

Distinguished expert series

by Peter Bósze

Saving the lymph nodes

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Introduction

Removal of locoregional lymph nodes forms a major part of gynecologic cancer surgery. Lymphadenectomy is considered a primary part of extended surgery for cervical and vulvar cancer, as well as an integral part of staging for ovarian and endometrial cancer. Nonetheless, the practicing gynecologic oncologist must understand the body of evidence surrounding lymphadenectomy in the surgical management of gynecologic malignancies.

There are several issues which a gynecologic oncologist must consider in deciding whether to remove lymph nodes and how extensive a dissection to perform. First, what is the risk of acute and chronic morbidity associated with lymph node resection? Second, how critical is the assessment of regional lymph nodes in cancer staging? Third, what is the impact of lymphadenectomy itself upon the effectiveness of cancer therapy. These issues must be faced for each cancer site, as the role of lymphadenectomy differs somewhat among cancers of the vulva, cervix, endometrium, and ovary.

For all cancers, however, tumor cells appear to avoid destruction by inducing immunologic anergy or tolerance. Those T-cells which become activated move from the draining lymph nodes in two directions. First, they migrate toward the cancer via the lymphatics and the feeding capillaries, then squeeze through the vascular endothelium into the tissue surrounding the cancer. Second, they migrate to other lymph nodes all over the body to provide ongoing surveillance against the antigens which activated them initially. Removing the draining lymph nodes, as we do in a lymph node sampling or dissection, will remove only a small proportion of the activated T-cells. Thus, the lymph node removal will not affect an individual's immunologic response to cancer [1].

Ovarian Cancer

Let us now consider ovarian cancer. For women with disease grossly confined to the ovaries or pelvis, lymph node sampling is critical. Identification of metastatic disease in the pelvic or para-aortic lymph nodes will upstage a patient to stage III disease. Such an upstaging has major implications for both cancer prognosis and cancer treatment. Nonetheless, we know that many women with presumed early stage ovarian cancer do not undergo lymph node sampling [2]. For the properly trained surgeon, the risks of acute and chronic morbidity associated with such lymph node sampling are minimal. Further efforts at educating physicians as to the importance of comprehensive surgical staging for early ovarian cancer are needed.

What about women with gross disease in the upper abdomen? We know that the majority of these women will also have metastatic disease in the retroperitoneal lymph nodes. Should efforts at surgical cytoreduction include therapeutic pelvic and para-aortic lymphadenectomy? First, it would seem unrealistic to attempt retroperitoneal cytoreduction in a patient who cannot be optimally cytoreduced intraperitoneally. It may be reasonable to consider resection of grossly enlarged pelvic and para-aortic lymph nodes. The surgeon must, however, balance the potential benefits of such retroperitoneal debulking with the intraoperative and peri-operative risks, particularly hemorrhage. If the intraperitoneal debulking has engendered major blood loss, requiring support with blood products, then foregoing retroperitoneal lymph node dissection may be safer for the patient. In addition, these patients will require systemic chemotherapy to kill cancer cells remaining in the peritoneum, retroperitoneum, lymphatic system, and elsewhere in the body. Even the most

aggressive of our gynecologic surgeons have not yet advocated mediastinal and scalene lymph node dissections for women with stage III and IV ovarian cancer [3].

Carcinoma of the endometrium

What is the role of lymph node resection in endometrial cancer? From the landmark staging studies conducted in the past we know the risks of pelvic and para-aortic lymph node metastases associated with tumor grade and depth of invasion [4]. From pilot data conducted at MD Anderson we know that lymphatic drainage of the uterus is highly variable [5]. Several retrospective studies suggest that there might be a survival advantage associated with an extensive lymph node sampling [6]. This improved survival, however, may be due in part to more accurate staging and identification of women who might benefit from adjuvant chemotherapy or radiation therapy. As overall survival for women with endometrial cancer is so good, a phase III trial comparing hysterectomy alone to hysterectomy plus pelvic and para-aortic lymph node dissection would need to be very large. In addition, the design of such a trial would also need to take into account the use of postoperative adjuvant chemotherapy and radiotherapy. The British Medical Research Council has initiated such a trial, but the results will not be available for 5-7 years. In addition, the morbidity of a complete pelvic and para-aortic lymph node dissection in an obese patient with endometrial cancer should not be underestimated. We have all treated large patients in whom we felt lucky to be able to complete just an abdominal hysterectomy.

Certainly, it is reasonable to resect grossly enlarged lymph nodes in women with endometrial cancer. Prospective reports suggest that adjuvant pelvic and para-aortic radiotherapy may be able to yield some of these women long-term survival [7, 8]. On the other hand, most women with endometrial cancer are treated in the community by hysterectomy alone. At this point, we need both improved imaging capabilities, to diagnose the woman with metastatic disease involving lymph nodes, as well as improved adjuvant therapy, to cure women found to have disease outside the uterus at time of diagnosis. Until then, we should probably save most of the pelvic and para-aortic lymph nodes in women with endometrial cancer. The major exceptions, as mentioned above, are grossly enlarged lymph nodes and lymph nodes removed for sampling, as clinically indicated.

Squamous cell carcinoma of the uterine cervix and vulva

With squamous cancers of the cervix and vulva, we have stronger data supporting the therapeutic benefit of lymph node resection. In addition, in cervical cancer we know that lymph node resection is not indicated for women with cancers invading less than 3 mm and without lymph-vascular invasion [9]. For women with FIGO stages IA2 to IIA, however, it is recommended that pelvic lymphadenectomy accompany radical hysterectomy. Nonetheless, the risk of pelvic lymph node metastasis for women with stage IB disease is around 15% [10]. The other 85% of women derive no benefit from the lymphadenectomy.

Among women undergoing pelvic lymphadenectomy, the risk of developing a lymphocyst is about 20%, while the risk of developing a symptomatic lymphocyst is 2%. The risk of lymphedema is about 8-10% [11]. Improvements in imaging, to help delineate those women who do have metastatic lymph node involvement and thus need the lymphadenectomy, as well as improvement in adjuvant therapy, are clearly needed.

It is unclear, however, what should be done in the case of a woman found to have multiple, grossly positive pelvic lymph nodes at the time of radical hysterectomy. Completing the lymphadenectomy will reduce the challenge we pose to the radiation oncologist who must push the radiotherapy dose to sterilize lymph nodes involved with cancer. On the other hand, using two modalities, namely radical surgery and radiation therapy, does increase the patient's chance of postoperative complications.

It is also unclear when paraaortic lymph node resection is indicated in cervical cancer. Identification of metastatic disease in the para-aortic lymph nodes will help identify patients who would benefit from para-aortic radiation therapy. In some cases this identification can be accomplished by imaging, such as CT or MRI, followed by CT-directed biopsy [12]. Extraperitoneal lymph node sampling will reduce the risk of postoperative complications. There have also been suggestions that resection of enlarged para-aortic lymph nodes may improve survival. As with early stage disease, improvements in imaging, to help delineate those women who do have metastatic paraaortic lymph node involvement, as well as improvement in adjuvant therapy, are clearly needed. A phase III clinical trial, in which women with stage IIB-IV disease, and grossly

positive para-aortic lymph node involvement, randomized to chemoradiation with or without para-aortic node debulking would be necessary to provide definitive guidelines in this situation.

Turning now to vulvar cancer, the lymphatic drainage of the vulva has been well established. We know that tumors with a thickness of 1 mm or less carry little risk of lymph node metastasis and do not warrant inguinal node dissection [13]. We know that lateralized lesions have little risk of contralateral lymph node involvement. We know that pelvic lymph node resection is not indicated for vulvar cancers.

A complete inguinal node dissection is associated with a 30% risk of groin complications, including breakdown, lymphocytes, and lymphangitis, as well as a 10-15% incidence of lower extremity lymphedema. Several groups have recommended that women with tumors 1-2 cm in size and less than 5 mm of invasion may be treated with radical local excision and a superficial inguinal node dissection [14, 15]. The superficial inguinal node dissection uses the traditional lateral margins, the inguinal ligament, sartorius muscle, and adduction longus muscle, but stops at the cribriform fascia. The superficial dissection decreases the risk of groin complications and lymphedema. Nonetheless, a negative superficial lymphadenectomy is associated with a 4% incidence of groin failure.

Several groups have reported pilot studies using dye or radioactive techniques to identify sentinel lymph nodes in women with vulvar cancer. In theory, women found to have no metastatic disease in their sentinel lymph nodes could be spared inguinal lymph node dissection altogether. These experiences need to be confirmed in a large multicenter trial before sentinel lymph node evaluation can be considered as a standard of care for women with vulvar cancer.

In the past, it has been thought that women found to have metastatic disease in the inguinal lymph nodes were best treated with inguinal node dissection followed by pelvic and groin irradiation. The combination of two modalities in the groin does increase the risk of groin and extremity complications, particularly lymphedema. The development of improved radiation therapy suggests that primary radiotherapy may be able to control metastatic disease in the pelvic lymph nodes [16]. If this is confirmed, then sentinel lymph node evaluation to confirm groin node metastasis, followed by pelvic and groin radiation, would decrease the risk of complications.

Summary

We need improved imaging and staging techniques to identify metastatic disease in the lymph nodes. Once we are able to do this accurately, then we can save the lymph nodes. Until that time, however, gynecologic oncologists should give careful thought as to which nodes they choose to remove and how lymph node removal may affect short-term and long-term morbidity.

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