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Surgical staging, the meaning of life, and other existential ponderings

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Countless academics have contemplated life's many unanswered questions. What existed before the universe? Will we ever discover life on other planets? Does free will truly exist? Why does a round pizza come in a square box? For years gynecologic and radiation oncologists have pondered the question of surgical staging for women with locally advanced cervical cancer (stages IB3–IVA). Does pathologic assessment of para-aortic lymph nodes improve survival by extending the radiation field in patients with microscopically positive para-aortic nodes while decreasing morbidity by limiting the radiation field in those patients who are negative for metastases?

The rationale for surgical staging stems from the inadequacies of current radiologic modalities to detect metastatic disease. MRI has a sensitivity of only 38% in detecting lymph node metastases while CT scan performs somewhat better, finding metastatic disease in lymph nodes 67% of the time.¹ More recently, fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been commonly used in the initial work-up of patients with newly diagnosed cervical cancer as PET scans have a sensitivity of 84% in identifying metastatic disease in para-aortic lymph nodes.^{2,3} In other words, even with our best imaging modality, PET scan, 16% of women with locally advanced cervical cancer will have undetected disease in para-aortic nodes, probably leading to under-treatment, with radiation fields limited to the pelvis. One would assume that surely this equates with increased recurrence and decreased survival for these patients.

Retrospective studies on this topic, however, have been anything but conclusive. Early studies showed surgical staging detects more disease in nodes than imaging and but failed to show that finding this microscopic disease changed survival.^{4,5} However, more recently larger retrospective studies have shown a survival benefit from surgical staging compared with clinical and radiologic staging. Gold et al⁶ evaluated 685 patients who had participated in three Gynecologic Oncology Group (GOG) chemoradiation studies. In two of those studies, surgical staging was mandatory and in the third it was optional. In comparison with patients who had only radiologic staging (n=130), women who underwent surgical staging (n=555) had significantly better 4-year progression-free survival

(36% vs 49%) and overall survival (40% vs 54%). With data like these in mind, many have been optimistic that a well-designed, prospective clinical trial would finally show that surgical staging improves outcomes for women with locally advanced cervical cancer.

In this issue of the *International Journal of Gynecological Cancer*, we are honored to publish the much-anticipated results of Uterus-11.⁷ The investigators must first be commended on completing a prospective, randomized clinical trial of surgical staging in patients with locally advanced cervical cancer when other attempts were closed well before accrual was completed.^{8,9} Although the trial did not show a difference between the two arms in progression free or overall survival (we will get to that below), they did prove other important outcomes. First, they demonstrate a trial for surgical staging in patients with locally advanced cervical cancer is feasible and can be completed in a reasonable period of time. Second, they prove that pre-therapeutic surgical staging does not significantly delay initiation of definitive chemoradiation. Third, in line with previously published reports, the study confirms a high rate of upstaging of disease, with 33% of patients who undergo surgical staging having microscopic metastatic disease in lymph nodes detected that otherwise would not have been found on a pre-therapeutic CT scan. Finally, they show that laparoscopic staging using a transperitoneal approach does not significantly increase radiation toxicity. This is an important outcome as many have argued against surgical staging because of concerns about increasing long-term morbidity of radiation when administered after surgical exploration.

Although all of these outcomes are favorable for surgical staging, the most important endpoints of improving progression free and overall survival were not met. There was no difference between the two arms in progression free survival, the primary endpoint, and although the hazard ratio for recurrence was 0.71 favoring surgical staging and although this did not meet significance, the p value of 0.08 certainly showed a trend towards supporting surgery. The secondary endpoint of overall survival was also not statistically different between the two groups, but again the hazard ratio for death of 0.69 (p=0.07) showed a trend towards favoring surgery in

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these patients. The authors performed post hoc analyses and were able to show that surgery improves cancer-specific survival as well as improving survival for patients with stage IIB disease. Although these are interesting, hypothesis-generating outcomes, there is no hiding the fact that this is a negative study.

So, have we finally answered the age-old question of surgical staging for locally advanced cervical cancer? I'm not so sure. The fatal flaw of this study, I believe, is in the sample size calculation (admittedly it is easy to criticize in hindsight decisions made many years ago). The authors estimated a 5-year-disease free survival of 36.5% for the control arm of clinical staging. In the era of chemoradiation, a more reasonable recurrence rate in patients with locally advanced cervical cancer (stages IB3–IVA) staged clinically/radiologically is probably closer to 50–60%.¹⁰ In fact, in this study (Uterus-11) the recurrence rate in the group that was clinically staged was 55%. The experimental arm (surgery), on the other hand, was estimated to improve 5-year disease-free survival by 50%. This is an ambitious estimate when surgical staging has traditionally found only an additional 33% of patients with unrecognized disease in para-aortic nodes compared with a CT scan.¹ With more accurate estimates of disease-free survival in clinically staged patients and more modest predictions of how much surgical staging would improve survival, sample sizes would be much larger and the trends towards progression-free and overall survival seen in this study would probably become statistically significant. If that were the case, we might be celebrating a positive, practice-changing study. This study demonstrates the importance of making realistic assumptions when calculating the sample size as opposed to choosing the sample size and then 'massaging' the data to arrive at the sample size one wants to obtain.

So, where do we go from here? I do not believe we should abandon the concept of pre-therapeutic surgical staging for patients with locally advanced cervical cancer. As this study shows, transperitoneal surgical staging for these patients is safe and does not delay the start of definitive chemoradiation nor does it increase radiation morbidity. Second, a study with adequate sample size is likely to show an improvement in survival for surgically staged patients. I would strongly encourage any collaborative group or groups that have the funding, the will, and the patient volume to consider an adequately powered study

comparing surgical staging with PET staging in patients with locally advanced cervical cancer.

And now onto other important questions like, do penguins have knees?

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