Clinical Commentary

Lymphadenectomy for endometrial cancer: The controversy

Comprehensive surgical staging for endometrial cancer, including hysterectomy, bilateral salpingo-oophorectomy, pelvic washings, and pelvic-aortic lymphadenectomy, defines disease biology and facilitates triage of tailored adjuvant therapy. Recent publication of two randomized trials has cracked the foundation of the house lived in by those believing in the absolute value of endometrial cancer surgical staging—or has it? (Table 1) [1,2].

The first study (Panici trial) randomized clinical stage I endometrial carcinoma patients to systematic pelvic lymphadenectomy vs. no lymphadenectomy (control) [1]. Eligible patients included those with frozen sections demonstrating myometrial invasion (stage T1b grade 1 excluded) who were also ≤75 years old with a Karnofsky performance status ≥80 with no previous malignancy, chemotherapy, or radiation. A sample size of 524 patients was estimated to detect a 8% difference (80 to 88% 5-year overall survival, HR 0.52) with an alpha of 5% and beta of 80%. The study accrued 514 patients at 31 centers in 2 countries over 10 years (10 patients short of the trial design). While an increase in early postoperative complications was demonstrated in the lymphadenectomy arm, conclusions may be limited due to failure to adjust the rates for adjuvant therapy. Importantly, the trial did note an increase in the lymph node-positivity rate when systematic lymphadenectomy was required in the lymphadenectomy arm; however, 12% had nodes removed. As expected, the median operative length was longer in the lymphadenectomy group; however, 12% had nodal dissection (boundaries undefined); however, aortic sampling was not required. Although the trial was randomized, baseline disparity for key covariates, such as histologic subtype and depth of invasion, was notable.

Regardless of lymph node status, women were postoperatively assigned as follows: low-risk early stage (TiA1B N x M x and grade 1–2), intermediate and high-risk early stage (TiA1B N x M x and grade 3, papillary serous or clear cell histology; or TiC or IIA N x M x) and advanced stage (TiB, IIA B1B N x M x). Postoperative treatment was not standardized for low-risk early or advance stage; however, the trial controlled for adjuvant treatment in intermediate and high-risk early stage patients by randomization into a radiation protocol [8]. Thus, half the patients in the intermediate and high-risk early stage subgroup were randomized to receive external beam radiation ± brachytherapy and the other half received observation ± brachytherapy. Thus, the potential benefit of the lymphadenectomy in triaging patients into the proper adjuvant therapy, is potentially obscured because half the patients did not receive treatment.

The sample size (N=1400) was calculated to detect a 10% improvement in 5-year overall survival for all stages combined (5% alpha, 90% beta). Given the excellent survival for stage I and II, disease-specific survival rather than overall survival may be a better endpoint. In this trial, patients were randomized to standard surgery (N=704) or lymphadenectomy (N=704); thus, the study was adequately powered to detect a 10% difference overall survival (all stages combined). While most baseline characteristics were similar between the two groups, there were notable differences in pathology. When compared to the standard arm, the lymphadenectomy group had significantly more patients with disease spread beyond the uterus (21% vs. 19%), increased proportion of clear cell or serous vs. endometrioid subtype (7% vs. 4.5%), and more stage TiC N x M x vs. stage TiA1B N x M x.

The median number of lymph nodes removed was 12 in the lymphadenectomy group; however, 12% had <5 nodes removed. Sixty-five percent assigned to the lymphadenectomy arm had an “adequate” dissection of ≥10 nodes (35% had <10 nodes removed) and 5% in the standard no-lymphadenectomy arm had nodes removed. As expected, the median operative length was longer in the lymphadenectomy group (90 minutes vs. 60 minutes). While the overall complication rate was low, lymphadenectomy patients had more complications (ileus 3 vs. 1%, DVT 1 vs. 0.1%, lymphocyst 1 vs. 0.3%, major wound dehiscence 1 vs. 0.3%). Some of these patients...
received dual-modality therapy that is known to increase morbidity without survival advantages [9]. These complications were not adjusted for adjuvant therapy, thus limiting conclusions regarding lymphadenectomy adverse events independent of radiotherapy.

Although 67% did not receive adjuvant radiotherapy, inequalities between the arms are noted among individual risk groups. In addition, most women were low-risk and would not have benefited from lymphadenectomy or radiation (49% control, 42% lymphadenectomy). The patients thought to most benefit from adjuvant therapy (intermediate and high-risk early stage) comprised <37% in each arm. As expected, there was a higher rate of positive nodes detected in the lymphadenectomy arm. However, only 3.1% in the lymphadenectomy group vs. 0.6% standard arm were intermediate high-risk

<table>
<thead>
<tr>
<th></th>
<th>Panici treatment arm</th>
<th>Panici control arm</th>
<th>ASTEC treatment arm</th>
<th>ASTEC control arm</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>514 patients</td>
<td>1408 patients</td>
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<tr>
<td>Eligible patients</td>
<td>Clinical stage I, frozen section with myometrial invasion, Karnofsky score ≥80, no previous malignancy, chemotherapy, or radiation</td>
<td>2 countries, over 10 years</td>
<td>Clinical stage I or II</td>
<td></td>
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<tr>
<td>Treatment arm</td>
<td>Hysterectomy, BSO, washings, systematic pelvic lymphadenectomy</td>
<td>Hysterectomy, BSO, washings, iliac and obturator node dissection, aortic node palpation, suspicious aortic nodes removed at surgeon's discretion</td>
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<tr>
<td>Control arm</td>
<td>Hysterectomy, BSO, washings, removal of bulky nodes (&gt;1 cm)</td>
<td>Hysterectomy, BSO, washings, aortic node palpation, suspicious pelvic or aortic nodes removed at surgeon's discretion</td>
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<td>Aortic dissection required in treatment arm?</td>
<td>No</td>
<td>No</td>
<td></td>
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<tr>
<td>Median follow-up</td>
<td>49 months</td>
<td>37 months</td>
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<td>Median number of lymph nodes removed (range)</td>
<td>30 (IQR 22–42)</td>
<td>0 (IQR 0–0) Note: 16% and 11% of patients had &gt;6 and 10 nodes removed, respectively</td>
<td>12 (1–59) Note: 12% and 35% of patients had &lt;5 and &lt;10 nodes removed, respectively</td>
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<td>Postoperative therapy standardized?</td>
<td>No</td>
<td>Low-risk early stage and Advanced advanced stage: No; Intermediate high-risk early stage: secondary randomization to radiation vs. no radiation</td>
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<td>Brachytherapy allowed?</td>
<td>Yes</td>
<td>Yes</td>
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<td>Brachytherapy controlled for in analysis?</td>
<td>No</td>
<td>No</td>
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IQR: 25th–75th percentiles or interquartile range. * Stage T1 grade 1 excluded (1988 FIGO staging).

As described above, both studies create more questions than they can potentially answer. These trials were not powered to solve the most important clinical question: Do intermediate/high-risk patients benefit from lymphadenectomy? Is lymphadenectomy therapeutic? Without a prespecified criteria for the application and standardization of adjuvant treatment in all arms, no conclusions can be made regarding independent effects of lymphadenectomy. In the United States, is it possible to ethically design a trial in which adjuvant therapy is withheld from node-positive patients?

Currently, preoperative and intraoperative prediction of who will and will not benefit from a lymphadenectomy is inaccurate and unreliable. Preoperative grade is not indicative of postoperative grade with 15–25% of preoperative grade 1 endometrial cancers upgraded on final pathology [11–13]. In fact, surgical staging for grade 1 patients will impact adjuvant therapy decisions in approximately 30% of patients [11] and is the most cost-effective treatment strategy [14]. At many institutions, frozen section has poor negative-predictive value. On final pathology, 46% with uterine confined tumor on frozen section are upstaged and 38% have higher histologic grade than reported by frozen section [15]. In addition, isolated aortic metastasis occurs in up to 16% of patients with endometrial carcinoma [16]. Aortic dissection in the lymphadenectomy arms of both trials was left to surgeon discretion. In the Panici study, aortic dissection or sampling was performed in 26%, while this proportion remains undefined in the ASTEC trial. If we could precisely and accurately predict which patients will have node-negative, uterine confined disease (without surgery), these patients would not benefit from lymphadenectomy or radiation.

While the investigators are to be commended for attempting to answer important clinical questions, the fundamental trial designs introduce bias that call to question their conclusions. There is no perfect trial design to determine the therapeutic effectiveness of lymphadenectomy. Perhaps, one approach would be to enroll patients...
with preoperative endometrioid histology to an intraoperative assessment for intermediate high-risk features, randomize only these patients to aortic and pelvic lymphadenectomy or no lymphadenectomy. Following surgery, adjuvant therapy would be standardized, regardless of lymph node status. This approach would allow one to determine the true independent “therapeutic” effects of lymphadenectomy. Given the low node-positivity rate in the ASTEC trial, a large number of patients would be required for adequate power. In addition, most US physicians would not randomize patients to a study that withholds adjuvant therapy from node-positive patients.

Are we forsaking progress by focusing efforts on whether or not a lymph node dissection is “therapeutic” when lymphadenectomy clearly has prognostic significance? The role of lymphadenectomy is to accurately triage adjuvant therapy—sparing radiation in cases of limited benefit and providing opportunities for adjuvant therapy in more advanced disease. Both trials deemphasize the prognostic benefit of lymphadenectomy and its role in tailoring therapy, which is not without merit [17–21]. We are challenged not only to educate our colleagues and patients regarding the prognostic benefits of lymphadenectomy, but we are also confronted with placing these trials in perspective. The underlying principles are unchanged—regardless of “therapeutic” value, lymphadenectomy remains the cornerstone to accurate staging and the foundation for tailoring adjuvant therapy.

Conflict of interest statement
The authors declare that there are no conflicts of interest.

References

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