



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

Ainhoa Madariaga ¹, Lawrence Kasherman, ¹ Kathy Han, ² Stephanie Lheureux, ¹ Amit M Oza ¹

¹Medical Oncology & Hematology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada

²Radiation Oncology, Princess Margaret Cancer Centre, Toronto, Ontario, Canada

Correspondence to

Dr Ainhoa Madariaga, Medical Oncology & Hematology, Princess Margaret Hospital Cancer Centre, Toronto, Canada; ainhoa.madariaga@uhn.ca

Received 7 July 2020

Accepted 8 July 2020

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 and Obstetrics (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.

Twitter Ainhoa Madariaga @AinhoaMada

Contributors All authors contributed in writing and reviewing the manuscript.



© IGCS and ESGO 2020. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Madariaga A, Kasherman L, Han K, *et al.* *Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2020-001840

Commentary

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests SL is principal investigator of cervical cancer studies of Regeneron and Merck. She reports grants and personal fees from Astra-Zeneca and GSK, and personal fees from Merck and Roche, outside the submitted work.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

ORCID iD

Ainhua Madariaga <http://orcid.org/0000-0001-7166-9762>

REFERENCES

- 1 Cohen PA, Jhingran A, Oaknin A, *et al.* Cervical cancer. *Lancet* 2019;393:169–82.
- 2 Sedlis A, Bundy BN, Rotman MZ, *et al.* A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage Ib carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. *Gynecol Oncol* 1999;73:177–83.
- 3 Rotman M, Sedlis A, Piedmonte MR, *et al.* A phase III randomized trial of postoperative pelvic irradiation in stage Ib cervical carcinoma with poor prognostic features: follow-up of a Gynecologic Oncology Group study. *Int J Radiat Oncol Biol Phys* 2006;65:169–76.
- 4 Peters WA, Liu PY, Barrett RJ, *et al.* Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000;18:1606–13.
- 5 Huang H, Feng Y, Wan T, *et al.* Sequential chemoradiation versus radiation alone or concurrent chemoradiation in adjuvant treatment after radical hysterectomy for stage IB1-IIA2 cervical cancer (STARS study): a randomized, controlled, open-label, phase III trial. *J Clin Oncol* 2020;38:6007.
- 6 Shrivastava S, Mahantshetty U, Engineer R, *et al.* Cisplatin chemoradiotherapy vs radiotherapy in FIGO stage IIIB squamous cell carcinoma of the uterine cervix: a randomized clinical trial. *JAMA Oncol* 2018;4:506–13.