Surgical staging for locally-advanced cervical cancer: the answer remains ‘NO’

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No rational argument will have a rational effect, on a man who does not want to adopt, a rational attitude
Karl Popper

The para-aortic nodal region is considered to be a site associated with advanced stage and worse oncologic outcomes in patients with cervical cancer. A legendary point of discussion is whether resection of para-aortic lymph nodes serves a therapeutic or a diagnostic role. Those who propose there is a therapeutic role provide no basis for rationale as to the impact of removing pathologically negative lymph nodes, or whether removing pathologically positive lymph nodes incurs an advantage over standard chemotherapy and radiation with extended field. Similarly, the claim that routine resection of the para-aortic lymph nodes to the renal vessels should be performed, fails to substantiate an argument as to why one must stop at the level of the inferior mesenteric artery or the renal vessels for that matter. Is there a ‘nodal gate’ that prevents further metastases to lymphatic basins above these sites?

In cervical cancer, 3 year overall survival with para-aortic nodal involvement—now classified according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 as IIIC2—is approximately 34–39%, if treated with extended field radiotherapy plus chemotherapy.1 The most advanced diagnostic tool we have to date, in the pre-treatment evaluation of patients with locally advanced cervical cancer, is positron emission tomography/computed tomography (PET/CT), with a sensitivity and specificity of 75% and 92%, respectively, to detect metabolically active disease in the para-aortic region.2 That is the reason why some propose it is logical to ‘surgically stage’ this anatomical region, in order to detect the true positive cases and thus offer extended field radiation therapy. The question at large remains: does surgical staging of para-aortic nodes in locally advanced cervical cancer really make a difference in outcomes when compared with radiologic staging?

This month’s lead article by Naslioudis et al.,3 on a population-based analysis using the National Cancer Database, evaluates utilization rate and impact on survival of surgical para-aortic lymph node staging compared with imaging, in patients with locally advanced-stage cervical carcinoma managed with definitive chemoradiation. It includes 3540 patients with locally advanced cervical carcinoma with squamous, adenocarcinoma or adenosquamous histology, FIGO 2009 stages IB2 to IVA, of whom 333 (9.4%) underwent para-aortic lymphadenectomy. There was a decrease in use from 15.7% in 2010 to 8.9% in 2015. The rate of para-aortic lymphadenectomy was 11.3% for patients diagnosed between 2010–2012 compared with 7.9% for those diagnosed between 2013–2015 (p<0.001). As expected, patients undergoing surgical staging had more positive lymph nodes compared with those who had imaging only (27.31% vs 13.2%, p<0.001) and had longer time to initiation of radiation (median 55 vs 38 days, p<0.001). After a median follow-up time of 40.25 and 41.1 months in the radiologic and surgical para-aortic staging groups, respectively, there was no difference in overall survival between the groups. After controlling for age, race, insurance status, tumor stage, histology, comorbidities, history of other tumor, and receipt of vaginal brachytherapy, surgical staging was not associated with a survival benefit. Also, no differences were found after excluding patients who did not receive brachytherapy, or had at least 10 nodes removed. Patients with pathologically proven para-aortic nodal involvement had worse survival than those without it, after controlling for comorbidities, stage, patient age, and receipt of brachytherapy.

The first attempt to address the oncological outcome associated with surgical staging, compared with radiological assessment of the para-aortic region, was conducted by Lai et al.,4 in a two-step randomized trial; the authors aimed to compare clinical staging (arm A) versus surgical staging (arm B), and to compare the laparoscopic with the extra-peritoneal approach in previously untreated women diagnosed with locally advanced cervical cancer. After a planned interim analysis, when the authors recruited 61 patients (arm A, 29; arm B, 32), no differences were found regarding peri-operative outcomes or early and late toxicity. Para-aortic metastatic nodes were documented in 25% of patients in arm B and these had significantly worse progression-free survival than those in arm A. The patient accrual was terminated according to the early stopping rules.
Authors concluded that there was a detrimental effect in surgical staging arms and that the benefit of pretreatment surgical staging for cervical carcinoma remained unproven.

The only prospective randomized completed trial evaluating minimally invasive transperitoneal lymphadenectomy versus imaging staging (CT) in patients with locally advanced cervical cancer was UTERUS-11. This was, in fact, a negative trial as the authors did not find any difference in progression-free or overall survival after a median follow-up of more than 8 years. In that study, the authors report on an unplanned post-hoc analysis that demonstrated a higher disease-specific survival, and a potential benefit of surgical staging in patients with stage IIB disease. Such post-hoc analyses are often associated with notable shortcomings as outlined in an article by Christogiannis et al, titled ‘The self-fulfilling prophecy of post-hoc power calculations’. In it, the authors explain the futility of making considerations on these kind of results and the negligible scientific value that such considerations have. Nevertheless, it should be recognized for its contribution in that it solidified the lack of benefit of surgical staging in locally advanced cervical cancer.

The authors should be commended for conducting this review that will add valuable information on the futility of performing surgical staging in locally advanced cervical cancer patients. The authors should also be applauded for highlighting the limitations of the study, including the absence of a central pathology review or information on the size of metastasis in the resected nodes, lack of information on chemotherapy agents or compliance with treatment, missing information on sites and patterns of relapse or data on the type of imaging performed, lack of information on radiotherapy fields extension, or on route of lymphadenectomy, data on quality of life and complications, or information on biopsies in radiologically staged patients, and level of training of participating surgeons.

We must move forward in our current standards of practice by implementing approaches that are supported by science and valid data, rather than by presumptions based on anecdotal or poorly designed studies. In this month’s lead article, we have further evidence to support the proposal that routine para-aortic surgical staging provides minimal value to the patient’s prognosis, while potentially exposing the patient to risks associated with the procedure.

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