform type (Table 4).

The authors found that LCIS specimens were:

- in 38/63 (60.32%) cases, LIN I;
- in 24/63 (38.09%) cases, LIN II;
- in 1/63 (1.59%) case, LIN III.

The follow-up was negative in all patients undergoing quadrantectomy or mastectomy immediately after the first diagnosis (14 patients, 21.54%).

Five recurrences occurred in 51 patients (9.8%) undergoing to follow-up (Table 5). In all cases the finding that led to a new biopsy had been the presence of suspicious calcifications at mammographic examination. In two cases the authors found unifocal LCIS, occurring respectively 12 (LIN I) and 24 (LIN II) months after initial diagnosis. In one case (LIN 1), which occurred three years after initial diagnosis, histology showed the presence of a multifocal LCIS. In two cases (LIN I and II), one year after the first diagnosis, they found an infiltrating ductal carcinoma (IDC) associated with LCIS; patients then underwent mastectomy.

Discussion

Understanding the biological evolution of LCIS and lobular neoplasia (LN) is the key to determine the most appropriate management. Although Foote and Stewart [9] have recognized a spectrum of LN, they thought that even the lightest of this process could constitute an “extreme hazard”. On the contrary, Haagensen et al. [10] have suggested, based on data of long period follow-up, that the LCIS was an increased risk factor for cancer in both breasts, and then required close monitoring. They also proposed that similar lesions were called “lobular neoplasia (LN)” rather than carcinoma in situ. To date, this term has been accepted by WHO beside the classical distinction LCIS / atypical lobular hyperplasia (ALH) [11]. The argument that LN is a risk factor and not a true precursor of invasive disease is based on important observations [11]:

- Low risk of development of invasive cancer;
- The development of the disease in both breasts with relatively equal frequency;
- Invasive cancer after the lobular tumor is ductal or lobular with equal probability.

However, molecular studies have shown that the genetic profiles of LCIS and synchronous invasive lobular carcinoma are often similar to each other [12-14]. Therefore are there forms at higher risk of invasive transformation, which
could be considered precursor of cancer? The tumor exhibits a spectrum of lobular acinar involvement that can be divided into LCIS and ALH. The criteria for the diagnosis of LCIS include nuclear, cytological, and architectural characteristics [15] and a variability has been established in the relative risk for subsequent development of cancer between ALH (relative risk 5.5) and LCIS (relative risk between 8 and 10) [16-20]. Furthermore, a subtype of pleomorphic lobular neoplasia (pleomorphic lobular carcinoma in situ - PLCIS) is widely recognized [21-22]. The PLCIS cells may show apocrine differentiation, necrosis, and microcalcifications mimicking high-grade ductal carcinoma in situ (DCIS). The division of lobular neoplasia in three subclasses of LIN (lobular intraepithelial neoplasia) [11, 23] has been also introduced: the frequency associated with invasive carcinomas (ductal and lobular) would increase from 14% in LIN 1 to 23% for LIN 3. Figure 1 shows histological features of LIN.

In addressing the management of diagnosis of LCIS, given the recent achievements in human pathology, it is desirable to know ab initio the subtype of LCIS, for different invasive potential of non-classical forms. Actually, in the present study the authors found just one case of LIN III, and it was associated with an infiltrating lobular carcinoma.

In contrast to ductal lesions, lobular neoplasia usually has no clinical or mammographic signs. It is usually an incidental finding in a biopsy specimen which is performed for other reasons [4,5]. In the present series, approximately 82% of women were negative at physical examination, and the remaining percentage had no relevant clinical findings and were not absolutely correlated with the presence of LCIS (i.e., fibroadenoma). Equally nonspecific mammographic findings: the LCIS was contained in regular, irregular or stellate nodular lesions, or simply in areas of architectural distortion associated with calcifications. However the data shows the prevalence of calcifications associated with LCIS (70%). This association between LCIS (or more generally, lobular neoplasia) and calcification is an important key in the management of lobular neoplasia at core biopsy. The calcifications are associated with lobular neoplasia between 8% and 53% of core biopsies containing classical lobular neoplasia [24], therefore the percentage is placed above the upper limit. This discrepancy could be due to the lack of separation between pleomorphic and classical forms, the first presenting calcifications more frequently than the latter. Malignancy can be an incidental finding in a biopsy for calcifications associated only with benign disease [24-25].

Two forms of calcifications are, however, recognized in association with LCIS [11]: pleomorphic necrotic LCIS calcifications are associated with necrotic debris and resemble the calcifications of high-grade DCIS comedocarcinoma. The classic form, not necrotic, of LCIS is associated with calcifications that are similar in appearance to those of benign proliferative changes. However, the majority of these proliferative lesions does not appear as a mass and neither contains microcalcifications [11].

The ultrasound examination performed to complement mammography was negative in a high percentage of cases (78.46%), revealing a method without a good sensitivity for the diagnosis of LCIS. The ultrasound appearance of lesions, in addition, has presented a wide variability, and this translates into a low specificity.

Women diagnosed with LCIS should undergo annual bilateral mammography; in women with dense breast an additional ultrasound should be considered [26]. Further studies are recommended to determine whether women diagnosed with LCIS should or should not undergo MRI for intensified surveillance, as has been recommended in women with increased genetic risk [11, 25].

In the present series, approximately 70% of patients underwent excisional surgical biopsy. When diagnosed at surgical biopsy, generally the LCIS does not require further investigation, even if present at the surgical margin [11], except for LIN III subtypes. Some studies [27-28] recommend surgical excision to exclude lesions that require immediate therapy. Some authors [27] have suggested that surgical excision may not be necessary when focal lobular neoplasia is diagnosed at core biopsy.

In the present series, the indication for mastectomy was greatly variable. The authors considered treatments done in a wide range of time, from 1996 to 2012, and surgical approach changed towards a more conservative surgery. Probably, patients who underwent mastectomy, nowadays, would have undergone just a quadrantectomy. Sometimes, mastectomy was a patient’s choice. The authors biopsied all suspicious areas in the breast.

A diffuse lobular neoplasia may indicate an associated invasive carcinoma and should lead to excision [27-28]. The present series confirms this finding: in four cases, following an excisional biopsy, a multifocal LCIS was found and the extension has suggested to extend the excision with quadrantectomy. In one case out of four, the pathological examination revealed the presence of an infiltrating lobular carcinoma in a context of multifocal LCIS.

The surgical aspect of the problem justifies the radiodiagnostic aspect; cases where more aggressive surgical treatment is indicated should be carefully selected, while the majority of patients diagnosed with LCIS will be allocated to radiodiagnostic follow-up, keeping in mind that it is useless the excision of a classic LCIS (not pleomorphic/ not necrotic) incidentally found in a breast, when it is probable that there are other LCIS in the same breast and in the contralateral breast, given the high rate of multicentricity and bilaterality of LCIS.

Radiation therapy and chemoprevention have been considered as treatment choices for management of LCIS. Nonetheless, there is not enough literature addressing the benefits of radiation therapy, while chemoprevention is
thought to significantly reduce the percentage of progression towards invasive forms [11].

Bilateral mastectomy is to be considered an overtreatment in most cases (no genetic predisposition), as the LCIS very frequently does not evolve. Fisher et al. [28], in a follow-up of 12 years of patients diagnosed with LCIS, treated with local excision alone, showed the progression to invasive lesions in 5% of cases for the ipsilateral breast at first diagnosis of LCIS, and in 5.6% for the contralateral breast. Anquer et al. [29] indicated a risk of 4.2% for the ipsilateral breast and 3.5% for the contralateral breast, but stressed the wide variability between studies. The present case series indicated that invasive carcinoma developed at a rate of just below 4% (two cases).

According to the literature, the authors believe that excision appears mandatory when:

- There is discordance between pathological changes at biopsy and clinical or radiographic findings, and this factor could be the cause of progression according to many studies, like those of Menon et al. [24] and Nagi et al. [30]. The findings are considered discordant when: 1) the radiological finding was a mass but pathologic diagnosis at core biopsy was lobular neoplasia or 2) X-ray shows suspicious calcifications that were not represented in the sample of core biopsy;
- Lobular neoplasia is associated with another lesion generally to excise in the core (for example, atypical ductal hyperplasia, ADH);
- There is a lobular neoplasia with atypical features (such as pleomorphic LCIS).

Hwang et al. [27] reported that, after excluding cases in which evolution was associated with non-classical morphology, association with invasive carcinoma was present in only 1%.

In opposite to the present results, Destounis et al. [31] concluded that the diagnosis of LCIS at needle core biopsy revealed that 84% of lesions either were malignant or were atypical or high risk surgery, of which 33% were found to be carcinoma; they suggested that LCIS should be excised when noted at core biopsy.

In conclusion, LCIS is certainly an important risk factor for developing invasive cancer, even after many years of diagnosis. When this finding is revealed at biopsy, the histological type should be necessarily clarified, to perform surgical excision of the area in which one type is present that is at increased risk of association with invasive carcinoma (LIN 3), or when there is a discrepancy between the report of pathological and diagnostic suspicion generated from imaging techniques. When a LCIS form is found which does not respond to these two previous conditions, if LCIS is present at the margin of surgical specimen excised, the literature does not counsel to perform additional diagnostic samples. In any case, women with this lesion should undergo a close follow-up, in order to identify as early as possible, the presence of an infiltrating carcinoma.

References


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Management of a primary retroperitoneal mucinous cystadenocarcinoma: case report

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Summary

Purpose: To review the treatment of primary retroperitoneal mucinous cystadenocarcinoma (PRMC). Case report: A 30-year-old woman had a large retroperitoneal mucinous adenocarcinoma treated with conservative laparoscopic surgery. Two years later, she was found to have bilateral ovarian cysts at the time of cesarean section. Since cystectomies revealed mucinous adenocarcinoma, she underwent complete surgical staging and adjuvant chemotherapy at this time. Conclusion: A rare case of similar cancer in the ovary following treatment for PRMC was described. It is unclear whether the prognosis is improved by oophorectomy. Further cases and long-term follow-up are necessary.

Key words: PRMC; Ovarian cancer; Laparoscopy; Oophorectomy.

Introduction

Primary retroperitoneal mucinous cystadenocarcinoma (PRMC) is a rare tumor, the pathogenesis of which remains unclear and controversial. Most authors support the theory of coelomic metaplasia [1-3]. Supernumerary ovary or heterotopic ovarian tissue has also been considered a possible source of retroperitoneal mucinous cystic tumors [4, 5]. Another possibility is that this may be an outgrowth of münnous epithelium over other components from a primary teratoma of the retroperitoneum [6]. Some authors have also mentioned the possibility of enterogenic duplication cyst as the origin [7].

Recently, coelomic metaplasia is being considered as a possibility for ovarian epithelial neoplasms. The process is just like the neoplastic development in the primary Müllerian system [7-9]. Therefore, some patients have undergone not only tumor resection, but also hysterectomy and bilateral salpingo-oophorectomy [1, 4, 8], notwithstanding the fact that in all these cases, the resected genital organs showed no evidence of involvement or tumor infiltration. To improve clinical outcomes, oophorectomy is advocated [1].

Laparoscopy has become the standard approach for the treatment of female patients with an abdominal mass. On the other hand, some problems may occur when tumors provisionally diagnosed as benign preoperatively turn out to be malignant.

A case of similar cancer that occurred in the ovary following treatment for PRMC is presented. A laparoscopic procedure was done for PRMC. On the basis of a review of the literature, management of such cases is discussed.
Figure 1. — (a) This magnetic resonance image demonstrates a large, monolocular, cystic mass. (b, c) Laparoscopic findings: (b) A large cystic mass arising from the retroperitoneum in the right iliac fossa was found displacing the ascending colon to the left side. (c) Bilateral ovaries are normal in shape and size.

Figure 2. — (a) Microscopically, the wall of the cystic lesion is lined by mucinous columnar epithelium showing mild to moderate nuclear atypia, papillary projections, and mild stratification. A focal, apparently stromal lesion. The features are consistent with mucinous adenocarcinoma. (Hematoxylin and eosin at ×40 magnification) (b) Mucinous metaplasia was adjacent to the mesothelium. The benign single layer of mucinous epithelium is seen in transition to the stratified layer of epithelium of the malignant area. (Hematoxylin and eosin at ×100 magnification) (c) Positive staining for CEA was seen in this area of malignant neoplastic cells.
tic ovarian tumors were confirmed. The right and left ovaries measured 6 × 4 cm and 4 × 3 cm, respectively. Bilateral cystectomy was done, and the same mucinous adenocarcinoma was diagnosed microscopically. The staging procedure included a total abdominal hysterectomy with bilateral salpingo-oophorectomy, appendectomy, omentectomy, and both pelvic and para-aortic lymphadenectomy. The appendix and the pancreas were grossly normal in size and shape. Remaining cancer was found at both the site of adhesion of the ovary and the pouch of Douglas. Washing cytology was negative. The final diagnosis was Stage IIb with Grade 1 mucinous ovarian cancer. Chemotherapy with six courses of paclitaxel 180 mg/m² and carboplatin (AUC = 5) was administered. The patient was doing well without evidence of disease eight months later.

Discussion

Mucinous cystadenocarcinoma is not an uncommon gynecologic malignancy. Mucinous tumors of the ovary are occasionally associated with mucinous tumors at other sites, such as the cervix or appendix. They may sometimes involve two different organs with the same histology, so it is difficult to determine both the primary and metastatic sites. When retroperitoneal mucinous cystadenocarcinoma is assumed to be the result of coelomic metaplasia, the possibility exists that a similar ovarian cancer can occur from a metaplastic change.

Is adjuvant bilateral salpingo-oophorectomy justified at the first laparoscopic operation? Reports regarding the extent of surgical treatment of PRMC were investigated, and these are summarized in Table 1. Many authors advise hysterectomy with bilateral salpingo-oophorectomy [3, 4, 8, 9], either simultaneously or later at re-exploratory laparotomy accompanied by peritoneal washing and lymph node sampling [2-4, 8, 9]. It has been reported that patients who undergo hysterectomy and bilateral salpingo-oophorectomy were free of recurrence [3, 8, 9]. The tumor has been said to be affected by female hormones [4]. However, some of those patients who had metastases in organs other than the ovary developed recurrence and died [4-6]. The question remains as to whether bilateral salpingo-oophorectomy improves the prognosis. Considering conception and ovarian function, sufficient evidence was required to resect ovaries without pathological changes. It is recommended that adjuvant bilateral salpingo-oophorectomy be restricted to women who have completed their child-bearing or are postmenopausal [4].

Choosing between laparoscopy and laparotomy for the treatment of abdominal tumors is difficult. In this case, a laparoscopic procedure was performed because the tumor was preoperatively diagnosed as a benign serous tumor. When serous fluid was aspirated, some of the fluid may...
have leaked. A retroperitoneal approach was taken for the retroperitoneal tumor. With the normal left approach, it is difficult to see the right iliac fossa. It was necessary to aspirate the fluid because of the size of the tumor. It has been reported that cyst rupture is more frequent during laparoscopic management, suggesting that laparoscopy may increase the risk of dissemination [10]. However, metastasis of the cancer affected only the ovary. It is hard to ascribe the metastasis in this case to leakage. Moreover, it has been reported that port-site metastasis is linked to unprotected extraction [10]. A recovery bag was used in this case.

In the present case, recurrence was seen two years after the first operation. There is little literature reporting long-term follow-up, but long-term follow-up is required to determine the time of recurrence.

In conclusion, a rare case of a similar cancer that occurred in the ovary following treatment for PRMC was presented. It is unclear whether the prognosis of PRMC is improved by oophorectomy. More cases and long-term follow-up are necessary.

References

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Transection of the obturator nerve by an electrosurgical instrument and its immediate repair during laparoscopic pelvic lymphadenectomy: a case report

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Summary
Obturator nerve injury seldom occurs in gynecologic surgery. However, gynecologic oncologic surgery, including pelvic lymph node dissection, increases the risk of this type of injury. Microsurgical techniques are usually performed for the repair of the nerve injury. Herein the authors report a case of obturator nerve injury caused by an electrosurgical instrument during laparoscopic pelvic lymphadenectomy, and its prompt repair by laparoscopic procedure in a 44-year-old patient with cervical cancer.

Key words: Obturator nerve injury; Laparoscopic neurorrhaphy; Pelvic lymphadenectomy.

Introduction
Obturator nerve injury is a rare complication in gynecologic surgery [1,2]. However, performing pelvic lymphadenectomy during a radical pelvic surgery or staging surgery for gynecologic malignancies increases the risk of obturator nerve injury [3,4]. Surgical treatment is mandatory in the management of the injured obturator nerve during lymphadenectomy. The options for surgical treatment are laparoscopic and transabdominal approaches [5]. Herein, the authors report a case of an obturator nerve that was transected and thermally injured by an electrosurgical device during laparoscopic radical hysterectomy, pelvic lymphadenectomy, and para-aortic lymph node dissection, and the immediate repair of the nerve using the laparoscopic approach.

Case Report
A 44-year-old Korean woman (gravida 7, para 2) had a four-month history of post-coital bleeding. The results of cervical liquid-based cytology examinations and DNA-based assays showed high-grade squamous intraepithelial lesions and infection with human papillomavirus type 16. A colposcopically directed biopsy and a subsequent conization by the loop electrosurgical excision procedure of the uterine cervix revealed a moderately differentiated large cell, non-keratinizing, squamous cell carcinoma. A bimanual rectovaginal examination revealed a 2.5 × 2.0 cm, moderately differentiated, large cell, non-keratinizing, squamous cell carcinoma confined to the cervix without lymph involvement. Cystoscopy and proctosigmoidoscopy demonstrated no infiltration of the bladder or rectum. A metastatic workup, which included magnetic resonance imaging (MRI) of the abdomen and a pelvis positron emission tomography (PET) scan of the torso, revealed no evidence of distant metastasis. The International Federation of Obstetrics and Gynecology (FIGO) clinical Stage of the disease was IB1.

The patient underwent laparoscopic radical hysterectomy, bilateral pelvic lymphadenectomy, and para-aortic lymph node sampling with a three-port transperitoneal laparoscopic approach (Figures 1A and B). During right pelvic lymphadenectomy, the right obturator nerve was inadvertently transected by an electro-surgical device (Figure 1C). The injury occurred because the right obturator nerve was extremely superficial compared to its usual location. The Department of Orthopedic Surgery and Neurosurgery was consulted to learn how to perform precise surgical techniques and choose appropriate suture materials during the surgery in relation to this injury. After the laparoscopic lymphadenectomy was safely completed, a careful inspection showed that the nerve was transected and had thermal injury at the ends. After debridement of the thermally injured ends, they were re-approximated laparoscopically end-to-end with two 6-0 polypropylene sutures for perineural repair and three 6-0 epineural sutures for achieving a tension-free anastomosis (Figures 1D, E, and F). Because the debrided portion of the nerve was only six mm (three mm at each end), a tension-free repair without further mobilization of the nerve appeared to be possible. An immediate laparoscopic repair of the nerve was performed by the gynecologic surgeon. The total operative time was five hours, and the blood loss was 180 ml. The postoperative course was uneventful. Histologic examination revealed a 2.5 × 2.0 cm, moderately differentiated, large cell, non-keratinizing, squamous cell carcinoma confined to the uterine cervix without lymph involvement.

The patient noted mild weakness of the right leg on the operative day when she awoke from the anesthesia. However, she was able to ambulate on the first postoperative day and did not show any clinical evidence of abnormal adductor function or any other neurologic deficit on neurologic examination. She was discharged on the seventh post-operative day, and no specific physical or medical therapy was performed. At 12 months postoperatively, she is doing well and is healthy without any neurologic deficit.

Discussion
The obturator nerve is a mixed sensorimotor nerve that originates from the lumbar spine (L2–L4) and innervates the adductor muscles of the medial thigh [3]. The nerve trav-
Figure 1. — Image of the obturator fossa seen in laparoscopy. The image shows the repaired obturator nerve with the epineural end-to-end tension-free reattachment. A) right obturator lymph node dissection; B) injured obturator nerve; C) transected right obturator nerve; D), E), and F) laparoscopic neurorrhaphy for transected right obturator nerve with 6-0 polypropylene suture and 6-0 suture.
Transection of the obturator nerve by an electrosurgical instrument and its immediate repair during laparoscopic pelvic etc.

Transection of the obturator nerve by an electrosurgical instrument and its immediate repair during laparoscopic pelvic etc.

els through the pelvis within the obturator fossa and then leaves the pelvis with the obturator artery and vein via the obturator foramen. In gynecologic surgery, injury of the obturator nerve is extremely rare, and is most frequently associated with endometriosis, obstetrical forceps injury, obturator hernia, pelvic lymphadenectomy for the treatment of gynecologic and urologic malignant lesions, and a prolonged dorsal lithotomy position [1-3,5,6]. Neurotmesis of the obturator nerve by surgical instruments during surgery is rarely reported as a complication in gynecologic surgery [3,7]. Because the obturator nerve is surrounded by adipose tissue, soft tissues, and lymph nodes in the obturator fossa, the identification of the nerve prior to the removal the tissues and lymph nodes is usually difficult. Therefore, the obturator nerve can undergo complete transection or thermal damage by various surgical instruments as a result of blunt or sharp dissections during pelvic lymphadenectomy. In the present case, the right obturator nerve underwent complete division and thermal damage by an electrosurgical device. Injury of the obturator nerve usually causes pain extending down the medial thigh into the knee and hip (Howship-Romberg sign), gait disturbance due to weakness of the adduction of the thigh, and sensory loss of the medial thigh [3]. If the obturator nerve is cut during the surgical procedure, its immediate repair is mandatory. Repair is generally performed with microsurgical techniques. However, laparoscopic surgical techniques are considered to be useful alternatives to microsurgical techniques in this case, since laparoscopy is usually able to show a magnified view sufficient for performing a meticulous repair with very thin sutures. The most important step in the repair is the epineural end-to-end tension-free coaptation [3,7]. Resolution of the symptoms from the obturator nerve injury depends on the severity and nature of the injury. However, patients with immediately repaired nerve injury usually show complete resolution of the symptoms within one year after injury [7]. In this case, a notable point is that the right obturator nerve was injured with thermal damage by an electrosurgical instrument. After debridement at both ends of the cut, an epineural end-to-end tension-free coaptation was performed. Within six months after immediate repair, the symptoms were completely resolved. In the case of nerve injury with thermal damage, immediate repair also seems to be mandatory and to be able to minimize the sequelae. If tension-free reattachment of the nerve ends is impossible due to extensive nerve damage or loss, immediate grafting of the nerve may be necessary [4,8].

Conclusions

This case suggests that laparoscopic repair of the transected obturator nerve is a feasible surgical technique alternative to microscopic surgery, and a divided nerve with thermal damage also can also be completely recovered by meticulous debridement and repair.

References


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Axillary lymph node metastasis as first presentation of peritoneal carcinomatosis from serous papillary ovarian cancer: case report and review of the literature

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Summary

Ovarian cancer usually spreads into abdominal cavity and to the loco-regional lymph nodes. Extra-abdominal metastases are less frequent and isolated axillary metastases are very rare. The authors describe the case of a 49-year-old woman who was diagnosed with a peritoneal carcinomatosis from ovarian cancer by mean of an enlarged axillary lymph node biopsy, whose histological examination identified as a ovarian cancer metastasis. Patient was treated by peritonectomy and intraperitoneal chemohyperthermic perfusion (HIPEC). Although patients with axillary lymph node metastasis from ovarian cancer are though to be metastatic (FIGO Stage IV), surgical radical treatment and adjuvant systemic chemotherapy can achieve the same prognosis of Stage IIIb-c patients, suggesting they could be a particularly good prognosis subset of patients. Early differential diagnosis between ovarian or breast cancer in axillary lymph node metastasis is crucial but not always very simple, because of the very different course and treatment of these tumours.

Key words: HIPEC; Peritonectomy; Ovarian carcinoma; Axillary lymph node metastasis.

Introduction

Ovarian cancer usually spreads into the abdominal cavity as the first site of extraovarian diffusion. Due to the peritoneal fluid circulation pattern, during its clinical history the disease involves the greater omentum, pelvic and para-colic gutter peritoneum, diaphragm, liver capsule and the serosal surface of small and large bowel, and often can be confined into the abdominal cavity for many years. Symptoms are generally related to intrabdominal compression by the growing pelvic mass, ascites or bowel obstruction due to peritoneal implants on bowel wall or rectal involvement by a pelvic mass.

However, more often later in the patient’s course, metastasis of ovarian cancer to retroperitoneal organs such as kidney, or distant metastasis to liver, lung or brain are seldom reported. Pelvic and para-aortic lymph nodes are usually affected by ovarian cancer with a rate reaching 67%, while extra abdominal lymph node involvement is less common. Although this pattern of spread can be possible in N+ patients, the involvement of supradiaphragmatic lymph nodes without metastases in para-aortic or iliac ones is exceptional.

Isolated axillary metastasis as first sign of ovarian carcinoma without other loco-regional or distant lymph nodes metastases is a rare condition [1]; the authors describe the case of a 49-year-old woman who was diagnosed an axillary isolated enlarged lymph node during a screening ultrasound for breast cancer prevention, which was the first and only sign of a serous papillary ovarian carcinoma with peritoneal carcinomatosis without abdominal or other extra-abdominal lymph node metastases.

Case Report

A 49-year-old woman was diagnosed an enlarged right axillary lymph node during an ultrasound examination for breast cancer screening. A fine needle aspiration of the lymph node was done and the diagnosis was metastasis from unknown primary carcinoma. Breast ultrasonography and nuclear magnetic resonance (NMR) examination were negative for lumps. Patient medical history was negative for previous gynaecological or breast diseases.

Histological examination of surgical specimen from the excisional biopsy of the enlarged lymph node showed microscopic lymph node structure disrupted by neoplastic cells proliferation characterized by papillar architecture of columnar epithelium with hyperchromatic nuclei (Figure 1, hematoxylin and eosin [H/E] x2.5 high-power field [HPF]). Several psammoma bodies were present. At immunohistochemical evaluation, neoplastic population was found positive to anti CK-7 and WT-1 (Figure 2, x40 HPF) antibodies and negative for anti vimentin antibodies, thus suggesting an ovarian origin. Haematological tests were all unremarkable, with normal haemoglobin and WBC count, except for serum CA125 levels, (750 um/ml). A contrast enhanced whole body computed tomography (CT) scan was then performed and showed a bilateral ovarian neoplasm with involvement of the uterus and the pelvic peritoneum with mild ascites. No other enlarged lymph node was seen in abdominal or extra abdominal stations.

Patient underwent surgical treatment; cytological examination of ascites confirmed malignancy and a radical hysterectomy with bilateral salpingo-oophorectomy, complete omentectomy, appendectomy, and pelvic peritonectomy were performed. A complete iliac, para-aortic, and inferior mesenteric artery lymphadenectomy was
also performed. A number of scattered peritoneal implants on right paracolic gutter and Douglas pouch were ablated by means of an argon beam coagulator, and a three-cm bulky implant of the bladder peritoneum was excised. The remaining peritoneal surfaces, as well as the diaphragms, the liver capsule, and the small bowel loops were free from disease. Final peritoneal cancer index (PCI), according to Sugarbaker’s scoring system, was 9. Completeness of cytoreduction was considered optimal (CC-0 at CC-score by Sugarbaker). At the end of the surgical procedure, the patient underwent hyperthermic intraperitoneal chemotherapy (HIPEC) with the closed technique, using a 75 mg/m²/l cisplatin (CDDP) solution at 43°C for 60 minutes, following Sugarbaker’s criteria [2].

Histological examination of the surgical specimen confirmed the diagnosis of a poorly differentiated serous papillary cystoadenocarcinoma of the ovary (Figure 3, H/E x5 HPF), with implants on the left adnexa, on the uterus surface with early myometrial infiltration and with peritoneal carcinomatosis on omental surface, on the Douglas, and right paracolic gutter peritoneum. The 34 lymph nodes removed were all negative for neoplastic involvement.

Immunohistochemical evaluation of the sample confirmed anti CK-7, CK-20, WT1 positive staining, anti vimentin, and GCDFP-15 negative staining of the neoplastic population.

Postoperative course was uneventful and the patient was discharged after 18 days in good general conditions. She underwent an adjuvant six courses systemic chemotherapy with carboplatin and paclitaxel. Ca125 normalized during therapy, reaching the final value of five um/ml. Patient underwent a six-month periodical follow-up, including clinical evaluation, serous markers determination, and a whole body contrast-enhancement CT scan for the first two years and then every year.

To date, she is alive and disease free after seven years of follow-up.

Discussion
It is well known that the principal and earliest way of diffusion of ovarian carcinoma is the peritoneal spread. Peritoneal fluid circulation “drives” the neoplastic cells towards their final destinations on the peritoneal surface [3]. Limited or diffused peritoneal carcinomatosis is present at the first diagnosis in more than 75 percent of patients. Iliac and para-aortic lymph node metastases are less frequent, although not exceptional [4, 5]. Systemic metastases are present in 38 percent of patients late in disease history [6] and in eight to 22 percent at the time of first diagnosis [7]. One of the first clinical signs of the presence of an ovarian carcinoma is the development of high volumes of ascites, together with variable signs of intestinal obstruction due to small bowel implants or the development of a pelvic mass with involvement of the sigmoid colon. Extra-abdominal lymph node metastases are less frequent, especially in serous carcinoma, and follow the lymphatic way involving progressively the loco-regional lymph nodes and the para-aortic chains [3, 7-9].
The presence of an extra-abdominal lymph node metastasis alone as first and unique sign of the disease is very rare [1]. The diagnosis of ovarian carcinomatosis from an axillary lymph node metastasis is exceptional. In a recent article by Euscher et al., on a sample of 35 patients affected by ovarian carcinoma, peritoneal carcinoma or carcinoma of the fallopian tube with loco-regional lymph node metastases, the incidence of axillary metastases in patients with ovarian carcinoma was 0%, while more frequent were metastases to supravacuclavicular or inguinal lymph nodes [3]. Zang et al., in their series of patients affected by ovarian cancer with extra-abdominal diffusion, found only six and five patients with supraclavicular and inguinal lymph node metastases, respectively. [8]

Literature report very scarce data about extra-abdominal lymph nodes involvement in primary advanced ovarian cancer. In a review by Cormio et al. [7], five cases of extra-abdominal lymphatic spread are reported on a group of 162 patients with epithelial ovarian cancer.

The neoplastic involvement of supra-diaphragmatic lymph nodes without loco-regional ones is not easy to explain. Some studies proposed that serous carcinoma could follow the central lymphatic duct without interesting iliac or para-aortic stations [10, 11]. However the real anatomic or physiopathological basis of this pattern of spread is still unknown.

Synchronous axillary lymph nodes involvement in ovarian cancer is not exceptional, reaching in some studies the rate of 60% to 70% of the patients [12,13], but the presence of an isolated axillary metastasis in an asymptomatic patient has been reported only in a few patients [1, 3].

In the present patient, the only metastatic lymph node was the axillary one, without any involvement of iliac, para-aortic or supra-diaphragmatic chains. In such a patient, to assess whether the lymph node is a primary cancer or is a metastasis from an ovarian cancer or of a primary undiagnosed breast cancer, seems to be an issue of primary importance. Immunohistochemical studies, especially the evaluation of the WT-1 expression, seem appropriate for such differential diagnosis [14]: in the present patient positivity was found both in axillary lymph node and in the ovarian surgical sample. Other authors have focused on the key role of the GCDFP-15 evaluation to rule out the ovarian or breast origin [15]. In agreement with the present finding, Monteaudo et al. demonstrated that more than 71 percent of metastatic breast cancers express the GCDFP-15, while it is always negative in primary ovarian carcinoma [16].

The presence of psammoma bodies or calcifications is also important to determine the origin of the primary cancer: in the present patient, they were present both in the axillary lymph node and in the ovarian carcinoma, suggesting, together with a negative mammography, the ovarian origin of the axillary metastasis. Nevertheless, diagnostic problems may arise because in fact axillary metastatic ovarian cancer may sometimes appear as lymph node calcifications at mammography [17].

Although prognosis in patient with axillary or breast metastasis from ovarian carcinoma is poor and the reported median survival rate accounts for 13 months (range 7-66) [12], the present patient is still alive and disease free after seven years.

In conclusion, metastatic ovarian carcinoma presenting with an isolated axillary lymph-node metastasis is an uncommon event; its recognition and differential diagnosis with metastatic breast carcinoma to the ovary is of great important because of the very different prognosis and treatment.

Patients with peritoneal carcinomatosis and single extra-abdominal lymph node metastasis from ovarian carcinoma are a particular subset of ovarian cancer patients who are able to be treated by radical surgery, intraperitoneal hyperthermic chemotherapy, and systemic adjuvant chemotherapy with a reasonable hope of good prognosis and long life expectancy. Clinical history and histological and immunohistochemical accurate comparison of the WT-1 and of the GCDFP-15 expression between the ovarian cancer and axillary metastasis are helpful to determine the correct diagnosis and therefore the more appropriate treatment.

References


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Leiomyosarcoma of the broad ligament: a case report with CT and MRI images

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Summary
Primary leiomyosarcoma of the broad ligament is a very rare and highly malignant gynecological tumor. The authors report a 61-year-old postmenopausal woman with signs and symptoms of malignant ovarian tumor. Preoperative magnetic resonance imaging (MRI) was interpreted as being suspicious for malignant tumors, such as an ovarian cancer or a leiomyosarcoma of the broad ligament, so laparotomy was performed. Macroscopically, the tumor was revealed as a 18×13.7×9.5 cm degenerated, multiple cystic part and solid whitish part arising from broad ligament which on histopathology proved to be leiomyosarcoma. To the best of the authors’ knowledge, primary leiomyosarcoma of the broad ligament has been documented in 21 reports or so, and no imaging findings are available. Here the authors present the MRI findings of primary leiomyosarcoma of the broad ligament.

Key words: Leiomyosarcoma; Broad ligament; Pelvic tumor; MRI.

Introduction
Primary leiomyosarcoma of the broad ligament is a very rare and highly malignant gynecological tumor.

To the best of the authors’ knowledge, primary leiomyosarcoma of the broad ligament satisfying the strict criteria provided by Gardner et al., has been documented in 21 cases [1-3]. Imaging findings are not available in any of these reports [4]. Here the authors present the magnetic resonance imaging (MRI) findings of primary leiomyosarcoma of the broad ligament.

Case Report
A 61-year-old, gravid 2 para 2 postmenopausal woman with a sense of abdominal fullness presented to the present hospital under suspicion of an ovarian carcinoma. She had no significant gynecological or past medical history. The lower abdomen was distented with a firm and immobile mass. The serum LDH level was 233 IU/l (reference level, 115~217 IU/l). Ultrasonography documented a 14.5 cm diameter solid mass filling the pelvis. Contrast-enhanced computed tomography (CT) of the abdomen also suggested the presence of a 11.2×15.6 cm mass in the pelvis (Figure 1), which was enhanced heterogeneously. The liver and lungs were normal and there was no para-aortic or iliac lymphadenopathy. MRI of the pelvis was performed. T2-weighted scan demonstrated a mass beside the right ureterine wall with cystic and solid components containing hemorrhage or necrosis (Figure 2a). The right ovary and uterus were identified as normal and separate from the mass (Figure 2b), and flow voids were seen within the pedicle of the tumor. Dynamic contrast-enhanced MRI of the pelvis showed that with the exception of the necrotic components, the mass was enhanced in the early phase (Figures 2c 1-2-3). Since the authors could not rule out a malignant tumor, such as ovarian cancer or leiomyosarcoma of the broad ligament, based on these radiologic findings, the patient was admitted to this institute to undergo surgical resection. After a complete workup, laparotomy was performed, which revealed a large, lobulated, firm mass in the lower abdomen, and pelvis. The mass was adherent to the right broad ligament and the right fallopian tube. So, the mass was resected en bloc with the right uterine appendages.

Macroscopically, the tumor was white, multinodular, solid, measuring 18×13.7×9.5 cm. Cut surface showed solid whitish tissue and multiple small cystic spaces with central degenerated yellowish area. Foci of hemorrhage and necrosis were seen. The right ovary and fallopian tube were found to be normal and completely independent of the mass. Macroscopically, the tumor was composed of malignant spindle cells characterized by high mitotic activity and nuclear pleomorphism (Figures 3a, 3b). Subsequent immunohistological examination showed diffuse positivity for alpha-smooth muscle actin (α-SMA) and desmin (Figure 3c). The histological and immunohistochemical profiles of this tumor matched a diagnosis of leiomyosarcoma. Because there was no relationship between the tumor and ovary, fallopian tube, and uterus, the primary site of the tumor was estimated as broad ligament. After providing detailed patient counseling, total abdominal hysterectomy with left salpingo-oophorectomy (TAH-LSO) was recommended. TAH-LSO and histological examination of the internal genitalia did not show any signs of disease dissemination. In the view of the localized leiomyosarcoma of the broad ligament, adjuvant postoperative combination chemotherapy was not given.

The woman developed lung and pelvic lymph node metastasis six months after undergoing the second operation, so combination chemotherapy (gemcitabine; 900 mg/m² on days 1 and 8, and docetaxel; 100 mg/m² on day 8) was administered [5].

Discussion
Primary leiomyosarcoma of the broad ligament of the uterus is a rare neoplasm. Gardner et al. proposed the definition of tumors of the broad ligament, requiring that they
“occur in or on the broad ligament, but are completely separated from and in no way connected with either the uterus and the ovary”[6]. According to this definition, only 21 cases have been reported in the English literature [1-3].

Primary leiomyosarcoma of the broad ligament of the uterus is characterized by the presence of no symptoms, i.e., abdominal pain, abdominal distention, constipation, pollakiuria, urine retention, and anorexia, and is characterized by the absence of specific symptoms [7]. However, many patients with broad ligament cancer display a lack of symptoms and are most often diagnosed with advanced stage at initial presentation and treatment. So, the clinical aspect of broad ligament tumors is similar to that of the ovarian and uterine tumors. Optimal management of leiomyosarcomas of the broad ligament is controversial. In most cases, the same management as in leiomyosarcoma of the uterus is followed [8].

No cases have been diagnosed correctly before surgery, and there have been few descriptions of their appearances.

Figure 1. — Contrast-enhanced axial CT of the pelvis. Contrast-enhanced axial computed tomography scan of the pelvis demonstrates the mass (arrows), which is enhanced heterogeneously.

Figure 2. — MRI of the pelvis.
2a: Sagittal T2 weighted MRI demonstrates a mass (arrows) beside the right uterine wall with cystic and solid component.
2b: Note that the right ovary (circle) and uterus (arrowhead) are normal.
2c: Dynamic contrast-enhanced MRI (1: preintravenous gadolinium, 2: early phase, 3: delayed phase).
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Under such circumstances, preoperative characterization of the tumor is judged as fundamental when planning surgery for pelvic tumors. MRI is important through cartographic studies of tumor and it seems to be capable of identifying the anatomic relationship with adjacent viscera and determining resectability [9]. In the presented case, a normal uterus and normal ovary could be identified on MRI. The major differential diagnosis of leiomyosarcoma of the broad ligament, include gynecological, urological and gastro-intestinal tumors, and lymphoma and metastatic tumors [10]. When experiencing a case of a pelvic tumor of unknown origin, it must be considered to make differential diagnosis of tumors derived from the broad ligament.

Conclusion

The authors have experienced a case of primary leiomyosarcoma of the broad ligament representing as ovarian carcinoma. Malignant tumor that occurs in the broad ligament is rare, and the incidence of leiomyosarcoma is very low among them. Preoperative diagnosis of leiomyosarcoma of the broad ligament is so difficult that more sophisticated diagnostic imaging tools and accumulation of clinical cases, including treatment and prognosis, are needed.

Acknowledgement

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References


Figure 3. — Histology and immunohistochemistry of leiomyosarcoma.
3a: The tumor consisted of pleomorphic spindle cells showing fasciculation. (HE, S ×100) mitosis and pleomorphism.
3b: Tumor cells showed marked nuclear pleomorphism. Abnormal mitotic figures were prominent (HE, S ×400).
3c: Tumor cells showed diffuse positivity for α-SMA staining of smooth muscle myosin antibodies (×400).


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Chylous ascites after retroperitoneal aortocava lymphadenectomy for endometrial cancer: a case report

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Summary
This is a case report of chylous ascites after retroperitoneal aortocava lymphadenectomy for endometrial cancer. There are few reports of chylous ascites in gynecologic surgery. Treatment is primarily conservative. The present case was resolved with a low fat diet with medium-chain triglyceride (MCT) supplements and somatostatin IV.

Key words: Chylous ascites; Gynecologic surgery; Para-aortic lymph node dissection; Somatostatin.

Introduction
Chylous ascites is the accumulation of chyle in the abdominal cavity. It is an uncommon occurrence in the course of treatment for gynecological cancer. In this setting, it can be caused by several mechanisms: leakage from severed lymphatic channels following para-aortic lymph node dissection or as a secondary effect of radiotherapy. Metastatic blockage of the lymphatic channels may also have this effect [1].

Most cases of chylous ascites in gynecologic oncological patients occur in patients who have received radiation therapy after para-aortic lymph node dissection. There are rare reports of chylous ascites following para-aortic lymphadenectomy for gynecological cancer [2-4].

The authors present a case of postoperative chylous ascites in a patient with endometrial cancer, which was successfully managed with conservative measures (paracentesis, low-fat diet, somatostatin IV, and medium-chain triglyceride supplements (MCT).

Case Report
A 61-year-old woman, gravida 1, para 1, was diagnosed with endometrial adenocarcinoma via hysteroscopic biopsy after presenting several episodes of postmenopausal bleeding. Her previous medical history included menopause at 52 years and an abdominoplasty. She had been taking tibolone until a few months prior to the diagnosis.

Preoperative magnetic resonance imaging (MRI) revealed a tumor measuring 33 x 26mm, with myometrial infiltration >50%.

Following hospital protocol, she underwent laparoscopic hysterectomy, adnexectomy, bilateral pelvic lymphadenectomy, and retroperitoneal aortocava lymphadenectomy extending to the left renal vein. She was discharged two days later.

On the 9th postoperative day she came to the emergency room complaining of back pain. Pelvic ultrasound revealed a liquid collection in the right hypocondrum, compatible with a lymphatic cyst. A computed tomography (CT) scan showed no signs of internal bleeding and confirmed the finding of a retroperitoneal periaortic liquid collection extending into the pelvis, and compressing the inferior vena cava, which suggested a hematoma without active bleeding. She remained hospitalized for three days and required analgesia with intravenous morphine. After discharge the patient came to the emergency room a second time, where she remained one day for intravenous pain control.

After this episode the patient did not consult again until eight days later (22nd postoperative day), this time complaining of progressive abdominal distension during the last three days. Her abdomen was distended and fluctuating, and pulmonary auscultation revealed diminished ventilation in the lower quadrants. Blood work evidenced moderate hypoproteinemia: total proteins were 4.4 g/dl (range 6.4 - 8.3 g/dl) and albumin 23.6 g/l (range 36 - 51 g/l). Her leukocyte, hemoglobin, and hematocrit levels were within the normal range.

Ultrasound revealed a moderate amount of abdominal fluid as well as a retroperitoneal liquid area measuring nine by eight cm. Paracentesis yielded 2.5 l of milky fluid, which led to a diagnosis of chylous ascites.

Treatment was begun with somatostatin IV (six mg / 24h continuously for three days), and a no fat diet with MCT supplements (15 ml / six hours). On the third day of treatment the authors suspended MCT administration due to diarrhea.

The patient improved dramatically and was discharged eight days later. Slight hypoproteinemia persisted (5.5 g/dl), which returned to normal levels in the following weeks. An ultrasound on the day of discharge still showed moderate ascites.

The diet was maintained for three months, and chylous ascites did not recur after suspending it.

Discussion
Chylous ascites are a rare complication of mediastinal and retroperitoneal surgery, such as aortic aneurysm repair [5] or aortocava lymphadenectomy [2]. It is the result of interrupted intestinal lymphatic flow in its trajectory to or up the thoracic duct [1].

Most reports related to gynecologic oncology are women who developed chylous ascites after lymphadenectomy and abdominal radiotherapy [6]. However in recent years there
has been an increase of reports of chylous ascites in the postoperative period [4, 7]. The initial presentation is usually as painless abdominal distension, usually within days after surgery. If left untreated, it can result in malnutrition and hypoproteinemina, as well as lymphophenia and hypogammaglobulinemia [8]. The diagnosis is aided by paracentesis, which yields a milky white fluid with high triglyceride content [1].

The objective of conservative management is to reduce lymphatic flow and maintain nutrition to facilitate healing of the damaged lymphatic channels. In the present case, this was achieved with a fat-free diet with MCT supplements, as well as somatostatin IV. Total parenteral nutrition is also an option [2].

Long-chain triglycerides enter the blood stream through the lymphatic channels, forming chyle, which is an emulsion of chylomicrons in lymphatic fluid. Eliminating them greatly reduces chyle production. MCTs are absorbed through the portal system, and are a good option for maintaining adequate fat intake during conservative management of the lymphatic leak [9].

Somatostatin or its analogue octreotide decrease the intestinal absorption of fat and reduce lymph production, and are important weapons in the conservative management of chylous ascites.

Conservative management is the cornerstone of postoperative chylous ascites treatment. Evans et al. report a 77% success rate in their series of 23 patients with postchemotherapy postoperative chylous ascites [10].

More aggressive interventions include direct surgical repair or peritovenous shunts.

In conclusion, chylous ascites is a rare complication of gynecologic oncologic surgery. Conservative management, consisting of somatostatin IV with or without total parenteral nutrition, is usually effective.

References

Malignant mixed Müllerian tumor with small cell neuroendocrine differentiation: a case report and review of the literature

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Summary
Introduction: Small cell neuroendocrine differentiation (NE) in malignant mixed Müllerian tumors (MMMTs) is a rare and unusual occurrence with very few previously reported cases. There is no consensus regarding its diagnosis, classification, and optimal treatment options. Case: The authors report a patient with endometrial MMMT and NE differentiation who initially received comprehensive surgery followed by adjuvant chemotherapy containing cisplatin and etoposide. She further underwent metastasectomy and received carboplatin and paclitaxel for the relapse. She is still alive 12 months after the diagnosis. The authors performed a review of literature in order to characterize the clinical phenotype. These patients have a very aggressive disease. Median life expectancy seems to be less than a year. Conclusions: It is reasonable to perform comprehensive staging surgery followed by adjuvant chemotherapy irrespective to stage of the disease.

Key words: Malignant mixed Müllerian tumor; Small cell neuroendocrine differentiation; Endometrium.

Introduction
Malignant mixed Müllerian tumors (MMMTs) are aggressive biphasic neoplasms histologically composed of both malignant epithelial and mesenchymal components. The epithelial component may be of different Müllerian types, often a high-grade carcinoma such as serous, endometrioid, clear cell or undifferentiated. Whereas the sarcomatous component may be homologous or heterologous depending on whether it is composed of native mesenchymal elements of the Müllerian tract, such as endometrial stroma, fibrous tissue, smooth muscle or other non-native elements such as osteogenic, chondroblastic, lipoblastic or rhabdomyoblastic element [1].

Small cell neuroendocrine (NE) differentiation in MMMTs is quite rare as an epithelial component [2-7]. Herein the authors report a case of homologous endometrial MMMT with small cell carcinoma component with a brief review of the literature.

Case Report
A 67-year-old woman with neglected postmenopausal bleeding admitted to the present clinic with an endometrial biopsy of high-grade endometrial adenocarcinoma. On physical examination, she had an unremarkable cervix with a 16-week in size uterine mass extending to the umbilicus. Transvaginal ultrasound revealed an enlarged uterus with an irregular mass located within the uterine cavity. Bilateral adnexae were normal. An abdominal computed tomography revealed a 15 x 12 x 10 cm in size mass within the endometrial cavity and multiple pelvic-paraaortic lymphadenopathies. No distant metastases were detected. The patient underwent exploratory laparotomy. The uterus was enlarged with irregular and nodular serosal surface. There were suspicious small peritoneal implants on the serosa of the urinary bladder. Both ovaries were grossly described as atrophic. Inspection of the abdomen and pelvis revealed no other abnormalities. Peritoneal washings from the pouch of Douglas and bilateral para-colic gutters were obtained. A comprehensive staging surgery, including total abdominal hysterectomy with bilateral adnexectomy, infracolic omentectomy, and pelvic-paraaortic lymph node dissection up to the renal vessels, was performed. Biopsy samples were taken from the suspicious peritoneal surfaces. The patient had an uneventful postoperative course.

Figure 1. — Macroscopic appearance of the tumor.
Uterus was 15 × 15 × 15 cm in size on macroscopic examination. The serosal surface was fragile, tense, and nodular (Figure 1). Uterine cavity was filled with a bulky mass, 15 cm in diameter, with a lobulated cut surface and extensive necrosis. The mass showed a deep invasion into the myometrium extending to the outer surface of the serosa. The cervix, ovaries, fallopian tubes, and omentum were grossly unremarkable.

A biphasic tumor containing poorly differentiated malignant glands and sarcomatous elements was detected on microscopic examination (Figure 2). The epithelial component was the predominant element of tumor (Figure 3). It was highly cellular containing solid sheets of small uniform cells with a high nucleocytoplasmic ratio. The tumor cells had small round nuclei and scanty cytoplasm. Extensive tumor necrosis was evident.

On immunohistochemical staining, the epithelial component of the tumor showed diffuse and strong immunoreactivity for synaptophysin and CD 56; and focal positivity for pan-cytokeratin (pan-CK) (Figure 4a-c). Staining with chromogranin A and cytokeratin 7 (CK7) was negative. The mesenchymal component showed immunoreactivity for CD 10 (Figure 5a-b). However, staining for caldesmon and myoglobin were negative. These morphologic and

<table>
<thead>
<tr>
<th>Reference</th>
<th>Case</th>
<th>Age</th>
<th>Origin</th>
<th>Sarcomatous Component</th>
<th>FIGO Stage</th>
<th>Primary Treatment</th>
<th>Survival Status</th>
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<td>NR</td>
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<td>3C2</td>
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ADJ: adjuvant; RT: radiotherapy; NR: not reported; NED: no evident disease; CT: chemotherapy.

Figure 2. — Histologic appearance of the tumor: A biphasic tumor composed of poorly differentiated malignant glands and sarcomatous elements (H&E, x10).
immunohistochemical findings were consistent with homologous endometrial MMMT with small cell carcinoma component. The cytological examination of peritoneal washings was positive for malignant epithelial cells. There were no cervical or omental involvement. Tumor emboli were evident in lymphovascular spaces. Microscopic foci of metastatic carcinoma were seen in the left ovary, pelvic-paraaortic lymph nodes, and serosa of the bladder. Tumoral invasion was also detected within the associated soft tissues of the involved lymph nodes. The post-operative positron emission tomography computed tomography (PET CT) scan revealed no evidence of distant metastasis. Thus, the patient was surgically staged as FIGO IIIC2 disease.

Adjuvant chemotherapy with cisplatin (100 mg/m², intravenously on day one) and etoposide (75 mg/m², intravenously on days one to three) was commenced. A total of six 28-day cycles were given with no serious adverse events. At the tenth month of follow-up, PET CT scan revealed a three-cm sized mass protruding from the lower pole of the left kidney (SUV max. of 13.8) and a lymphadenopathy 2.5 cm in size located beneath the left renal vein (SUV max. of 21.7). Re-laparotomy was performed. Peritoneal surfaces were unremarkable. Metastatic tumoral foci were completely resected.

The renal metastatic mass was invaded by the sarcomatoid component of the MMMT. Tumoral cells in mass showed immunoreactivity for actin and vimentin. However, HMB-45, chromogranin A, myoglobin, CD 10, CD 56, synaptophysin, and pan-CK were negative. Interestingly, associated lymph node was infiltrated by small cell carcinoma component of the MMMT. Tumoral cells in lymph node were focally positive for pan-CK, diffuse positive for CD 56 and synaptophysin; and negative for CK7, CD 10, caldesmon, chromogranin A, and myoglobin.

Table 2. — Positive immunohistochemical neuroendocrine markers of the patients.

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<th>Reference</th>
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NR: not reported; NA: not applied.

Discussion

MMMTs are rare, high-grade neoplasms arising from structures that are embryologically related to the Müllerian system along the female genital tract and in peritoneum [1]. Those are more common in uterus than elsewhere, probably because the epithelium and mesenchyme in this site have a common embryologic origin [8].

MMMTs are currently thought to be undifferentiated or metastatic carcinomas rather than sarcomas [1]. They contain malignant endometrial glands admixed with sarcomatous elements with the dominant element often being the epithelial component yet distinct from endometrial carcinoma [9]. The lack of difference in antigen expression profile between the epithelial and the sarcomatous components supports that the histogenesis of this tumor is probably from a single pluripotential malignant clone with distinct histological differentiation [10, 11]. The carcinomatous component is usually serous (2/3 of cases) or endometrioid (1/3). However, it may rarely be clear cell, mucinous, squamous cell carcinoma, or others [8]. Up to 80% of patients have grade III disease [12]. Median survival is inferior in comparison to endometrial cancer (18 vs 36 months, respectively) [13].

NE differentiation in tumors arising from genital tract is uncommon and little is known. The 1997 College of American Pathologists Workshop proposed a classification system for NE tumors of the cervix, which includes typical carcinoid tumor, atypical carcinoid tumor, large cell NE carcinoma, and small cell NE carcinoma. However, tumors of the endometrium and ovaries were not addressed [14].

Carboplatin (5AUC) and paclitaxel (175 mg/m²) regimen was started following the second surgery. The patient received the second cycle of chemotherapy and is still alive 12 months after the first operation.
The 2003 World Health Organization (WHO) histological classification of tumors of the uterine corpus recognizes small cell carcinoma of the endometrium as a distinct type of epithelial endometrial carcinoma, but it does not even mention any other type of NE differentiation such as MMMT with small cell NE carcinoma component [15].

There are only a few reports addressing NE differentiation in MMMTs [2-7]. Manivel et al. first described a case of endometrial MMMT with an extensive small cell NE carcinoma component [2]. George et al. reported eight cases of NE differentiation in a total of 47 endometrial MMMTs. Van Hoeven et al. reported a case series of the endometrial small cell carcinoma in ten patients. Only one of those was diagnosed as endometrial MMMT with small cell carcinoma component [4].

All 14 previously reported cases of MMMT with NE epithelial component, including the current report, had the small cell type (Table 1). Eleven out of 14 cases were located in the endometrium [2-4]. Other localization sites were the adnexae, mesentery, or cervix [5-7]. Sarcomatous component was homologous in four and heterologous in seven patients. Heterologous differentiation patterns were predominantly in forms of rhabdomyosarcoma and chondrosarcoma. Four out of five patients had a grade III tumor. Most authors place emphasis on the aggressive nature of MMMTs with small cell NE differentiation. Follow-up data were reported for 11 patients. Median follow-up was nine (one to 12) months. Seven out of 11 patients died within the first year of diagnosis. Two out of four so-called alive patients had a follow-up less than six months. Only two patients received radiotherapy. Three out of four patients of those reported to be alive received adjuvant chemotherapy, whereas none of patients lost were given chemotherapy.

The distinctive appearance of small cell NE differentiation necessitates immunohistochemical examination to confirm the diagnosis. NE markers include neuron-specific enolase (NSE), synaptophysin, chromogranin A, leu-7 (CD 57), CD 56, and several neuropeptides. Tumoral cells may be stained in a focal manner. For definitive histopathological diagnosis for small cell NE differentiation, sheet-like growth of small tumor cells, and at least one positive NE marker are required [4,16]. Current report showed prominent NE differentiation including an extensive small cell NE carcinoma component with diffuse and strong positivity for synaptophysin and CD 56. Among the cases, the most commonly observed marker was NSE in 91% of patients (10/11). Other common NE markers were chromogranin A, leu-7, and synaptophysin, observed in 46% (6/13), 80% (8/10), and 67% (8/12) of patients, respectively (Table 2).
Conclusions

MMMT with NE differentiation is a rare entity. It should be considered during histopathologic examination of endometrial tumors. Most of the patients have a dismal prognosis. Hence, comprehensive staging surgery followed by adjuvant chemotherapy may be mandatory. However, due to scarcity and heterogeneity of clinical data, it is not possible to draw a definite conclusion about the optimal treatment strategy.

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TT and TS treated the patient as a team and reviewed the literature. GTY and SK performed histopathological examination. TT, TS, GTY, and SK drafted the manuscript.

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Minimal deviation endometrioid adenocarcinoma of the endometrium and its MRI findings

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Summary

Minimal deviation endometrioid adenocarcinoma (MDA-E) of the endometrium is a rare pathological entity, and its radiological features are rarely documented. A 73-year-old Japanese woman was referred to the authors when an endometrial biopsy revealed moderately differentiated endometrioid adenocarcinoma. Preoperative radiological examinations, including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) showed no evidence of cancer nests. In the hysterectomy specimen, mildly atypical glands were scattered throughout the entire depth of the myometrium, without stromal desmoplastic reaction, and a tiny focus of typical, ruptured, endometrioid adenocarcinoma glands was found in the atrophic endometrium. MRI had not been able to identify this unusual, scattered, myometrial invasion. It should be kept in mind that in cases showing Stage IA endometrial carcinoma without endometrial thickening on MRI, this rare form of invasion may be present.

Key words: Endometrial carcinoma; MRI; Minimal deviation endometrioid adenocarcinoma of the endometrium; Myometrial invasion.

Introduction

Minimal deviation endometrioid adenocarcinoma (MDA-E) is a rare pathological variation of endometrioid adenocarcinoma, observed mostly in the cervix [1, 2] and rarely found in the endometrium [3-6]. It is defined by a proliferation of mildly atypical endometrial glands with zero to minimal stromal reaction [6, 7]. Recently, the authors encountered a patient with MDA-E and a poor prognosis; her cancer was under-diagnosed by preoperative magnetic resonance imaging (MRI) as Stage IA endometrial carcinoma. In this report, the authors present the clinico-pathological and radiological features of this case.

Case Report

A 73-year-old gravida 7, para 4, Japanese woman was referred to Saga University Hospital because of the presence of endometrial adenocarcinoma on endometrial biopsy. Review of the biopsy specimen showed a proliferation of atypical endometrial glands consisting of endometrioid adenocarcinoma with moderate cellular atypia. The endometrial smear showed a high cellularity and many small clusters of neoplastic glandular cells. Palisading of the peripheral cells was present, as were cubical atypical cells with small, hyperchromatic nuclei.

The results of abdomino-pelvic examination were within the normal range. Transvaginal ultrasonography revealed an atrophic endometrium. There were no neoplastic lesions found in the uterine cavity or the uterine corpus by T2-weighted, gadolinium enhanced T1-weighted, or dynamic contrast-enhanced MRI (Figures 1a-c). Computed tomography (CT) showed no evidence of lymphadenopathy or metastatic disease. Serum levels of tumor markers such as CA 125, CA 19-9, and carcinoembryonic antigen were all within normal limits. International Federation of Gynecology and Obstetrics (FIGO 1988) staging was determined to be endometrial carcinoma, Stage IA. The patient subsequently underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and a sampling biopsy of the para-aortic lymph nodes.

The cancer consisted of well-differentiated small glandular cells, extending deeply into the myometrium, almost to the serosal surface. The glands were lined by relatively uniform cubical to columnar cells, closely resembling proliferative phase glands of the endometrium. Two striking features were the lack of desmoplastic stromal reaction, and the infiltrate of chronic inflammatory cells around the majority of glands through the entire depth of the myometrium. MRI had not been able to identify this unusual, scattered, myometrial invasion. It should be kept in mind that in cases showing Stage IA endometrial carcinoma without endometrial thickening on MRI, this rare form of invasion may be present.

Discussion

The depth of myometrial invasion is one of the single most important prognostic factors in endometrial carcinoma, as it correlates with tumor grade, tumor extension into the cervix, and the prevalence of lymph node metastases [8]. Myometrial invasion depth can be assessed preoperatively by several imaging modalities; MRI is believed to be the most reliable tool for this diagnosis. As the authors described in a previous study, MRI is highly accurate for detecting deep myometrial invasion, however, the neg-
ative predictive value for shallow myometrial invasion is very low [9]. MDA-E is characterized by scattered growth throughout the myometrium, and it does not result in endometrial thickening. Furthermore, the deep, wide spread of MDA-E cells makes it difficult to detect tumor invasion in the myometrium, due to loss of contrast between normal myometrial and cancer cells.

Pure MDA-E is a very rare pathological variant of endometrial adenocarcinoma [7, 10]. Landry et al. described four cases of endometrioid adenocarcinoma of the uterus, with a minimal deviation invasive pattern, among 168 hysterec-tomy specimens designated as endometrioid adenocarcinoma [7]. In the case of the present patient, there were small fragments of typical moderately-differentiated endometrioid adenocarcinoma on the surface of the endometrium. These typical adenocarcinoma cells were detected by both endometrial biopsy and cytology. Therefore, it was much more difficult to make the preoperative diagnosis of pure MDA-E or MDA-E dominant endometrial carcinoma.

This case demonstrates one of the unusual pitfalls of diagnosing the depth of myometrial invasion by MRI. When we meet a patient with Stage IA endometrial adenocarcinoma by MRI, with no endometrial thickening, we should consider the possibility of MDA-E.

References
 Minimal deviation endometrioid adenocarcinoma of the endometrium and its MRI findings


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Leiomyomatosis peritonealis disseminata: an additional case

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Summary
Leiomyomatosis peritonealis disseminata (PPD) is a rare smooth muscle tumour of women in the reproductive age. It is characterized by multiple small nodules on the peritoneum or serosa, as well as colon and rectum wall in a patient without signs of excess of estrogen, progesterone, or steroid hormones. Exploration laparotomy showed innumerable, firm, pink-grey, smooth nodules on the surface of the omentum, the parietal peritoneum, and on the muscular layer of colon and rectum wall. Excision of several of these masses was performed.

Medical history revealed a laparoscopic uterine myomectomy two years prior. There were no signs of excess of estrogen, progesterone or hormonal steroids, and the patient was not treated with hormones. Exploration laparotomy showed innumerable, firm, pink-grey, smooth nodules on the surface of the omentum, the parietal peritoneum, and on the muscular layer of colon and rectum wall. Excision of several of these masses was performed. On macroscopic examination, all the lesions were similar. They were solid, firm and whitish, and ranged in size from 10 to 75 mm in maximum diameter (Figure 1). Nodules presented smooth external surface and pale, whorled cut surface. Pinpoint hemorrhages were found but there was no macroscopic evidence of necrosis. Microscopic examination showed well circumscribed nodules, embedded in fat tissue (Figures 2, 3). The nodules consisted of bundles of spindle-shaped smooth muscle cells, without atypia, necrosis, or mitosis (Figure 4). Some lesions showed extensive hyaline degeneration and foci of calcification. Immunostaining revealed positivity of neoplastic cells for smooth muscle actin (SMA) (Figure 5), caldesmon (Figure 6), desmin, HHF-35, estrogen (Figure 7) and progesterone receptors, and negativity for cytokeratins. Proliferative index (Ki-67) was about 8% (Figure 8). Cytological examination of the peritoneal liquid revealed only reactive mesothelial cells and foamy histiocytes. The final diagnosis was LDP.

Discussion
LDP is a rare condition which is known to often simulate intra-abdominal carcinomatosis. Firstly described by Wilson and Peale in 1952 [7], only in 1965 [1], the condition was named “leiomyomatosis peritonealis disseminata” and characterized as an entity related to uterine leiomyomas. Since then, 103 cases have been reported. Its exact pathogenesis remains obscure. The associations with pregnancy, prolonged oral contraceptive use, subserosal uterine leiomyomata, functional granulosa cell tumors, and endometriosis indicate hyperestrogenic states as a causal factor. Tavassoli and Norris [8] proposed that LDP is due to smooth muscle metaplasia of the sub-
Figure 1. — Macroscopic appearance of the nodules
Figures 2-4. — Histologic aspect, leiomyomata
[2-4: Haematoxylin and Eosin; Original Magnification (OM),
2-3: x5; 4: x10; 4, bottom right x20].

Figure 5. — SMA stain, OM x20.
Figure 6. — Caldesmon stain, OM x20.
Figure 7. — ER stain, OM x20.
Figure 8. — Proliferation index (Ki-67), OM x20.
coelomic mesenchymal stem cells (the so-called pluripotent Mullerian stem cells), which are distributed throughout the subperitoneal mesenchyma, promoted by hormonal stimulation. Some authors have suggested that in cases of individual predisposition (abnormality in chromosomes 17, 12, and 18) and hormonal stimulation, Mullerian stem cells proliferate along the line of myofibrous differentiation. In fact, pluripotent mesenchymal stem cells are capable of metaplastic change into leiomyocytes, myofibroblasts, endometrial stromal cells, and decidual cells [6]. Other papers suggest that LPD may be a result of fibrosing deciduosis under the influence of steroid hormones [9, 10]. However, decidual cells and fibrocytes are not always found in LPD nodules, therefore it may be concluded that fibrosis of decidual cells is a process not related to LPD. The reported cases of association between LPD and endometriosis, although few, favor a common origin for both the lesions. However, the mechanisms involved in this association are unknown. It is not clear whether the leiomyomatous nodules originate from foci of endometriosis, or if both the conditions are due to a common metaplastic phenomenon [1]. All these hypotheses do not explain the four cases of LPD in postmenopausal women without hormonal treatment and one case in a male patient. The identification of luteinizing hormone (LH) receptor in LPD nodules from a postmenopausal woman has suggested that the typical postmenopausal increase in LH levels might play a role in the pathogenesis of the condition [11]. Etiological mechanisms are still obscure in cases diagnosed in males and Halama et al. [12] hypothesized that LPD may represent an autosomal dominant condition with varying degrees of penetrance.

A possible iatrogenic cause for the disease has also been suggested [1], since increasing cases of LPD have been reported after laparoscopic myomectomy where the myoma was minced to be removed from the abdominal cavity. It is possible that fragments of the myoma, scattered in the peritoneal serosa, grow to become LPD. Miyake et al. [13] and Al-Talib et al. [2] supported this hypothesis because they found LPD nodules around the laparoscopy scar of a previous myomectomy in a patient who did not receive any hormonal treatment. These are findings in favour of an iatrogenic origin of LPD, as well as in the present case, since the patient did not show excess of estrogen, progestrone or steroid hormones and had no hormonal treatment. Malignant transformation of LPD and its metastases are uncommon and only some require gonadotropin-releasing hormone agonists or surgical castration. In contrast, malignancy is an event predicting an early death despite multimodality combination therapy [16].

The present patient was treated with laparoscopic surgery of many of the greater nodules. One year after surgery she continues to be well.

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Leiomyomatosis peritonealis disseminata: an additional case


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A large pedunculated leiomyoma with two-sided cystic degenerations mimicking a bilateral ovarian malignancy: a case report

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Summary

The authors present an unusual case of a large, pedunculated uterine leiomyoma with two-sided cystic degenerations, which mimicked a bilateral malignant ovarian tumor on ultrasonography and magnetic resonance imaging (MRI). A 32-year-old unmarried female patient presented to our outpatient clinic with complaints of abdominal distention and a palpable abdominal mass extending into the upper abdomen. Ultrasonography and MRI revealed a large solid mass with bilateral cystic areas extending into both uterine adnexa. The patient then underwent a laparotomy. Gross examination revealed normal ovaries and a pedunculated mass with two-sided prominent cystic structures originating from the uterine fundus. The tumor was excised through the peduncle and pathologic evaluation revealed a uterine leiomyoma with cystic degenerations. In conclusion, a large, pedunculated leiomyoma with two-sided cystic degenerations can mimic a bilateral malignant ovarian neoplasm on imaging studies. Therefore, uterine leiomyomas with bilateral cystic degenerations should be considered during the differential diagnosis of malignant ovarian masses.

Key words: Leiomyoma; Ovarian neoplasms; Ultrasonography.

Introduction

Pelvic masses are frequently encountered in daily gynecological practice, and the correct preoperative diagnosis of these masses is of paramount importance. However, differential diagnosis of pelvic masses can be challenging for practitioners. Among the pelvic masses, leiomyomas originating from the uterus are the most common neoplasms, which develop in 20%–30% of women during their reproductive years [1]. Imaging methods such as ultrasonography and magnetic resonance imaging (MRI) can identify the typical appearance of leiomyomas without difficulty; however, degenerative changes in these pelvic masses may cause atypical expression on images and lead to confusion in their diagnosis [2, 3]. Ovarian cancer is one of the most common gynecologic cancers, which carries a lifetime risk of development between 1%–1.5%. Ovarian cancer is considered the most lethal malignancy of the female genital tract and continues to be one of the main causes of female cancer death. Early and accurate diagnosis of this condition is necessary to improve overall patient survival. Here, we report a case of a large, pedunculated, and subserosal uterine leiomyoma with bilateral cystic changes that mimicked an ovarian malignancy.

Case Report

A 32-year-old unmarried female patient presented to our outpatient clinic with complaints of abdominal distention and a palpable abdominal mass extending into the upper abdomen. Upon physical examination, a mobile abdominal mass with irregular contours extending four to five cm above the umbilicus was discovered, whereas the uterus and uterine adnexa could not be examined individually. Pelvic ultrasonography revealed a predominantly solid, intra-abdominal 19 × 15 × 10-cm complex mass located just above the apparently normal uterus. The mass contained bilateral unilocular cystic areas without any papillary projections and was located within a solid neighborhood, suggesting an ovarian malignancy. The ovaries were not distinctly observed, and a minimal amount of free pelvic fluid was detected. The levels of the serum tumor markers beta subunit of human chorionic gonadotropin (β-hCG), carcinoembryonic antigen (CEA), and alpha-fetoprotein (AFP) were within normal limits, whereas the cancer antigen 125 (Ca 125) level was determined to be 87 IU/ml (> 35 IU/ml is abnormal). MRI of the abdominopelvic region showed a large, well-defined pelvic mass measuring 20 × 15 × 12 cm. Although normal ovaries were not identified individually, evidence of hyperintense cystic areas were observed bilaterally on T2-weighted MRI images. No regional lymphadenopathies were detected on MRI (Figure 1).

Although uterine leiomyoma with possible two-sided cystic degenerations was suspected on the basis of the preoperative diagnosis, the possibility of bilateral malignant ovarian cystic masses with concurrent leiomyoma or a complex malignant mass of ovarian origin that was invading the uterus could not be ruled out. Consequently, abdominal exploration using laparotomy was performed and a large, pedunculated tumor originating from the fundus of a normal looking uterus was encountered. Both uterine adnexa and other pelvic organs were found to be normal upon inspection. The mass was incised through its peduncle and removed completely, followed by closure of the abdomen. Upon gross examination of the specimen, bilateral outgrowth of masses with cystic appearances, arising from the main mass, was noted (Figure 2). A solid mural nodule, which was apparent on MRI, was
observed inside the right cystic lobule (Figure 1). Pathological evaluation of the surgical specimen revealed a uterine leiomyoma with two-sided cystic degenerations.

Discussion

Leiomyomas arise from smooth muscle and connective tissue and are most commonly found in the uterus [1]. Histologically, these tumors show monoclonal proliferation and may undergo different types of degenerations, such as hyaline, cystic, calcific, malignant, or red degeneration. Among the degenerative changes, hyaline degeneration is the most commonly noted, whereas cystic changes can be seen in 4% of all cases [4]. In this report, the authors present the case of a large, pedunculated uterine leiomyoma with bilateral cystic degenerations, which mimicked an ovarian malignancy on imaging studies. A few reports have previously described uterine fibroids with unilateral cysts thought to be ovarian malignancies [5-7]. However, a search of the current literature failed to identify any previous studies describing uterine leiomyomas with two-sided cystic degenerative areas mimicking bilateral ovarian malignancy.

Ultrasoundography is considered to be the initial and most cost-effective method for the evaluation of pelvic masses. Uterine leiomyomas constitute a considerable proportion of the solid pelvic masses and are usually seen without difficulty as hypoechogenic masses on ultrasonography images. However, degenerative changes may result in diagnostic confusion due to the unusual heterogeneous appearance of the leiomyomas on the ultrasonography images [3]. In the present case, the presence of bilateral cysts suggested the possibility of ovarian cystic masses, leading to diagnostic confusion. MRI can be readily used to detect leiomyomas [1]; however, degenerated leiomyomas show variable intensities on MRI images. Cystic changes within the leiomyoma appear as hyperintense regions on T2-weighted images, and a malignant cystic mass may also have a very similar appearance. In the present case, the authors observed bilateral, hyperintense cystic areas on T2-weighted MRI images (Figure 1). In conclusion, these imaging methods can provide general information about a pelvic mass; however, unusual or heterogeneous appearance of the mass due to degenerative changes may lead to preoperative diagnostic confusion.

In the present case, one of the preoperative diagnoses was uterine leiomyoma with possible two-sided cystic degenerative areas. Up to 66% of serous ovarian cancers are well known to be present bilaterally [8], and in ovarian tumors with solid and cystic areas, the malignancy rate is reported to be higher [9]. Therefore, the possibility of ovarian malignancy could not be ruled out because of the two-sided development and complex nature of the pelvic mass. A pedunculated leiomyoma apart from the uterus may mimic an ovarian neoplasm because of its proximity to the ovaries and possible cystic degeneration [2]. In the present case, the peduncle between the mass and the uterus was not apparent on ultrasonography, although a possible continuity between the mass and uterus was observed on MRI. Consequently, imaging methods such as ultrasonography may fail to detect an anatomic connection between the mass and the uterus, and the possibility of an ovarian mass may arise.

Figure 1. — MRI image of the mass. A coronal T2-weighted fat-saturated image showing a well-defined semi-solid pelvic mass extending into both uterine adnexal areas. The mass contains obvious two-sided cystic areas, which present as hyperintense regions on T2-weighted images. A likely continuity exists between the mass and the uterine fundus. A solid area within the wall of the right cyst is apparent in the right cystic lobule of the mass (asterisk). A minimum amount of free fluid is noted in the pelvis (arrows show the uterus).

Figure 2. — Laparotomy showed the presence of a large pelvic mass. The pelvic mass presented with bilateral cystic areas. The right cyst contained a solid area within the wall (asterisk). Another smaller cyst is also evident (arrow).
Serum levels of Ca 125 are not considered to be a specific marker of malignancy and are elevated (> 35 IU/ml) in various malignant (ovarian cancer) and benign (leiomyoma) conditions. In the present case, the level of this serum marker was slightly elevated but the marker provided little information about the preoperative diagnosis of the mass.

In conclusion, uterine leiomyomas can be detected using ultrasonography or MRI without difficulty. However, a large, pedunculated leiomyoma developing two-sided cystic degenerations was found to mimic a bilateral malignant ovarian neoplasm on imaging studies and was a diagnostic challenge. Therefore, uterine leiomyomas with bilateral cystic degenerations should be considered in the differential diagnosis of malignant ovarian masses.

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Benign pulmonary metastasizing leiomyomatosis: case report

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Summary

The authors report a rare case of leiomyomatosis of the lung diagnosed in a 43-year-old woman, with uterine intravenous leiomyomatosis. Benign metastasizing leiomyoma (BML) is an extremely rare lesion characterized by usually multiple, benign-appearing smooth muscle tumors of the lung in females with coexisting uterine leiomyoma. On the basis of their histological and immunohistological features, a unified histogenetic view of leiomyomas with vascular invasion (LWVI) and BML of the uterus is proposed. LWVI and BML may be the same pathological entity and microscopic vascular invasion may represent the metastatic mechanism of BML. LWVI seems to be the precursor of BML.

Key words: Benign metastasizing leiomyoma (BML); Uterine intravenous leiomyomatosis (LWVI); Pulmonary nodules.

Introduction

Benign metastasizing leiomyoma (BML) is a lesion extremely rare characterized by usually multiple, benign-appearing smooth muscle tumors of the lung [1,2] in females with coexisting uterine leiomyoma [3]. The entity is not described in the Word Health Organization (WHO) blue book. Less than 100 cases of leiomyomas of the lung have been reported in the literature [4-8].

The nature of BML has been debated since it was first reported in the English literature in 1939 [9]. In contrast to the original hypothesis that this was a benign leiomyoma colonizing the lung, some investigators believed it was a low-grade leiomyosarcoma [10] while others argued that it may represent primary pulmonary leiomyomatosis coexisting with a uterine leiomyoma. New evidence supports the notion that BML is clonally derived from benign-appearing uterine leiomyomas [3].

Total resection of the multiple nodules can only be performed in a very limited number of cases [11, 12]. These patients are usually asymptomatic and the clinical suspicion begins with the incidental discovery of pulmonary lesions [13]. The authors report here an interesting case of BML in a 43-year-old woman.

Case Report

A 43-year-old woman was referred to the authors’ attention, at the Second University of Naples, for the appearance of cough lasting about one month, with expectoration of thick and dark mucus, but any other respiratory symptoms like hemoptysis, purulent sputum or exertional dyspnea were absent. She denied any fever, chills, weight loss, headache, myalgia or any other major symptoms. Her past medical history was remarkable in that she was previously diagnosed with uterine leiomyoma and underwent myomectomy with right-sided oophorectomy approximately 12 years ago. She also underwent surgery for two cesarean sections.

Laboratory studies including a complete blood count, a serum metabolic assay with liver function tests, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, and anti-nuclear antibodies; all the tests showed normal results. Routine urine analysis for the cell count and casts, and the thyroid function test were also normal. Tumor markers: CEA, CA 19.9, CA 15.3, CA 125, and AFP were all negative.

Therefore, a chest radiograph was taken, which showed the presence of bilateral parenchymal nodules. Further evaluation led to a computed tomography (CT) scan of the chest (Figure 1: A, B) which showed: multiple parenchymal nodules, recurring type, in both lung fields, of which the most left upper lobe of 2.5 cm, and the basal of 1.86 cm. Bilateral axillary lymph node with package of 2.03 cm on the right. A CT scan of the abdomen and skull, mammography, and breast ultrasound were also performed to search for the primary origin of suspicious metastatic lung nodules. CT abdomen-pelvis (Figure 1: D) showed inhomogeneous uterus with heterogeneous impregnation area of about four cm.

After, the patient underwent a gynecological consultation, with a pelvic ultrasound which showed the presence of a solid formation of 35 x 24 mm at the bottom of the uterus and at the right side wall, with medium vascularization (R.I. 0.51), likely to be due to submucosal-intramural leiomyoma. Irregular endometrial echoes with thickness of five mm at the bottom were also seen, and hysteroscopy confirmed dimensions of 55 x 28 x 30 mm. Di-agnostic hysteroscopy was also attempted, although during which the uterine cavity was not explored due to difficulty in passing the internal uterine orifice, probably due to a myomatous formation. Pap-test was negative.

Positron emission tomography-CT (PET-CT): high glucose metabolism in the following anatomical was performed in the following areas: basal anterior, basal-lateral, and angular inferior segments of the left lung (Figure 1: C). Basal anterior segment of the right lung, and cervix-body of the uterus (Figure 1: E). All these areas are related to etioproliferative injuries.

In November 2012 the patient was hospitalized at the Operative Unit of Thoracic Surgery where she was subjected to atypical resection of the lingula and the culmen of the upper lobe of the left lung through video-assisted thoracic surgery (VATS). The patient was discharged in good general condition, afebrile, and with regular breathing at rest.

Subsequently, anatomical and histological analysis of the specimens resected was performed, and histological specimens were further analyzed at the National Cancer Institute of Milan.
Macroscopically two nodular lesions of about 0.4 cm in diameter in the lingula, and a whitish nodule of 0.8 cm in the culmen of the upper lobe were described. Both lesions appeared to consist of proliferative spindle-shaped elements without marked nuclear atypia, a nodular growth, with net margins, compared with bronchiolar structures. A significant mitotic index was not observed (< 1 x 10 HPF), or necrosis (Figure 1: F, G). The immunohistochemical examination showed: caldesmin +, smooth muscle actin +, S100 -, Ki67 < 7%, hormone receptors estrogen-progestin +, WT1 (180 and C19) +, TFE3, and FLI1 -. The overall finding is attributable to well-differentiated smooth muscle tumors, gynecological type, with multiple locations in the lungs, consistent with the entity described as BML [3].

The patient was then admitted to the Second University of Naples, where she underwent in January 2013 total hysterectomy, left salpingectomy and oophorectomy, partial omentectomy, and omental biopsy. Macroscopically a 3 x 3 x 3.5 cm intramural nodule was seen, surrounded by other nodules of...
about one cm, all sorted-homogeneous appearance, whitish and smooth margins. Microscopically: endometrium poorly represented with diffuse atrophy from compression. The nodules (Figure 1: H), described macroscopically, appeared to be composed of a proliferation of smooth muscle (desmin and smooth muscle actin +) and showed no necrosis, a high mitotic index (<1/10 HPF), and nuclear atypia, negative for S100, CD10, and CD34; focal positivity for p16 and p53, Ki67 5%. The morphological and immunohistochemical appearance seem consistent with leiomyomatosis of the uterine wall with a focal growth pattern paravenous (intravenous leiomyomatosis).

The patient was discharged from the hospital without any early postoperative complications. She will undergo close follow-up.

Discussion

The authors observed a patient with BML, which is an extremely rare lesion characterized by usually multiple, benign-appearing smooth muscle tumors of the lung [1, 2] in females with coexisting uterine leiomyoma [3]. The entity is not described in the WHO blue book. Approximately 100 cases have been reported in the literature, and the lungs were the most common site of metastases [5-8, 14, 15].

The nature of BML has been debated since it was first reported in the English literature in 1939 [9]. In contrast to the original hypothesis that this was a benign leiomyoma colonizing the lung, some investigators believed it was a low-grade leiomyosarcoma [15] while others argued that it may represent primary pulmonary leiomyomatosis coexisting with a uterine leiomyoma. New evidence supports the notion that BML is clonally derived from benign-appearing uterine leiomyomas [2].

The pathogenesis of this disease is unclear. Of the several possible mechanisms, hormone-dependent tumor growth might be most popularly accepted as spontaneous regression of the disease in pregnancy [16] and during the menopause [11] has been reported. Generally, uterine leiomyomas are known to be estrogen sensitive. In fact, both estrogen and progesterone receptors were identified in the lung tissues of the presented case, which is similar to other cases, suggesting that the pulmonary lesions represented metastatic nodules from benign tumors [13].

Uterine leiomyoma is the most common gynaecological neoplasm, with a prevalence of more than 50% of women above the age of 30 years. The majority of uterine leiomyomas are benign, and malignant behaviour was presented only in 0.13 to 6% of them [17].

Recently it has been suggested that BML is a result of monoclonal, hematogenous spread of benign-appearing uterine leiomyoma. The morphology, molecular, and immunohistochemical futures are characteristic of benign neoplasms in spite of the metastatic potential. As was shown in the presented case, as in others presented in the literature [14], BMLs have a low mitotic rate and MIB-1 index supporting the low proliferate activity of these tumors [12, 18-30].

Most of the BML patients have undergone a hysterectomy 0 to 24 years earlier [22] (in the presented case, the patient had already performed a myomectomy ten years before).

Patients are generally asymptomatic; therefore, the initial detection of the disease derives from other examinations for other purposes, like an annual health check examination. Yet there are a few cases presenting with symptoms such as dyspnea, dry cough, or chest pain [22, 23].

BML usually express estrogen and progesterone receptors, and the specimens from the presented patient were positive for sex hormone receptors [12, 15, 19-20]. This observation led to treatment based on antihormonal therapy and/or surgical resection [3, 12, 24-29].

Another new therapeutic option is tyrosine kinase inhibition. An overexpression of c-kit was shown in low-grade leiomyosarcoma and gastrointestinal stromal tumours, and suppression by imatinib was beneficial. It was suggested that this type of treatment might also be useful in BML patients [30]. It has also been postulated that BML may be the results of vascular invasion of a uterine leiomyoma or it may be related to intravenous leiomyomatosis [13, 30].

In conclusion, the authors report here a rare case of leiomyomatosis of the lung diagnosed in a 43-year-old women with uterine intravenous leiomyomatosis. Despite their histological benignity, these lesions have a strong tendency to metastasize and are closely related to the so-called BML. From a clinical point of view, the pulmonary nodules of LWVI are stable or slow-growing. On the basis of their histological and immunohistological features, a unified histogenetic view of LWVI and BML of the uterus is proposed. LWVI and BML may be the same pathological entity and microscopic vascular invasion may represent the metastatic mechanism of BML. LWVI seems to be the precursor of BML [30].

References


Ovary-preserving tumorectomy for immature teratoma in an adolescent – Case report

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Summary
The authors present a case of a 14-year-old premenarchal girl with a large solid tumor of the left ovary. The rim of normal ovarian tissue was visible around the tumor on ultrasonography scan. Although the levels of two tumor markers, LDH and CA125, were elevated, the authors performed an organ-sparing tumorectomy. The final pathology report revealed foci of immature neural tissue, with a final diagnosis immature teratoma Stage Ia.

Key words: Ovary; Tumor; Ultrasound; Immature teratoma.

Introduction
The ultimate goal in the treatment of pediatric and adolescent patients with ovarian tumors is to preserve the tube and the ovary whenever possible. Normal ovarian tissue or ovarian crescent sign relies on the fact that healthy ovarian tissue can be seen adjacent to the cyst or tumor within the ipsilateral ovary [1]. This morphological ultrasound sign has a potential to become a simple and effective way of excluding an invasive ovarian malignancy [1, 2]. The crucial dilemma that arises when deciding the extent of surgery in adolescent with large solid ovarian tumor is whether to perform ovariecotomy or adnexectomy when ovarian crescent sign is present, or to go for ovary-sparing tumorectomy.

Case Report
A 14-year-old premenarchal girl was referred for abdominal discomfort. She was otherwise healthy with negative family history for breast/ovarian disease or malignancy. Abdominal palpation revealed a mobile mass extending from the pelvis to the umbilicus. Abdominal ultrasound examination showed a 16-cm, predominantly solid tumor, arising from the left ovary. A rim of normal ovarian tissue was observed adjacent to the tumor, within the ovary (Figures 1A and 1B). Doppler pulsatile index was 1.3 in peripheral vessels. To eliminate bias the patient was assessed independently by two gynecologists with sonographic experience longer than 15 years with ovarian tumors. The serum level of LDH was 1054 IU/l and of CA 125 - 216 mIU/l, while alpha-fetoprotein, beta hCG, inhibin B, CA 19-9, estradiol, testosterone, neuron specific enolase, and lab works - electrolytes, liver function tests, and urine analysis, were within normal limits. The laparoscopy was excluded due to the tumor volume and structure, and presence of the ovarian crescent sign lead the authors to consider tumorectomy as a treatment of choice. Upon entering the abdominal cavity, a large smooth mass was found arising from the left ovary. There were few proliferative changes in the omentum and peritoneal surface in the pelvis. Peritoneal washings were obtained. A superficial linear incision was made along the antimesenteric border of the ovarian tumor, approximately three cm from the ipsilateral tube, parallel to it. Next, the thinned ovarian cortex was gently peeled off the tumor wall by blunt and sharp dissection (Figure 1C). The goal was to enucleate the neoplasm without opening it (Figures 2A and 2B). The tumor weighed 1,000 g. It was sent to frozen section analysis, which revealed benign mature teratoma with preponderance of mature neural elements. The authors reconstructed the remaining ovarian tissue. Appendectomy was performed due to enlargement of the appendix, and due to the presence of neural elements; they proceeded with surgical staging, including biopsy of peritoneum, omentum, and pelvic lymph nodes. The blood loss during surgery was 300 ml. The patient was discharged from the hospital on the fifth day. Histopathology reported a mostly mature teratoma with few foci of immature neural tissue within the tumor mass. The lymph nodes, peritoneal washing, and appendix showed no presence of tumor tissue. Biopsy of the omentum revealed peritoneal deposits of mature glial tissue -gliomatosis peritonei. The final report was immature teratoma of the left ovary, Stage Ia, Grade I. Six-week follow up serum levels of LDH and CA 125 were normal, and the volume of the affected ovary was 7.5 cm³ (Figure 3). At 18 months follow up menarche occurred and ultrasonography showed no signs of relapse.

Discussion
Laparoscopic cystectomy is a safe and effective method of managing ovarian dermoid cysts in the pediatric and adolescent patient population [3]. In a low percentage of dermoid foci of immature teratoma can be found. The dilemma arises when deciding the type of surgery in adolescents with great solid ovarian teratoma. The ovarian crescent sign as a morphological ultrasonographic feature was first described in adult and later in pediatric and adolescent patients with ovarian masses [1, 2]. The authors reported that in children and adolescents who were surgically treated for benign adnexal
masses, the absence of the ovarian crescent sign was found in one-third of the masses complicated with torsion [2]. Absence of the ovarian crescent sign does not exclude a benign tumor, however its presence lowers the probability of an invasive ovarian malignancy in both adult and pediatric and adolescent patients [1, 2]. The absence of the ovarian crescent sign should be an indicator to refer a patient to a gynecologist specialized in practice with pediatric and adolescent population [2]. The pulsatility index appeared to be less sensitive than the ovarian crescent sign and the morphology index in dis-
Ovary-preserving tumorectomy for immature teratoma in an adolescent – Case report

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Criminating between malignant and benign tumors, which is similar to the reports on adult patients [2, 4]. Serum levels of LDH may be elevated in mature teratomas. Adding a single CA 125 measurement to the ultrasound imaging performed by an experienced examiner does not improve preoperative discrimination between benign and malignant adnexal masses even in adult patients [5]. It is generally accepted that small foci of immature neural elements can be readily missed on frozen section, especially if the tumor is large. Only very large immature teratomas Grade I, Stage 1 (greater than 1,500 g) warranted consideration of adjuvant chemotherapy [6]. Peritoneal gliomatosis occurs in 10% of patients with immature teratomas, and is biologically of benign nature [7]. An adolescent with immature teratoma Stage I Grade I was treated by Einarsson et al. with laparotomy and adnexectomy without chemotherapy. A full surgical staging procedure was based on preponderance of mature neural elements in the tumor on frozen section [8]. The authors decided against chemotherapy, based on the tumor weight and the stage of the disease. Six weeks similar as 24 months after surgery, they measured ovarian volume, which showed no significant difference between affected and contralateral ovary; without evidence of damage of ovarian reserve that was reported for laparoscopic excision of ovarian cysts [9].

Conclusions

The authors reported that the presence of the ovarian crescent sign may be a useful ultrasonographic morphological feature, which could support preservation of ipsilateral ovary, even in early stage of malignancy in adolescents. The visualization of healthy ovarian tissue does not require a high level of ultrasound skills and could be successfully included into a routine ultrasonographic practice of all operators who find adnexal tumors in young patients. Further prospective work could show whether the use of the ovarian crescent sign may provide a more effective path of managing pediatric and adolescent patients with adnexal masses.

References


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Foreword
The importance of this book is included in its very theme, as it presents gynecological cancer of the most unfavorable prognosis. In fact, despite the numerous advances in surgery, chemotherapy, and molecular therapies, the survival rates have only slightly improved. Selecting ovarian tumors as the object of study, as assessed by a multi-specialized team, can assist the gynecological oncologists, and also refine the approach to the disease and increase their professional standard.

This book, written by 32 international acknowledged experts, with rich and clear illustrations, offers an expert guide to all aspects of this neoplasia.

From the epidemiology, through risk, management in early and advanced stages, pediatric neoplasia, to the quality of life, the author explores all the possible aspects of this disease and all the implications that affect the outcome.

The chapters are all written very clearly, allowing anyone from the student to the expert to fully benefit from consultation of the manual, and the in-depth information makes it easier to understand its contents.

In conclusion, I believe that the comprehensive text conveys a significant progress in understanding this complex neoplasia.

M. MARCHETTI
A Manual for Cervical Cancer Screening and Control: Principles, Practice and New Perspectives

This book is edited by Margherita Branco, former Director of Cervical Cancer Screening and Cytopathology Unit, National Institute of Heath, Rome (Italy) and by Adhemar Longatto-Filho, of the Laboratory Medical Investigation 14, Faculty of Medicine, Sao Paulo (Brazil).

The topic covered in this book is connected to the prevention and early detection of cervical cancer.

Although cancer of the cervix is a disease that is well-detected and almost eradicated in developed countries that have introduced individual screening programs, it still remains the second or third most common cause of death in developing countries.

The 14 chapters of this textbook thoroughly examine all the “aspects” related to prevention and early detection.

From the general information on this neoplasia, through primary prevention, HIV infection, risk factors, methods of screening, study of biomarkers, organization of training for personnel involved in screening programs, to the general instruction for prevention, this manual offers a complete contribution to improve women’s health.

Contents


Chapter 3: Human Papillomavirus (HPV) infections. M. Branca and A. Longatto-Filho.

Chapter 4: Risk factors for cervical cancer. M. Branca.


Chapter 6: Cancer prevention in developing countries. A. Longatto-Filho.

Chapter 7: Cervical cytology and alternative methods of screening. A. Longatto-Filho.

Chapter 8: Management of women with abnormal cytological results. M. Branca and A. Longatto-Filho.


Chapter 10: Basic concepts of quality and accreditation in Health Care Services. M. Branca.


Chapter 13: Instruction and training of personnel in a cervical cancer screening program. M. Branca and A. Longatto-Filho.

Chapter 14: Universal hygienic measures and precautions for infection prevention in gynecological ambulatory centers and hospitals. M. Branca.

We believe that this book also provides comprehensive coverage and expert guidance of all persons implicated in screening programmes.

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