

# Prognostic and therapeutic importance of lymphadenectomy in gynecological cancers

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## Summary

Lymphadenectomy has been a matter of interest for years because of the increased morbidity rates in gynecological cancers due to the procedure itself and because the procedure requires experience. Although a number of alternative methods have been developed to find out the prevalence of gynecological cancers, dissection and histopathological evaluation of lymph nodes is still the gold standard in detecting disease. Even though there are opposing views regarding this approach, since the morbidity rate has decreased over the years many studies in the literature report that lymphadenectomy has prognostic and therapeutic value. Its contribution to survival can be attributed both to its being determinant in postoperative treatment modifications and to debulking and lymphadenectomy itself. In order to reap the prognostic and therapeutic benefit expected from lymphadenectomy, a sufficient number of lymph nodes must be dissected. Surgical experience is important both for the procedure itself and to reduce the morbidity due to the procedure. This study discusses the prognostic and therapeutic importance of lymphadenectomy in ovarian, endometrial, cervical and vulvar cancers.

*Key words:* Lymphadenectomy; Prognostic; Therapeutic; Ovarian cancer; Endometrial cancer; Cervical cancer; Vulvar cancer.

## Introduction

One of the most important prognostic factors in gynecological cancers is the prevalence of cancer. The lymphatic route is one of the main routes for the disease to spread to distant sites. Dissection and histopathological evaluation of pelvic and para-aortic lymph nodes in cervical, endometrial and ovarian cancers and inguino-femoral lymph nodes in vulvar cancer not only gives information about the prevalence and prognosis of the disease, but also poses therapeutic benefits under some circumstances. The debulking philosophy that aims at reducing the cancer load is based on the rationale of increasing the efficiency of adjuvant treatments used after surgery. The size of the lesion is a resistance factor for adjuvant treatments. As is known, a 6000 cGy radiation dose can control 90% of 2 cm lesions, 75% of 2-4 cm lesions, 65% of 4-6 cm lesions and 55% of 6 cm lesions [1]. A similar state of affairs is valid for chemotherapy and chemo-radiotherapy [1, 2].

Lymphadenectomy's contribution to survival may be attributed to itself through debulking; findings obtained as a result of lymphadenectomy suggest that it is also a determinant in the planning of postoperative adjuvant treatments that reportedly contribute to survival [3, 4].

Thus, retroperitoneal lymph node dissection has become at present an integral part of gynecological-oncologic surgical procedures because it provides prognostic information, enables regulating treatment modalities and contributes to survival.

This study discusses the prognostic and therapeutic value of lymph node dissection in ovarian, endometrial, cervical and vulvar cancers.

### **Anatomical sites of lymph nodes**

In order to reap the benefits expected from lymphadenectomy-like sufficient prognostic information and maximum therapeutic advantage, an adequate number of lymph nodes must be dissected. Therefore it is important to know the anatomy of the lymph nodes. In today's gynecological oncology practice, retroperitoneal lymph nodes are divided into two main groups as pelvic and para-aortic. Pelvic nodes are divided into subgroups like common iliac, external and internal iliac, obturator, presacral and para-metrial lymph nodes. Para-aortic lymph nodes are those around the aorta and inferior vena cava. These are also subdivided into groups like para-caval, precaval, retro-caval, deep inter-cava-aortic, superficial inter-cava-aortic, para-aortic and preaortic lymph nodes [5]. The topography of the inguinal lymph nodes has also been adequately studied due to its importance in vulvar cancer. Inguinal lymph nodes are placed in the femoral triangle while femoral nodes are located in the medial part of the femoral vein in the fossa ovalis [6, 7].

### **Complications due to the lymphadenectomy procedure**

The most common criticisms of lymphadenectomy are the increased operative morbidity, operation time, hospitalization time, cost and the need of experience. Intraoperative and postoperative complications arising from the procedure have decreased in recent years. The decrease in complications is most apparent in intraoperative vein injuries, severe hemorrhage, postoperative infection and formation of lymphocysts [8]. As experience has become enhanced throughout the years, operation time has fallen down to less than an hour in many centers and hospitalization time has also decreased. Surgical experience is important in the lymphadenectomy procedure; the more experienced the surgeon is, the fewer complications are seen [11]. When lymphadenectomies are performed by specialized gynecologist-oncologists, no extraordinary increase in patient morbidity is expected [6].

### **Lymphadenectomy in endometrial cancers**

Endometrial cancers have been surgically staged in accordance with the International Federation of Gynecology and Obstetrics (FIGO) suggestion since 1988 [8]. Studies show that there is a weak correlation between clinical and surgical staging. In a study comparing clinical and surgical staging Wolfson *et. al.* found that 12.4% of the cases that were clinically Stage I and 27.3% of the cases that were clinically Stage II were upstaged by surgery [9]. In the FIGO surgical staging there is a constant relation between stage and survival. Five-year survival rates in surgical Stage IA, IB, IC, IIA, IIB, IIIA and IIIB are 91%, 88%, 81%, 77%, 67%, 60% and 41%, respectively, while the same rate is 32% in Stage IIIC cases that have the retroperitoneal lymph nodes affected [10].

In staging surgery the uterus and both ovaries are extracted with tuba. In addition, the possibility of extra-uterine metastasis is investigated. At this point, the pelvic-para-aortic lymph nodes must be dissected and subjected to histopathological evaluation. If the cancer is restricted to the uterus when the diagnosis is made, the cure rate at the end of staging surgery is over 85%. But if extra-uterine disease is not identified, then the result of the treatment may not be pleasing and the patient may miss the opportunity of adjuvant therapy, from which she may benefit highly [11]. Accurate revelation of all dimensions of the disease determines the postoperative treatment and prevents over/under treatment. It was shown that in cases of no extra-uterine metastasis or malignant histopathology, adjuvant radiotherapy did not provide any advantage [4].

Endometrial cancers are divided into two groups as low-risk and high-risk according to prognostic factors. The low-risk group is defined as those cases where the disease is limited to the uterus, grade 1 and 2, endometrioid subtype and myometrial invasion lower than 50%. Categorization of endometrial cancers as low-risk and high-risk has a prognostic value on one hand and points out the decision of whether or not to perform lymphadenectomy on the other. It has been shown that the higher the grade and myometrial invasion, the more affected the lymph nodes are [12].

At this point there are some details that need consideration. Since in a study that investigated the compatibility between final histopathology and frozen examinations of the two important prognostic factors like

myometrial invasion and grade, which are closely related to nodal affection, results of five studies were evaluated and compatibility was 88 and 84%, respectively [13]. However, there are also studies that report higher rates of compatibility between frozen section results and final histopathology [14]. The compatibility between frozen and final histopathological results depends on many factors including the extent of experience of both the person and the center. Therefore, it may be suggested that lymphadenectomy be performed routinely in order to identify extra-uterine disease in centers that are in the process of gathering experience and/or centers where frozen studies are not made. This is because the incidence of lymph node metastasis in low-risk groups (Stage 1A, grade 1) is reported to be 2.5-4% [15, 16].

The gold standard in identifying lymph nodes is the surgical dissection and histopathological evaluation of the nodes. Preoperative evaluation offers some information about nodal affection but can not yet replace histopathological evaluation. The overall accuracy rate of magnetic resonance imaging, which is frequently used in preoperative staging, is reported to be 85% for endometrial cancer [17].

It has been shown that lymphadenectomy not only has prognostic importance but also therapeutic value in both early and advanced stage endometrial cancers. In a study by Chuang *et al.* cases that were found to be clinically Stage I and to have negative nodal affection developed retroperitoneal recurrences thought to originate from the lymph nodes. Thus, the manner by which lymphadenectomy was performed was reviewed. It was found that the recurrence was 8% in cases that did not have lymphadenectomy, 5% in cases in whom some lymph nodes were dissected and 0% in cases where had lymphadenectomy was performed in at least one of the right or left pelvic sites with paraaortic lymphadenectomy [18].

Mariani *et al.*, who pointed out the therapeutic importance of lymphadenectomy in advanced stage endometrial cancer, found in their study that of the patients who had pelvic or paraaortic lymph nodes affected, 5-year progression-free survival and overall survival rates were 76% and 77% in those who underwent paraaortic lymphadenectomy, while the same rates were 36% and 42% in those who did not have lymphadenectomy. It was reported in the same study that of the cases that had both macroscopic and microscopic nodal affection, recurrence due to lymph nodes was 0% in those who had paraaortic lymphadenectomy. Recurrence rates in those who did not undergo paraaortic lymphadenectomy were 16% in those with microscopic nodal affection and 46% in those with macroscopic nodal affection [19]. In a study by Kilgore *et al.* it was put forward that lymphadenectomy posed a manifest advantage in terms of survival in both low-risk (disease confined to the corpus) and high-risk (disease in the cervix, adnexa, uterine serosa or washings) patients [20].

In a previous study where we investigated the relation between nodal affection and nodal size in clinical Stage I endometrial cancers we found that 54.6% of the affected lymph nodes were 4-10 mm in size, 39% were 11-20 mm and 4.5% were over 20 mm. In this study it was shown that the size of the lymph node was not a reliable indicator of nodal affection [21]. Therefore, lymphadenectomy should be systematically performed in endometrial cancers.

### **Lymphadenectomy in cervical cancers**

Unlike other gynecological cancers, cervical cancer is staged clinically by FIGO. Although lymph node metastasis does not change the stage, it is the most important prognostic factor, particularly in early stage invasive cervical cancer [22]. The most reliable information about nodal metastasis can be obtained by dissection and histopathological evaluation of a sufficient number of lymph nodes.

In early stage cervical cancer, there is a close relation between the depth of stromal invasion used in staging and nodal metastasis. In minimally invasive lesions where invasion is up to 3 mm (Stage 1a1), the risk of lymph node metastasis is 1.2%; when the lesion is 3-5 mm (Stage 1a2) the risk of lymph node metastasis is 7.8%. Therefore, in cases where a lesion is up to 3 mm, either conization or simple hysterectomy without nodal dissection is preferred, whereas in cases where invasion is 3-5 mm radical surgery including lymphadenectomy should be performed [22].

Lymphadenectomy in early stage cervical cancers has an important place in conservative surgery planned for the young age group. The first requisite in this approach is the pelvic lymph nodes not being affected.

Therefore, pelvic lymph nodes must necessarily be evaluated. Considering the fact that cervical cancer is increasingly seen in earlier ages due to its relation with HPV and thereby, the increasing tendency towards conservative approaches, it is clear that pelvic lymphadenectomy plays a significant role [23].

At present there are two alternatives in the literature for the primary treatment of cervical cancers between Stage Ib and IIa. One alternative is radical surgery including radical hysterectomy and pelvic lymph node dissection, and the other is radiotherapy. Five-year survival rates for these two approaches are reported to be 87% and 92%, respectively, in the literature [24]. However, complications due to surgery and radiation therapy can be compared. Thus, optimum treatment for these patients may be decided by taking into account menopausal state, age, any other disease, cervical diameter and histological type [25].

There are a number of studies in the literature reporting the prognostic importance of lymphadenectomy as an integral part of radical surgeries in cervical cancers. Morice *et al.* conducted a study with 421 cases of Stage IB and II patients and found that the three-year survival rate was 94% in those cases with pelvic nodal affection, 64% in those with nodal affection and 35% in para-aortic nodal affection [26]. Besides the presence of nodal affection, the number and location of affected lymph nodes are also important. In a study conducted with Stage IB and IIA cervical cancer patients, Kim *et al.* found that 5-year survival rates in cases who had only one lymph node affected or lymph node metastasis below the level of the common iliac lymph nodes were 85% and 84.6%, while the same rates were 50% and 20% in those who had multiple nodes affected or extra-pelvic lymph node metastasis [27].

Lymph node dissection in cervical cancer not only has prognostic but also therapeutic value. One therapeutic advantage is that it enables the individualization of adjuvant therapy which gives better results in the clinical outcome of the lymph node. Odunsi *et al.* studied the importance of staging surgery before radiotherapy in bulky or locally progressed cervical cancer cases and the results led to a modification of treatment in 18% of patients [28].

Another therapeutic advantage is evaluating lymphadenectomy from a debulking aspect. More and more scientific evidence demonstrates that pelvic para-aortic lymph node dissection in cervical cancer contributes to survival through debulking even in later stages. At this point the study conducted by Cosin *et al.* is important wherein the contribution of staging surgery before radiotherapy in 266 Stage IB cervical cancer cases with bulky or locally advanced cervical carcinoma to survival was investigated. The five-year disease-free survival rate was found to be 75% in cases without nodal affection, 50% in cases with microscopic lymph node positivity, 46% in cases that had macroscopic affection and whose lymph nodes were dissected and 0% in cases whose macroscopically affected lymph nodes were not dissected. The authors of this study reported that dissection of positive lymph nodes might contribute to survival without increasing morbidity and mortality due to surgery beyond the acceptable limits [29]. Another study conducted by Kim *et al.* of Stage IB and IVB patients showed that of the cases whose para-aortic gross residual tumor was left only 6% survived in the 71-month follow-up, while of the cases where no para-aortic gross residual tumor was left, 31% survived in the 74-month follow-up [30].

Downey *et al.* studied the importance of dissecting metastatic pelvic lymph nodes before radiotherapy in cervical cancers at stages between IB2-IIIB. Five-year disease-free survival rate was 85% in cases without affected lymph nodes, 51% in cases whose macroscopic pelvic lymph nodes were dissected and 57% in cases whose microscopic nodal metastases were dissected. In case of the presence of macroscopically affected lymph nodes that could not be resected the same rate was 0%. It was recommended in this study to dissect large lymph nodes with radio-resistance before radiotherapy [3].

In the study carried out by Potish *et al.* the five-year relapse-free survival rate in Stage IB-IIIB patients was found to be 86% in cases without pelvic lymph node metastasis and 0% in cases with unresectable pelvic lymph nodes. Relapse-free survival was 56% in cases with microscopic lymph node affection and 57% in cases who had gross positive lymph nodes that were completely resected [31].

Hacker *et al.*, who studied the same subject, suggested that bulky lymph nodes should be investigated, and if found, be resected before radiotherapy in cervical cancer cases at Stage IB-IVA [32]. All of these studies reported that morbidity due to surgery was at an acceptable level.

## Lymphadenectomy in ovarian cancers

The primary treatment of ovarian cancer is surgery. Therefore in cases diagnosed as ovarian cancer it is necessary to have appropriate and optimal surgical staging including pelvic para-aortic lymphadenectomy. It is of utmost importance that staging be performed by experienced gynecologist-oncologists. Five-year survival in Stage I tumors that were not accurately staged was 60%, whereas this rate ranged between 90 to 100% in Stage I cases that were staged accurately [33].

Lymphatic metastasis is closely related to the stage of disease. As the stage advances, retroperitoneal lymph node affection increases. Burghardt *et al.* found in their study that lymph node affection was 24% in cases that were thought to be Stage I, 50% in Stage II, 74% in Stage III and 73% in Stage IV. It was reported in the same study that the 5-year survival rates were 69% in those who did not have affected lymph nodes, 58% in those with only one lymph node affected and 28% in those with more than one lymph node affected [34].

Young *et al.* performed additional surgery on 100 cases identified as having Stage I and Stage II disease and found that 28% of cases thought to be Stage I and 43% of cases thought to be Stage II were at later stages of disease. Upstaging was detected in 16% of Stage I cases, 34% of Stage II cases and 46% of Stage III cases [35].

Cases in which a sufficient number of lymph nodes cannot be dissected and thus are evaluated as a lower stage may miss the opportunity of postoperative chemotherapy. Therefore, the lymphadenectomy technique should be carried out properly. It was established that in cases in whom sampling or bulky nodes were resected by systemic lymphadenectomy, nodal affection was 19.3% in systemic lymphadenectomy and 9.9% in others [5]. Another problem in the evaluation of palpable nodes is that 55% of metastatic nodes are smaller than 2 cm [36, 37]. What should be known at this point is that not the size but the number of lymph nodes correlate with prognosis [38]. As can be understood from all this information, in order to reveal the prevalence of disease a sufficient number of affected lymph nodes should be dissected at every stage of the disease. This is possible only by systemic lymphadenectomy.

It was reported in the study carried out by Allen *et al.* in Stage III ovarian cancer patients that 5-year survival rates were 38% in those who had lymphadenectomy and 22% in those who did not [39]. Other researchers have also reported similar results. Di re *et al.* found that when the residual tumor was smaller than 2 cm, 5-year survival was 46% in cases that had lymphadenectomy and 30% in those who did not [40].

Burghardt *et al.* reported the effect of pelvic lymphadenectomy following maximal debulking on survival in patients between Stage IA and IV. In this study the 5-year survival rate was 74.7% in those with negative nodal affection, 45.9% in those with positive nodal affection, 53% in Stage III cases that had pelvic lymphadenectomy and 13% in those that did not have pelvic lymphadenectomy [41]. Scarabelli *et al.* conducted a study on ovarian cancer patients between Stage IIIC and IV and reported that the 5-year survival was 16% with cyto-reductive surgery and 59% in cases that also had lymphadenectomy [42].

In ovarian cancers lymphadenectomy is a part of cyto-reductive surgery. A high number of studies have demonstrated that the best survival in advanced stages is seen following appropriate cyto-reductive surgery at the beginning [33]. Liu *et al.* found that in Stage IV epithelial ovarian cancer patients the median survival was 37 months for those who had optimal debulking and 17 months for those who had sub-optimal debulking [43]. In a study with Stage III epithelial ovarian cancer patients Kigawa *et al.* performed hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic para-aortic lymphadenectomy in one group and conducted hysterectomy, bilateral salpingo-oophorectomy and omentectomy, but did not perform lymphadenectomy in another group. There was no difference between groups in terms of 5-year survival, whereas 2-year survival rates were similar in the lymphadenectomy group and in the group with negative lymph nodes [44].

However, there are also studies that state that there is no relation between nodal affection and survival. Onda *et al.* compared cases that were upstaged to Stage III based on lymph node metastasis (Group A) and Stage I or II cases who did not have nodes affected but only limited tumor in the pelvis (Group B) (Group C) in terms of survival. Five-year survival was 84% in Group A and 96% in Group B [45]. In a study with Stage III and IV patients, Parazzini *et al.* claimed that there was no relation between nodal affection and survival and reported that 3-year survival was 46.2% and 44.6%, respectively [46].

If lymphadenectomy is systemic its contribution to survival is increased. According to the results of a prospective study conducted recently by Benedetti *et al.* on advanced stage ovarian cancer patients, 2-year survival in cases who had systemic lymphadenectomy was 85.3% while in those cases whose bulky lymph nodes were dissected it was 58.9%. Disease-free survival was reported as 70.1% and 84.5%, respectively [5]. Therefore, systemic lymphadenectomy should be performed in ovarian cancers.

### **Lymphadenectomy in vulvar cancers**

Vulvar cancers constitute 3-5% of female genital diseases. They spread to neighboring organs directly and by lymphatic and hematogenous routes [47].

Of these, the lymphatic route is particularly important in vulvar cancers. Lymphatic metastasis happens mostly to inguinal lymph nodes first, from inguinal lymph nodes to femoral lymph nodes, from femoral lymph nodes to pelvic lymph nodes and especially to external iliac lymph nodes [47]. However, femoral lymph nodes may sometimes be affected without inguinal metastasis [48].

The most important prognostic factor in vulvar cancer is the presence of positive inguino-femoral lymph nodes. Therefore when vulvar cancer is diagnosed, whether the inguino-femoral lymph nodes are affected or not, all lesions deeper than 1 mm should be identified. Five-year survival rate for patients with negative inguinal lymph nodes is 98%, whereas the same rate is 29% in patients who have three or more unilateral or two or more bilateral lymph nodes affected [49].

There is a certain extent of correlation between FIGO staging and lymph node affection. However, studies that have been conducted until the present time indicate that the condition of the lymph node plays a bigger role in determining prognosis, irrespective of the stage. The effect of stage and lymphadenectomy on survival has clearly been demonstrated in Stage III patients. In the study carried out by a gynecological oncology group, patients were divided into four risk groups according to affected lesion diameter and the condition of the lymph nodes. Five-year survival rates for these groups were found to be 98%, 87%, 75% and 29%, respectively. It was shown that these cases had 98%, 85%, 74% and 31% survival for Stages I, II, III and IV, respectively, according to FIGO staging. However, five-year survival rates for low-, moderate- and high-risk patients in FIGO Stage III were found to be 95%, 74% and 34%, respectively [49].

It has been pointed out in several other studies that the most important prognostic variable in vulvar cancer is inguinal lymph node affection. Hacker *et al.* demonstrated in their study that the five-year survival rate was 96% in cases with negative lymph nodes, 94% in cases with one positive lymph node and 80% in those with two or more positive lymph nodes [50]. In addition, prognosis of all patients with negative lymph nodes is favorable, irrespective of tumor diameter, and there is no difference between survival rates of patients in Stage I and those in Stage II [49].

Moreover, lymph node dissection in vulvar cancer also has other therapeutic advantages. In early stage vulvar cancers, inguinal lymph node dissection is the only and the most important factor that decreases mortality [47]. When recurrence is seen in patients who did not have lymph node dissection, mortality rate increases [51, 52].

In vulvar cancer, lymphadenectomy should be in the manner of complete inguino-femoral lymph node excision. Stehman *et al.* identified inguinal recurrence in six out of 121 patients who underwent inguinal dissection. It is strongly probable that these recurrences arose from incomplete inguinal or femoral node excision [53]. In addition, it has been shown in several studies that there is a direct relation between the femoral nodes and the cribriform fascia, anterior vulva and clitoris [48, 54].

At present, there is no need for any additional treatment to local excision in cases of unilateral lesions smaller than 1 mm. Ipsilateral lymph dissection is adequate in larger unilateral lesions. If one lymph node is affected, no additional surgery or other treatment is necessary [55]. In cases where there are no suspected inguinal lymph nodes (inguinal and femoral), pelvic lymph node affection varies from two to 12%. Twenty percent of patients whose inguinal lymph node is affected also have the pelvic lymph node affected [47]. In cases of multiple lymph node affection, inguinal lymphadenectomy should be bilateral [47, 56]. Even if the tumor affects such median line structures such as the clitoris or Bartholins gland, the pelvic lymph node is rarely affected as long as the inguinal lymph node is negative [47]. Therefore, the indication for pelvic lymphadenectomy is similar

in the treatment of these tumors. However, inguino-femoral lymph node dissection should be bilateral. Adjuvant radiotherapy is given when the risk of pelvic lymph node affection increases as stated above [57].

In the last two decades there has been a disposition towards less radical approaches in vulvar cancer surgery. Sentinel lymph node techniques have been developed for this purpose. However, the concerned approach requires additional experience. Moreover, it still can not replace complete inguino-femoral lymphadenectomy with its positive predictive value of about 75% [58].

## Conclusion

Lymphadenectomy continues to be a matter of interest due to increased cost, advances in imaging methods and the required experience for the procedure. In expert hands, dissection and histopathological evaluation of a sufficient number of lymph nodes with an acceptable rate of morbidity is still the gold standard in determining the prevalence of gynecological cancers. Although there are opposing views, more and more scientific evidence suggests that the lymphadenectomy procedure has prognostic and therapeutic value in gynecological cancers.

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