Editorial

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Optimal therapy for IB2 and IIA2 cervical cancer: surgery or chemoradiotherapy?

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See accompanying article on page 226.

In this edition, Park et al. [1] provide a detailed, well organized, retrospective review of 215 patients with stage IB2 and stage IIA cancers >4 cm on MRI with either radical hysterectomy and tailored radiation or chemoradiotherapy (CRT). The authors have attempted to minimize selection bias and perform excellent methodology using univariate and multivariate analyses. Importantly, a low local failure rate was achieved in the surgical arm as well as the CRT arm 4.8% and 4.4%, respectively. Also, it is commendable that in this study, preoperative MRI was used in all patients. Interestingly parametrial extension was identified by MRI in 33% of patients in a population that clinically was found not to have parametrial extension. Park et al. documented that on multivariate analysis, patients who underwent CRT compared with upfront surgery had a higher rate of progression, hazard ratio 2.26; 95% confidence interval [CI], 1.24 to 4.14 and a lower rate of overall survival with a hazard rate of 3.02; 95% CI, 1.53 to 5.98, p=0.001. Given these interesting findings, the Korean Gynecologic Oncology Group is interested in embarking upon a phase III trial to compare radical hysterectomy and adjuvant radiotherapy or CRT versus upfront CRT.

In this review, 80% of patients in the radical hysterectomy arm required radiotherapy or CRT. This is nearly identical to the Landoni trial where 84% of patients with tumors >4 cm required adjuvant radiotherapy [2]. In the Landoni trial, morbidity was increased in patients who underwent surgery and radiotherapy compared to patients who underwent radiotherapy alone. An important conclusion from the Landoni trial is that toxicity is increased with multiple different therapies (i.e., surgery and radiotherapy). Of 343 randomized patients in the Landoni trial 48 (28%) surgery patients had severe morbidity compared with 19 (12%) of radiotherapy patients. It is important to remember as well in the Landoni trial, the patients did not receive concomitant chemotherapy with radiotherapy and their survival was equivalent to radical hysterectomy. Could survival be superior with CRT compared to radical hysterectomy? Since the Landoni trial was published in 1997 there have been significant changes in standard radiotherapy practice. First, cisplatin-based concomitant chemotherapy is standard, and secondly, imaging has improved [3]. Cross sectional imaging is widely available (CT and MR), and PET scanning has been found to be highly valuable in the prognosis and treatment planning of patients with cervix cancer [4]. Both advances in use of chemotherapy and imaging were incorporated in this review by Park et al., and hence, the question of optimal treatment remains.

Importantly, Park et al. also observe a low incidence of lymphedema in the CRT group of 1.5%. However, this was increased to 12.5% in the radical hysterectomy group and 9.1% in the radical hysterectomy and radiotherapy group. These data are supported by the breast cancer experience where upper extremity lymphedema is most often not caused by radiotherapy. Rather, radiotherapy serves to exacerbate the surgical insult after axillary dissection. Ideally, in a randomized trial, it would be important to include patient reported outcomes as well. This clearly eliminates bias as observed by physicians. In the experience by Park et al. acute complications were markedly higher in the CRT group.

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Why did CRT patients do worse in the review by Park et al. The lymph node failure rate was increased in the CRT arm to 14.7% versus 8.2% in the hysterectomy arm. This did not achieve statistical significance; however, it may account for the worse outcome in the CRT group. The methods do not state whether patients with radiographically identified lymph nodes received a boost to those nodes. Within the United States, it is not customary to deliver a dose of 41 to 50 Gy for radiographically identified positive lymph nodes in cervix cancer. A more standard boost dose for positive lymph nodes whether detected by CT, MRI, or PET is approximately 60 Gy depending on volumetric concerns of normal tissue. Additionally, the technique of radiotherapy may be important. Three-dimensional conformal radiotherapy should use at a minimum a 4-field beam arrangement in most cases. Additionally, the Radiation Therapy Oncology Group has performed a phase II trial of intensity-modulated radiation therapy (IMRT) after hysterectomy and observed 28% of patients had grade 2 or greater short term gastrointestinal side effects which was felt to be better than historical controls treated without IMRT.

The conduct of a phase III trial is expensive, and as such, each arm should be optimized. Quality assurance should be performed for the surgery and the CRT arms. For optimal CRT it will be important to achieve the appropriate dose, utilize brachytherapy, perform treatment timely, be compliant with chemotherapy, and omit unnecessary postoperative hysterectomies [5]. Treatment prolongation has been known to increase local failure at a rate of 0.7% to 1% per day for every treatment missed after approximately 8 weeks of therapy [6]. Additionally, the quality of brachytherapy is important as demonstrated by retrospective and prospective studies [7,8]. More recently, image guided brachytherapy in the prospective STIC trial demonstrated a 1.9 fold decrease in grade 3 and 4 urinary and gastrointestinal toxicity compared with two-dimensional imaging while achieving a statistically significant improvement in local control [9].

It would be of interest to determine the optimal therapy for adenocarcinoma histology in a randomized trial. In this report by Park et al. patients with adenocarcinoma histology had inferior progression-free survival and overall survival; however, this represented only 16% of patients and outcome was not presented by treatment arm for this subset. In the Landoni trial the surgery patients with adenocarcinoma histology had a better outcome with an overall survival and disease-free survival rate of 70% and 66%, respectively compared with 59% and 47% for the radiotherapy arm, respectively. I believe this is an intriguing question in gynecologic oncology.

Park et al. has provided a careful and detailed report comparing radical hysterectomy with tailored radiotherapy or CRT versus CRT alone. Importantly, in this experience, 20% of patients were able to not undergo radiotherapy, and these patients had a particularly good outcome. It will be of significant interest to compare CRT versus upfront surgery with tailored radiotherapy in the modern era. For the purpose of equipoise, optimal surgery should be compared with optimal CRT. Rigorous toxicity assessment and quality assurance will be essential. I congratulate Park et al. on their important contribution that poses interesting questions and shines light on the future.

CONFLICT OF INTEREST

No potential conflict of interests relevant to this article was reported.

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