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# Regional lymphatic spread in women with pelvic endometriosis

Yao Gong [a,b], Clemens B. Tempfer [c,*]

[a] Department of Obstetrics and Gynecology, Medical University of Vienna, Vienna, Austria
[b] Department of Obstetrics and Gynecology, Tongji University, Shanghai, China
[c] Department of Obstetrics and Gynecology, University of Bochum School of Medicine, Bochum, Germany

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ABSTRACT

Endometriosis is defined by the presence of endometrial tissue outside the uterine cavity and is associated with chronic pelvic pain and infertility. After surgical and/or medical treatment, endometriosis has a high recurrence rate which increases with the length of follow-up. To delay or to eliminate recurrence is a main task in the control of this disease. To date, little is known about the mechanism of recurrence and its management is not efficacious. Recently, it has been observed that regional lymph node involvement by endometriosis is a common phenomenon in women with endometriosis. Endometriotic cells in regional lymph node are a potential target of hormonal stimulation in the postoperative period and may be a major source of disease recurrence. We hypothesize that the resection of regional lymph nodes can decrease the recurrence rate of endometriosis and hence should become part of the surgical treatment of this disease.



## Background

Endometriosis is a common benign disorder defined by the presence of endometrial tissue outside the uterine cavity. It is predominantly found in women of reproductive age and is an established cause of infertility and chronic pelvic pain [1,2]. Surgery is the primary treatment of choice, since this approach allows for a histological diagnosis and excision of endometriotic lesions. A number of studies demonstrated that laparoscopic excision of endometriosis can significantly reduce pain and improve quality of life in women with endometriosis [3–5]. In deep-infiltrating rectovaginal endometriosis, for example, radical excision including bowel surgery has been reported to alleviate symptoms in up to 80% of affected women [6]. Despite the efficacy of surgical treatment, a high recurrence rate after surgery remains the biggest challenge in the treatment of endometriosis. The reported recurrence rates vary greatly among published studies presumably due to differences in postoperative treatment, definition of recurrence, i.e. pain recurrence versus objective recurrence measured by ultrasound or magnetic resonance imaging, or type of endometriosis. For example, in a retrospective study of 1106 women with >20 years of follow-up, Busacca et al. found that the recurrence rate was significantly higher in cases of deep-infiltrating rectovaginal endometriosis compared to ovarian and/or peritoneal endometriosis [7]. Based on follow-up data from 23 clinical studies of women undergoing treatment for endometriosis, Guo calculated a recurrence rate of 21% at 2 years and 40–50% at 5 years [8]. In order to minimize the risk of recurrence, it is recommended that post-operative adjuvant treatment should be initiated after surgical resection of all visible endometriosis lesions [9]. Medications such as oral contraceptives, androgenic agents, progestins, and gonadotropin releasing hormone (GnRH) agonists are widely used in an attempt to eliminate residual endometriotic cells and thus reduce the risk of recurrence. However, although surgery with subsequent adjuvant medical therapy can effectively treat endometriosis in many women, the value of some adjuvant treatment strategies has been questioned and recurrence rates remain high [7,10,11].

Currently, little is known regarding the mechanism of disease recurrence in women with endometriosis. Several studies suggest that recurrent lesions arise from residual lesions or cells which have not been removed during primary surgery [12–14]. According to the observation of patients with deep infiltrating recto-vaginal endometriosis who underwent a second surgery for recurrent disease, Vignali et al. found that newly developed lesions were often situated in the same area of the pelvis as they were during the first operation [14]. Exacoustos et al. found that in ovarian endometriosis, 88% of the recurrent cases developed in the ipsilateral ovary [12]. These findings suggest that recurrence seems to originate from residual lesions, which have been left behind in the course of the initial surgery. Other authors proposed that recurrent disease may be the result of de novo lesions due to retrograde menstruation. Supporting evidence for this hypothesis comes from a clinical study which found that none of 14 patients who underwent a combination of laparoscopy and endometrial ablation experienced recurrence of endometriosis in a two-year follow up [15].

* Corresponding author. Address: Department of Obstetrics and Gynecology, University of Bochum School of Medicine, Hölkeskampring 40, D-44625 Bochum, Germany. Tel.: +49 2323 499 1801; fax: +49 2323 499 393.
*E-mail address:* clemens.tempfer@marienhospital-herne.de (C.B. Tempfer).

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However, the power of this study was limited and recurrence was defined by the presence of recurrent lesions in a second-look laparoscopy, whereas dysmenorrhea, which occurred in some of these women at the end of 2 years, was not accepted as recurrence of disease. In other studies of women with endometriosis, pain related symptoms recurred or persisted even after hysterectomy [16,17]. In view of these data, recurrent endometriotic lesions after initial surgery as well as de novo endometriotic lesions subsequent to retrograde menstruation may contribute alone or in combination to the high rate of disease recurrence in women with endometriosis.

Another possible mechanism of endometriosis recurrence may be related to regional lymphatic spread. Lymph node (LN) involvement by endometriosis is defined as the presence of typical endometriotic lesions with glandular epithelial cells and surrounding stromal cells. It was first indentified incidentally in pericolic lymph nodes in patients with bowel endometriosis. Subsequently, endometriosis lesions in regional LNs have been described in a number of reports with prevalence rates between 20% and 30% [18–24].

The basic surgical strategy for the treatment of endometriosis is to remove all visible endometriotic lesions. This strategy is based on the assumption that the removal of all lesions excludes the possibility of hormonal stimulation, reactivation, and renewed proliferation of endometriotic cells left in situ after surgery. Endometriotic lesions located in the lymphatic system, however, are not visible. Therefore, endometriotic cells in regional lymph nodes are not surgically removed and are a target of hormonal stimulation in the postsurgical period. Endometriotic cells in the lymphatic system are thus potential sources of disease recurrence in all women undergoing surgical therapy of endometriosis. To date, endometriosis is considered a localized disorder and there is no indication for systematic regional LN dissection [2].

## The hypothesis

We hypothesize that regional lymphatic spread of endometriosis is a regular phenomenon in bowel, peritoneal, and ovarian endometriosis and that endometriosis in regional LNs is a source of recurrence of this disease, adding to the high burden of disease recurrence in affected women. We also hypothesize that regional lymphatic spread has a prognostic value regarding disease recurrence as well as a predictive value regarding the efficacy of adjuvant hormone treatment of women with endometriosis. We propose that systematic resection of regional LNs in women undergoing surgery for endometriosis may reduce the recurrence rate of endometriosis and will become an essential part in the surgical treatment of women with endometriosis. Sentinel LN sampling with intraoperative frozen section analysis may be an appropriate way of identifying women suitable for LN dissection.

## Evaluation of the hypothesis

The prognostic value of regional LN spread of endometriosis can be assessed in retrospective series of women with incidentally excised LNs such as those undergoing bowel resection for symptomatic bowel endometriosis. This has not been done to date. In other forms of endometriosis, incidental removal of LNs is not being performed and therefore, prospective series of women undergoing LN dissection is necessary. One such series involving 12 patients has been described by Mechsner et al. [21]. To date, no follow-up data have been published. In our institution, we currently perform an ongoing study of 40 women with peritoneal and/or ovarian endometriosis who agree to undergo pelvic sentinel LN dissection. To date, 16 women underwent the procedure and endometriosis has been identified in the pelvic sentinel LN in 1/16 women (unpublished data). Follow-up data with recurrence rates are not available at this stage of the study. Since the prognostic, predictive, and therapeutic value of LN dissection in women with endometriosis has not been proven yet, sentinel LN sampling is an appropriate attempt in order to minimize associated morbidity. Compared to systematic LN dissection, sentinel LN sampling is safer and less invasive compared to systematic LN dissection which has been verified in women with breast cancer [25,26] and other gynecological malignancies such as cervical and vulvar cancer [27,28]. Also, the feasibility of sentinel LN sampling in women with endometriosis has already been tested. Mechsner et al. described a technique using the injection of blue dye into the visible or palpable nodule in cases of deeply infiltrating rectovaginal endometriosis. Using this approach, sentinel LNs were indentified in the iliac region in 85% of cases [21]. In our ongoing prospective study, we apply the sentinel LN sampling procedure to women with peritoneal and/or ovarian endometriosis using an injection of blue dye into the cervix. Sentinel LNs were so far detectable in 13/16 cases and no complication with this procedure was observed except for a transient intense blue colouring of the facial skin in one case [29].

In order to test the hypothesis of a prognostic and predictive value of regional LN spread, series of prospectively evaluated women such as those by Mechsner et al. and by our group need to be performed. These studies allow the correlation of LN involvement with the likelihood of recurrence as well as treatment efficacy of adjuvant hormone treatment. To date, no such data are available. In order to test the hypothesis of a therapeutic value of regional LN dissection, a prospective, randomized trial has to be performed. For a proper sample size calculation, however, data on the prevalence of regional LN involvement in different forms of endometriosis, i.e. peritoneal, ovarian, and bowel endometriosis, as well as an estimation of a potential therapeutic effect, based on retrospective and prospective prognosis studies, must be available.

## Empirical data

Despite its benign nature, endometriosis shares some of the characteristics of malignancy, such as abnormal morphology, deregulated cell growth, cellular invasion and neoangiogenesis [30,31]. The glandular epithelium displays DNA aneuploidy [32] and in vitro evidence suggests that endometriosis has a monoclonal origin [33]. In addition to being monoclonal, endometriotic deposits show loss of heterozygosity – a characteristic feature of neoplastic transformation – in 28% of lesions [34]. Regional LN involvement is another characteristic feature of malignant lesions and has also described in women with endometriosis. This fact also raise doubts whether endometriosis can still be consider a clinically benign disease.

Insabato and Pettinato reported three cases of bowel endometriosis with LN involvement [18]. In a series of 35 women with rectosigmoid endometriosis, Abrao et al. reported LN involvement in 26% of pericolic LNs [19]. In a case report of a woman with rectovaginal endometriosis, Thomakos et al. identified pelvic LN involvement [20]. Mechsner et al. reported endometriotic lesions in 3/12 (25%) pelvic sentinel LNs in women with deeply infiltrating rectovaginal endometriosis [21]. Of note, the prevalence of LN involvement by endometriosis differs by the size and type of endometriosis. For example, in women with bowel endometriosis, Abrao et al. observed a significant association between the thickness and circumference of the primary endometriotic lesions and regional LN involvement in women with rectovaginal endometriosis [19]. Noel et al. reported similar findings in women with rectosigmoid endometriosis [22]. Our own group identified one case of endometriosis in pelvic sentinel LNs in a series of 16 women with peritoneal and/or ovarian endometriosis [29]. These studies show that regional LN involvement by endometriosis is not a rarity but a common phenomenon in endometriosis and that LN