Adjuvant treatment in early stage cervical cancer—does more equal better?

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COMMENTARY

Cervical cancer is the most common gynecologic malignancy worldwide.[1] The recommendation of adjuvant treatment following radical hysterectomy in early stage cervical cancer is usually tailored according to International Federation of Gynecology andObstetrics (FIGO) stage and risk factors.[1] The Gynecologic Oncology Group (GOG)-92 trial demonstrated that adjuvant whole pelvic radiotherapy improved recurrence-free survival with a trend towards overall survival benefit, compared with observation, in patients with stage IB cervical cancer and different levels of risk factors.[2 3] Additionally, the GOG-109 study assessed the role of chemo-radiation with cisplatin and 5-fluorouracil (two cycles concurrent with radiation and two cycles after completion of radiation) versus radiotherapy alone, including patients with stage IA2, IB, and IIA and high-risk features, and was associated with improved disease-free survival and overall survival.[4] It is unclear to what extent the benefit could be attributed to post-radiation chemotherapy. The standard management of early-stage cervical cancer and high-risk features following radical hysterectomy remains adjuvant concurrent chemo-radiation with weekly cisplatin.

There was an important presentation at the American Society of Clinical Oncology (ASCO) 2020 of a large randomized, open-label, phase III trial, the STARS (Comparison of Different Subsequent Treatments After Radical Surgery: NCT00806117) study. The trial recruited across eight centers in China between 2008 and 2015 and included patients with FIGO stage IB1-IIA2 squamous cell, adenosquamous carcinoma, and adenocarcinoma of the cervix, and at least one risk factor following radical hysterectomy including lymph node metastasis, positive parametrium or margin, lymphovascular space involvement, or deep stromal invasion.[5] One thousand and forty-eight women were randomized to adjuvant radiation (radiation arm), concurrent chemo-radiation with weekly cisplatin (concurrent arm), or sequential treatment with 3 weekly cisplatin and paclitaxel, administered two cycles before and two after radiotherapy (sequential arm). The majority of enrolled patients had squamous cell histology (>85%) and tumor size was ≤4 cm in approximately 75% of women. Lymph node metastases were more common in the chemotherapy arms (approximately 30%) versus the radiation arm (18%). Other risk factors were well-balanced between the three groups. Disease-free survival at 3 years was higher in the sequential arm compared with radiation alone (hazard ratio (HR) 0.52, 95% CI 0.35 to 0.76) and the concurrent arm (HR 0.65, 95% CI 0.44 to 0.96). Interestingly, 5 year overall survival was also higher in the sequential arm compared with radiation alone (HR 0.58, 95% CI 0.35 to 0.95), with no differences between the sequential and concurrent arms (HR 0.74, 95% CI 0.45 to 1.23). In terms of quality of life, no significant differences between the groups were seen long-term.

Treatment discontinuation rates were high in the chemotherapy arms,[5] with 62% completion in the concurrent arm and 73% in the sequential arm. These results are relatively similar to those reported in other cervical cancer trials, and highlight the importance of improving toxicity management in clinical practice and future studies.[4 6] Real-time assessment of patient-reported outcomes may be helpful towards improving treatment safety while maintaining adequate dose intensity.

The results of the STARS trial are encouraging, but some important questions remain unanswered. It is important to explore the impact of pharmacogenomics on therapy—is treatment impact limited by adverse effects, and are these influenced by patient characteristics, including ethnicity? Is the improvement in outcome in the sequential arm attributable to the addition of taxane, timing of chemotherapy and radiation, or differences in dose intensity? Another potential confounding factor is that patients who received neoadjuvant treatment were included, and their impact on treatment discontinuation, toxicity, and efficacy are yet to be presented. Prior to incorporation into standard of care, final STARS publication and results of other studies assessing the role of chemotherapy following chemo-radiation—including RTOG-0724 (NCT00980954) in high-risk early stage cervical cancer treated with radical hysterectomy—are awaited.

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