Role of lymphadenectomy in the staging of endometrial cancer

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Pelvic lymphadenectomy offers no therapeutic benefit to women diagnosed with early-stage endometrial cancer according to a new study. Lymphadenectomy can only be recommended as part of a clinical trial in this disease setting; however, it can offer valuable staging information in patients with advanced disease.

Endometrial cancer is the most common gynaecologic malignancy diagnosed in Western nations. Although most patients with endometrial cancer have uterine-confined disease, a subset of patients has retroperitoneal lymph-node metastasis, which is associated with a poor outcome. In 1988, the International Federation of Gynecology and Obstetrics introduced the current surgical staging system, which includes staging with hysterectomy, oophorectomy, peritoneal cytology and retroperitoneal lymph-node sampling. However, the extent of surgical staging and the use of adjuvant therapy for endometrial cancer is the most heterogeneous among gynaecologic malignancies. Randomised trials in patients with early-stage disease have not demonstrated a survival benefit with adjuvant whole pelvic irradiation, regardless of whether a lymph-node dissection was performed.[1,2] The rationale behind comprehensive surgical staging (pelvic and para-aortic nodes) is that patients found to have lymph-node metastases can benefit from appropriate and curative adjuvant therapy, sparing those with uterine-confined disease from treatment-related toxic effects. Although there are a limited number of retrospective studies demonstrating a therapeutic benefit to lymphadenectomy,[3,4] these studies are plagued by the biases inherent to retrospective studies. The role of lymphadenectomy in endometrial cancer has been investigated prospectively in the ASTEC trial (Adjuvant External Beam Radiotherapy in the Treatment of Endometrial Cancer).[5]

This trial assessed 1,408 women from 85 centres in four countries. Eligible women included those surgical

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candidates with clinical stage I endometrial cancer. The study aimed to detect a 10% improvement in overall survival with lymphadenectomy, requiring 1,400 women to be included. Randomisation at the time of surgery was a two-part process: women were randomly allocated to standard surgery (control arm), which included hysterectomy, oophorectomy, peritoneal washings and palpation of para-aortic lymph nodes, or standard surgery plus a systematic dissection of the bilateral pelvic (iliac and obturator) lymph nodes (experimental arm). In total, 704 women were randomly allocated to each arm. In the second randomisation, 507 patients with intermediate-risk or high-risk (IA or IB with high-grade histology, IC or IIA) early-stage disease, independent of whether lymphadenectomy was performed, were randomly allocated to pelvic teletherapy versus observation in order to control for differences in post-surgical adjuvant therapy dependent on node status. Patients with low-risk disease as well as patients with advanced disease were excluded from this randomisation and treated at the discretion of the investigator.

The median node count in the lymphadenectomy group was 12, with 12% of patients having fewer than five nodes removed. Operating time was longer with lymphadenectomy, and was associated with a nonsignificant increase in ileus, venous thromboembolism, lymphocyst formation and major wound dehiscence. Similar proportions of women in both groups received adjuvant radiation therapy. Following adjuvant therapy, more women who underwent lymphadenectomy reported moderate to severe treatment-related morbidity than women who underwent standard surgery alone (17% vs 12%).

A statistically significant difference in five-year recurrence-free survival was seen (hazard ratio 1.35, 95% CI 1.06–1.73, P=0.017) in favour of standard surgery. No difference in overall survival or disease- and/or treatment-related deaths was noted. Despite randomisation, considerable imbalances were noted between the arms; there were more aggressive tumours (serous, clear-cell, grade 3) and more deeply invasive tumours in the lymphadenectomy arm. Supporting the disparate randomisation, a higher number of disease-related deaths was seen in the lymphadenectomy arm (64 vs 56). It is likely that this rate is independent of lymphadenectomy and is a function of more 'high-risk' patients in the lymphadenectomy arm. When these imbalances are taken into consideration, reanalysis of the data shows the recurrence-free survival was no longer significantly different. The ASTEC investigators concluded that lymphadenectomy does not improve survival in endometrial cancer, even when controlled for adjuvant therapy. Similarly, the CONSORT trial demonstrated no survival difference attributable to lymphadenectomy when patients were randomly allocated to pelvic lymphadenectomy versus no lymphadenectomy, although these data did not control for the effect of adjuvant therapy.[6]

Although the ASTEC investigators must be commended for undertaking this study, there are a number of limitations that must be addressed. Primarily, the extent of lymph-node dissection and the number of lymph nodes collected in the lymphadenectomy arm seems insufficient. Although the median number of lymph nodes collected was 12, 35% of patients had fewer than nine nodes collected. A number of studies have indicated that increased lymph-node counts are associated with improved outcomes[7,8] in high-risk, early-stage patients. Chan et al. used a logistic regression model to determine that the largest increase in detecting a single positive lymph node among endometrioid endometrial cancers was when between 21 and 25 lymph nodes were resected, (P<0.01).[7] Independently, it has been shown prospectively that in patients with lymph-node metastases, over two-thirds have aortic node involvement,[9] with 16% having isolated aortic metastases. It seems unreasonable to conclude from ASTEC (or CONSORT) that systematic lymphadenectomy offers no benefit, if aortic nodes were not evaluated and residual aortic metastases might have been left behind.

A second limitation of ASTEC is that 45% of patients were determined to have low-risk intrauterine features and a significant number of participants had stage IA disease. In fact, when compared with other early-stage trials (CONSORT, PORTEC and GOG99), ASTEC had the highest proportion of stage IA tumours (13% vs 1.6%, 0% and 0% respectively).[6,10] Given that lymph-node involvement is quite uncommon in patients with low-risk intrauterine features and is 1% in the stage IA population,[10] a significant number of ASTEC patients would not benefit from lymphadenectomy *a priori*; thus, the absolute number of patients needed to demonstrate an improved survival from lymphadenectomy might have been underestimated from the start of the trial.

Although the second (adjuvant teletherapy) randomisation was performed in order to control for differences between the standard arm and lymphadenectomy arm, brachytherapy, chemotherapy and hormone therapy were used at the discretion of the treating physician. Thus, nonprotocol-directed therapy could have diluted any differences in outcome as a result of lymphadenectomy.

The ASTEC trial confirms that there was no survival benefit from adjuvant whole-pelvic irradiation, whether or not a pelvic lymph-node dissection was performed, in patients with early-stage endometrial cancer. This study was unable to demonstrate a direct therapeutic value of lymphadenectomy as it was probably underpowered owing to the high proportion of patients with low-risk disease, low pelvic lymph-node counts and lack of para-aortic lymph-node dissection.

The primary value of comprehensive surgical staging is to appropriately direct curative therapy for patients with extrauterine disease and to withhold potentially toxic therapy in those patients without extrauterine disease. Preoperative tumour grade and imaging, intraoperative palpation and frozen section have not proven to be as accurate or reliable as pelvic and para-aortic lymphadenectomy for identifying patients with occult disease spread.

In the sentinel surgical staging study by the Gynecologic Oncology Group (GOG),[10] over 10% of patients with myometrial invasion confined to the inner half of the uterus, as well as over 10% of those with grade 1 or 2 tumours, had lymph-node metastases. The omission of lymphadenectomy misclassifies patients with lymph-node involvement as 'stage I', which biases the results of studies aimed at assessing outcomes of early-stage disease, and leads to lost opportunities to treat patients with advanced disease with the appropriate adjuvant therapy.

Although the ASTEC trial greatly contributes to our understanding of the role of lymphadenectomy in endometrial cancer, it also raises many important questions that will lead to continued scientific interest in the value of this surgical intervention.

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Practice point

Routine pelvic lymphadenectomy does not offer a clear therapeutic benefit to women with early-stage endometrial cancer. Lymphadenectomy does, however, ensure that patients with advanced stage disease are correctly classified, and allows appropriate decision making regarding adjuvant therapy to take place. As such, it should remain a part of clinical practice.

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