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Status of Sentinel Lymph Node Biopsy in Gynecological Cancers

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In the last 15 years, sentinel lymph node biopsy has dramatically altered the practice of surgical oncology. Patients with small primary tumors of the breast or skin who have negative regional lymph nodes no longer suffer the consequences of regional lymphadenectomy, in particular lymphedema. The adoption of sentinel lymph node biopsy in patients with breast cancer and melanoma was based mainly on large single-institution series led by respected leaders in their fields. Since then, larger multi-institutional trials have been reported that complement the single-institutional series.[1] Sentinel lymph node status is part of the American Joint Committee on Cancer staging system for breast cancer[2] and cutaneous melanoma.[3]

The last 15 years have witnessed numerous studies of the sentinel lymph node biopsy technique in patients with gynecological cancers, including endometrial, vulvar, and cervical cancers. Despite this activity, sentinel lymph node biopsy has not replaced lymphadenectomy as the standard for surgical management of patients with such cancers.

Endometrial cancer is the most common gynecological cancer in the United States. Lymphatic drainage of the endometrium is complicated; because the uterus is a midline structure, this drainage is presumed to be bilateral. The lower uterine segment drains, as does the cervix, to the pelvic lymph nodes, whereas the uterine fundus drains along the gonadal vessels to para-aortic sites up to the left renal vein. These drainage patterns necessitate extensive pelvic and para-aortic lymphadenectomy to stage the patient's disease. Lymphedema does not appear to be a common complication of these operations, although it has not been well studied. Several intraoperative lymphatic mapping techniques have been reported for endometrial cancer, including the use of cervical, fundal,[4] and hysteroscopic injections,[5] the latter of which is the most promising in terms of sentinel lymph node identification. However, this technique can be quite cumbersome and has not progressed much beyond the feasibility-testing stage.

Vulvar cancer was the first and most promising gynecological site for the sentinel lymph node biopsy strategy. Because it involves a cutaneous tumor, peritumoral injections are easy; another factor making the vulva an ideal site for sentinel lymph node biopsy is that the sentinel lymph node is always located in the groin. Lower-extremity lymphedema is common, especially when postoperative radiotherapy is given to lymph node-positive patients. Because vulvar cancer is rare—only 4,000 cases are diagnosed each year in the United States—accrual to clinical trials of sentinel lymph node biopsy for vulvar cancers has been slow. A large validation trial conducted by the Gynecologic Oncology Group and including over 400 patients is awaiting completion. A large observational trial in the Netherlands is awaiting maturation of results and publication.[6] The current treatment guidelines for vulvar cancer call for regional radiotherapy to patients with positive lymph nodes. For

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this reason, gynecology oncologists (and patients) will be willing to accept sentinel lymph node biopsy alone, only if it is associated with a very low false-negative rate.

Cervical cancer, the most common gynecological cancer in the world, is a sexually transmitted disease resulting from infection with certain subtypes of human papillomavirus. The infection is associated with a premalignant phase that is protracted and detectable using an inexpensive screening test—the Pap smear. The incidence of this cancer continues to decline in populations with good pap smear screening programs (fewer than 10,000 cases are diagnosed per year in the United States), although it is still rising in unscreened populations.

The cervix is an excellent target for the sentinel lymph node mapping strategy. The cervix is a midline structure with complex lymphatic drainage to multiple pelvic, common iliac, and low para-aortic sites. Cervical tumors are visible to the naked eye and easy to inject, and all the potential drainage sites can be accessed through a single incision. In addition, sentinel lymph node biopsy for cervical cancer can be performed laparoscopically, an especially attractive feature as increasing numbers of radical hysterectomies are being performed using this technique. Sentinel lymph node biopsy is also a good complement to fertility-sparing procedures such as radical trachelectomy. However, the usefulness of such a biopsy in patients with cervical cancer has been questioned, since lower-extremity lymphedema in such patients undergoing standard lymph node dissection appears to be less common and less severe than in those undergoing groin dissection. In addition, parametrial lymph nodes that are immediately adjacent to the cervix cannot be imaged with lymphoscintigraphy and are difficult to observe in the operating room.

Coutant et al. [7] reported on experience with sentinel lymph node biopsy in patients with cervical cancer. This series included a heterogeneous group of patients with tumors ranging in size from microscopic to 7 cm and patients who are usually excluded from radical-hysterectomy sentinel lymph node biopsy series, such as those with stage-Ib2, -IIa, and -IIB disease. Some of these patients received neoadjuvant chemotherapy before surgical treatment of the cervix and 15% underwent lymphadenectomy only, without surgical treatment to remove the cervix after the sentinel lymph node biopsy (presumably because they had locally advanced disease or gross nodal involvement). There were 11 lymph node-positive patients in the series, and 2 (18%) were reported as having false-negative findings on sentinel lymph node biopsy, both of whom had stage-IIb disease. The false-negative rate in the stage-I patients was zero. These findings confirm clinical observations from multiple disease sites that sentinel lymph node biopsy is best performed in patients with small localized tumors and grossly uninvolved lymph nodes.

The results of the series reported by Barranger also confirm another common observation regarding sentinel lymph node biopsy for cervical cancer. Despite the midline position of the cervix, only a little more than half of all patients with cervical cancer were found to have bilateral sentinel lymph nodes (only 45% in the current series). It is not known what effect the exact injection site, obstetrical trauma, endometriosis, or pelvic inflammatory disease might have on lymphatic drainage.

Hauspey et al.[8] have recently reported their single-institution series of over 40 patients with stage-I cervical cancer and reviewed over 800 published cases. This group suggested that the false-negative rate for sentinel lymph node biopsy in these patients has been overstated in the literature and suggest two simple guidelines to protect against false-negative results. First, when a sentinel lymph node is identified on one side of the pelvis only, a lymphadenectomy should always be performed on that side. Second, the parametrium should always be removed with the cervix so that any parametrial sentinel lymph nodes are removed with the specimen. These guidelines will improve the safety of the sentinel lymph node biopsy procedure in these patients. However, the total number of node-positive cervical cancer patients reported in the literature is still under 200, a very small number on which to base change in standard practice. In addition, many innovative management approaches are being investigated—such as a two-step laparoscopic sentinel lymph node biopsy and a simple vaginal trachelectomy strategy described by Rob and colleagues[9]—and these need development. For cervical cancer, as in vulvar cancer, current treatment guidelines are heavily dependent on lymph node status; therefore, a low false-negative rate is necessary to avoid relapses in otherwise curable patients.

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