



Review article

Advancing clinical research globally: Cervical cancer research network from Mexico



Bryan J. Ager^{a,*,1}, Dolores Gallardo-Rincón^{b,1}, David Cantú de León^c, Adriana Chávez-Blanco^d, Linus Chuang^e, Alfonso Dueñas-González^f, Eva Gómez-García^g, Roberto Jerez^h, Anuja Jhingranⁱ, Mary McCormack^j, Linda Mileshkin^k, Carlos Pérez-Plasencia^l, Marie Plante^m, Andrés Povedaⁿ, David K. Gaffney^a

^a Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

^b Ovarian and Endometrium Program, Instituto Nacional de Cancerología, México City, Mexico

^c Sub-Direction of Clinical Research, Instituto Nacional de Cancerología, México City, Mexico

^d Grupo de Investigación en Cáncer de Ovario y Tumores Ginecológicos de México (GICOM), México City, Mexico

^e Department of Obstetrics, Gynecology, and Reproductive Science, Mount Sinai, New York City, NY, USA,

^f Biomedical Research Unit in Cancer, Instituto de Investigaciones Biomédicas UNAM/Instituto Nacional de Cancerología, Mexico City, Mexico

^g Centro Oncológico Estatal ISSEMyM, Toluca de Lerdo, Mexico

^h Centro Oncológico Hondureño, Honduras

ⁱ The University of Texas MD Anderson Cancer Center, Houston, TX, USA

^j University College London Hospitals, London, United Kingdom

^k Division of Hematology and Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

^l Genomics Laboratory, Instituto Nacional de Cancerología, México City, Mexico

^m Department of Gynecologic Oncology, Hotel-Dieu de Quebec, Quebec, Canada

ⁿ Department of Gynecologic Oncology, Instituto Valenciano de Oncología, Valencia, Spain

ARTICLE INFO

Keywords:

Cervix cancer

Cervical cancer

Radiotherapy

CCRN

Hypofractionation

ABSTRACT

Cervical cancer is the fourth most common cancer in women with 85% of the mortality burden occurring in less-developed regions of the world. The Cervix Cancer Research Network (CCRN) was founded by the Gynecologic Cancer InterGroup (GCIG) with a mission to improve outcomes in cervix cancer by increasing access to high-quality clinical trials worldwide, with particular attention to less-developed, underrepresented sites. The CCRN held its second international educational symposium in Mexico City with ninety participants from fifteen Latin America countries in January 2017. The purpose of this symposium was to advance knowledge in cervix cancer therapy, promote recruitment to CCRN clinical trials, and to identify relevant future CCRN clinical trial concepts that could improve global care standards for women with cervical cancer.

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide with > 85% of cervical cancer deaths occurring in less-developed regions of the world, corresponding to an 18-fold disparity in mortality rates (International Agency for Research on Cancer WHO, 2018). The Gynecologic Cancer InterGroup (GCIG) is a non-profit collaborative network of international and national research groups aiming to promote and facilitate high-quality clinical trials in order to improve outcomes for women with cervical cancer and other gynecologic malignancies. The Cervix Cancer Research Network (CCRN) was

founded by the GCIG to facilitate the mission to improve global cervical cancer outcomes by increasing access to high-quality cervix cancer clinical trials within regions around the world not currently represented by a GCIG member cooperative group (Gaffney et al., 2015). The inaugural international CCRN symposium held in Thailand in January 2016 encouraged recruitment to clinical trials in Southeast Asia, a region encompassing nearly half of the cervical cancer incidence and mortality in the less-developed world (Gaffney et al., 2016). In January 2017, the CCRN held its second annual symposium in Mexico City with 90 participants representing 15 countries across Latin America. The third annual CCRN symposium was held in Bucharest in January 2018,

* Corresponding author at: Department of Radiation Oncology, Huntsman Cancer Hospital, University of Utah, 1950 Circle of Hope, Room 1570, Salt Lake City, UT, 84112, USA.
E-mail address: bryan.ager@hci.utah.edu (B.J. Ager).

¹ Co-primary authors.

with attention to advancing cervix cancer care in Eastern Europe. The focus of these CCRN education symposiums is to provide a global perspective of treatment modalities, controversies, and trending subjects in the management of cervical cancer. The following report summarizes the proceedings of the 2017 annual symposium in Mexico City and highlights the ongoing work of the CCRN as it relates to Latin America in enhancing standards of care, improving clinical outcomes, and fostering access to clinical trials.

Approximately 15% of deaths from cervical cancer in the less-developed world occur in Latin America, corresponding to a mortality rate of about 28,000 per year ([International Agency for Research on Cancer WHO, 2018](#)). The necessary infrastructure, expertise, and funding required to deliver modern cervical cancer treatments remain significant barriers to executing clinical trials in Latin America. In Mexico, where only 15% of cervical cancers are detected at an early stage, a human papillomavirus (HPV) vaccination campaign was instituted in 2008 for girls 9–16 years old. Despite these efforts, the overall disease burden, treatment outcomes, and the numbers of women seeking care are still lagging when compared to more developed countries.

In addition to being potentially preventable with HPV vaccination and screening, cervical cancer has also become increasingly curable with contemporary chemoradiotherapy due to high rates of radiosensitivity and improved survival with concurrent cisplatin chemotherapy ([Chemoradiotherapy for Cervical Cancer Meta-Analysis C, 2008](#)). However, cervical cancer remains a leading cause of cancer death among women in countries with a low Human Development Index – a measure of socioeconomic development accounting for levels of education, life expectancy, and income ([Atun et al., 2015](#)). On average, only one radiotherapy machine is available for every 2 million people in Mexico, ranking among the lowest densities of radiotherapy access in Latin America ([Pinillos et al., 2017](#)). A Quality Assurance Team for Radiation Oncology (QUATRO) audit of 12 Latin American radiotherapy centers from 2008 to 2013 found local training programs and research activity to be scarce, in addition to discovering that 25% of centers lacked gynecologic brachytherapy and did not meet minimum infrastructure requirements ([Rosenblatt et al., 2015](#)).

In a survey of 47 Latin American participants at the 2017 CCRN symposium, 38% reported insufficient numbers of radiation machines as the most common barrier to the treatment of cervical cancer with curative intent. Radiating Hope, a nonprofit volunteer-run organization seeking to improve global access to modern radiotherapy technologies, is working to increase Latin American access to radiotherapy through established avenues in Guatemala, Honduras, Panama, Peru, and Chile. Despite these efforts, many additional barriers to treatment were cited, including presentation with disease too advanced (77%), long wait times (40%), and social issues (33%), emphasizing the complex challenges faced by Latin American providers. Approximately two-thirds of participants in the survey had never enrolled a cervical cancer patient on a clinical trial. The most commonly cited barriers were the lack of available open trials (66%), limited funding (58%), limited research support staff (39%), and lack of infrastructure (34%). Survey

responders represented a balanced, multidisciplinary group from across Latin America composed of gynecologist oncologists (38%), medical oncologists (19%), radiation oncologists (34%), and support staff (9%). To address these multifactorial challenges faced by Latin American healthcare providers, the CCRN is committed to expanding access to externally-funded high-quality clinical trials in Latin America. By supporting access to ongoing and future CCRN clinical trials through the development of new CCRN accredited sites in low- and middle-income countries, the CCRN aims to advance knowledge in cervical cancer therapy and to improve care standards throughout the world.

2. CCRN clinical trials

As of 2017, 29 cooperative research groups comprised the membership of the GCIG, including 8 in North America, 15 in Europe, 5 in Asia, and 1 in Australia/New Zealand. Currently, there are no GCIG member groups solely based in South America, because GCIG membership is based on a pre-existing established national or multi-national cooperative group eligible to join the GCIG. At the CCRN symposium in Mexico City, there was significant interest from different centers in working to establish national research groups with a view to joining GCIG. Participation in CCRN was seen as an attractive initial step towards this goal. Sites without GCIG representation that are interested in obtaining CCRN accreditation must comply with some basic radiation and research requirements, including completion of a radiologic/physics prequalifying questionnaire (courtesy of IROC, Houston, TX) and participation in a radiotherapy beam measurement program with thermoluminescence dosimeters or optically stimulated luminescence dosimeters every two years. Site reviews are then undertaken by a GCIG team to ensure treatment and research facilities have the necessary framework in place to ensure compliance with standards as dictated by the International Council for Harmonisation of Technical Requirements for Human Use Good Clinical Practice (ICH GCP). Continued quality assurance is performed according to individual clinical trial specifications.

Several publically funded, low-cost GCIG clinical trials are currently active at CCRN accredited sites ([Table 1](#)). The CCRN trial with the highest number of CCRN accruals to date is the Tri-weekly Administration of Cisplatin in Locally Advanced Cervical Cancer (TACO) Trial, developed by investigators from the Korean Gynecologic Oncology Group (KGOG) and Thai Cooperative Group. Based upon promising phase II data showing improved survival with cisplatin dosing every three weeks, eligible locally advanced cervical cancer patients receiving concurrent chemoradiation in this phase III study are randomized between 6 cycles of standard 40 mg/m² weekly cisplatin versus 3 cycles of 75 mg/m² cisplatin every 3 weeks ([Ryu et al., 2011](#)). If confirmed to improve overall survival, the administration of cisplatin every 3 weeks could result in significant cost savings for health systems, thereby improving outcomes while also increasing accessibility for patients. This trial remains open to accrual and has accrued patients from Asia.

To address high rates of distant failure in advanced cervical cancer

Table 1
Currently active CCRN clinical trials as of January 1, 2018.

Trial name	Phase	Study question	Status	Countries participating
TACO	III	Tri-weekly versus weekly cisplatin concurrent with radiotherapy	Open	South Korea, Thailand, Vietnam, China
INTERLACE	III	Weekly induction carboplatin paclitaxel chemotherapy followed by standard chemoradiation versus standard chemoradiation	Open	United Kingdom, Mexico, Italy
OUTBACK	III	Standard chemoradiation with or without adjuvant carboplatin paclitaxel chemotherapy	Closed, met accrual June 2017	Australia, Canada, China, New Zealand, Saudi Arabia, Singapore, United States
SHAPE	III	Simple versus radical hysterectomy with pelvic node dissection in low-risk early stage cervical cancer	Open	Canada, France, United Kingdom, Belgium, Netherlands, Austria, South Korea, Ireland, China, Russia, Germany
Hypofractionation trial	II	Standard chemoradiation 50 Gy in 25 fractions versus hypofractionated chemoradiation 40 Gy in 16 fractions, followed by surgery	Open	Mexico, Honduras

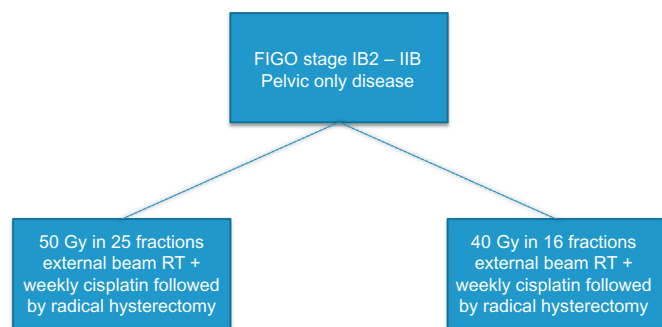


Fig. 1. Phase II Clinical Trial of Preoperative Hypofractionated Chemoradiation. Flow diagram of a phase II clinical trial of hypofractionated radiotherapy with concurrent weekly cisplatin followed by radical hysterectomy. Brachytherapy is omitted. This trial has been activated in Mexico and Honduras.

patients, two CCRN trials are focusing on potential benefits from neoadjuvant and adjuvant chemotherapy, respectively. The Induction Chemotherapy Plus Chemoradiation as First-Line Treatment for Locally Advanced Cervical Cancer (INTERLACE) Trial is a phase III randomized trial directed by the National Cancer Research Institute (NCRI) in the United Kingdom seeking to improve outcomes with neoadjuvant weekly carboplatin and paclitaxel followed by standard concurrent chemoradiation. This trial continues to accrue across the United Kingdom, Mexico, and Italy with 20% of patients enrolled from Mexico as of January 2018. The OUTBACK Trial (Cisplatin and Radiation Therapy With or Without Carboplatin and Paclitaxel in Patients with Locally Advanced Cervical Cancer), led by investigators from the Australia/New Zealand Gynecologic Oncology Group (ANZGOG), is a randomized phase III trial evaluating adjuvant chemotherapy with carboplatin and paclitaxel after standard definitive concurrent cisplatin-based chemoradiation for locally advanced cervical cancer. As of June 2017, this trial met its accrual goal with patients enrolled across North America, Asia, and Australia/New Zealand.

The Simple versus Radical Hysterectomy and Pelvic Node Dissection in Patients with Low-Risk Early Stage Cervical Cancer (SHAPE) Trial, led by the Canadian Cancer Trials Group (CCTG, formerly known as NCIC CTG), addresses potentially avoidable morbidities from parametrectomy in standard radical hysterectomy by randomizing patients with stage IA2 – IB1 < 2 cm cervical cancer between radical and simple hysterectomy. This trial is currently accruing with patients enrolled from North America, Europe, Russia, and Asia, and hopes to add patients from new CCRN sites in Brazil in 2018.

These publicly funded CCRN trials not only seek to answer fundamental questions in cervical cancer but also represent opportunities for patients from Latin America and other less-developed regions to receive low-cost, modernized treatment approaches while stimulating a local culture of research and clinical trial support. The CCRN encourages underrepresented sites to seek CCRN accreditation in order to gain access to these high-quality clinical trials and to work towards reducing global disparities in care standards and outcomes for cervical cancer.

3. Clinical trial development in latin america and globally

Multiple concepts for new CCRN and industry-sponsored trials were discussed at the 2017 CCRN symposium. An industry-sponsored phase III randomized trial entitled Advaxis Immunotherapy 2 prevent CERVical recurrence (AIM2CERV) is evaluating adjuvant and maintenance therapy with a novel immunotherapy approach. Axalimogene (AXAL) is a live-attenuated *Listeria monocytogenes* vector system developed by Advaxis that secretes an antigen-adjuvant protein targeting HPV. Although not an officially-sponsored CCRN trial, this placebo-

controlled trial randomizes women with high-risk node-positive and advanced stage disease who achieve a complete response to standard chemoradiation to adjuvant AXAL versus placebo. The primary endpoint is disease-free survival. Preliminary data from the GOG/NRG 0265 phase I/II trial of AXAL in metastatic cervical cancer patients who progressed through prior therapy demonstrated a promising 12-month overall survival rate of 38.5% with an acceptable toxicity profile (Huh et al., 2016). In addition to requiring resources and education for safe and proper administration of this Biosafety Level 2 experimental drug, interested sites must also seek approval from an Institutional Review Board (IRB) and an Institutional Biosafety Committee (IBC) prior to accruing patients onto the study. Despite support and funding from industry sponsors, these requirements may prove challenging for underdeveloped communities. Nonetheless, the AIM2CERV study has been approved by the FDA and aims to enroll 450 patients from sites in the United States, Latin American, Europe, and the Asian-Pacific, with GOG Foundation/Partners being the lead academic GCIG group.

One of the more intriguing topics focused on hypofractionated radiotherapy. Hypofractionation is more convenient for patients, reduces radiotherapy resources, and is known to be effective in the palliative setting (Mishra et al., 2005; Campbell et al., 2000). Hypofractionation has become the standard in breast cancer care (Haviland et al., 2018). Hypofractionated radiotherapy schedules present a pragmatic, cost-effective alternative approach for cervical cancer patients receiving concurrent chemoradiation with curative intent. A phase II trial was proposed and has since been activated in sites in Mexico City and Honduras. This trial randomizes patients with pelvic only FIGO stage IB2 – IIB disease to 50 Gray (Gy) in 25 fractions versus 40 Gy in 16 fractions of neoadjuvant chemoradiation with weekly concurrent cisplatin followed by definitive radical hysterectomy (Fig. 1). Brachytherapy is omitted from the trial to ensure availability to underdeveloped regions without access to brachytherapy as part of their currently available standard therapy. All patients are treated on a linear accelerator with four-field radiotherapy plans. An external review of radiotherapy plans is performed by the principal investigators for quality assurance. The primary outcome is toxicity assessment by patient-reported outcomes, with secondary endpoints of relapse-free survival, overall survival, pathologic response, and surgical complications, such as inpatient length of stay and need for blood transfusions. A second phase II trial was outlined for regions with access to brachytherapy that would randomize locally advanced patients to definitive concurrent chemoradiation with 45 Gy in 25 fractions versus 37.5 Gy in 15 fractions with weekly cisplatin, followed by a brachytherapy regimen per institutional protocol. Endpoints would be similar, with the primary outcome focusing on patient-reported outcomes and secondary outcomes assessing relapse-free survival, overall survival, and chronic complications. If proven to be similarly effective to existing standard fractionation, hypofractionation is potentially attractive in Latin America and other less-developed regions as it increases availability of radiotherapy machines by decreasing the number of patients being treated, increases convenience by reducing radiotherapy treatment duration, and limits the amount of time patients spend away from home.

4. Formation of a latin american cooperative group

The 2017 CCRN symposium highlighted the challenges in conducting clinical trials in Latin America including lack of funding opportunities; a need for per case reimbursement; cultural and ethical barriers; the need for ongoing oversight with trial conduct, quality assurance, and follow-up; a gap between sponsor requirements for insurance and indemnification, and national/institutional requirements with respect to clinical trials. The formation of the Grupo de Investigación en Cáncer de Ovario y Tumores Ginecológicos de México (GICOM) GCIG member group represents a significant advance in addressing these issues. Since the January 2017 CCRN Symposium, five

new CCRN sites have been approved in Cuba, Peru, and Brazil. However, opportunities exist for continued expansion of CCRN accredited sites across Latin America as well as for the creation of pragmatic new clinical trials relevant to Latin America. Current and proposed publically funded CCRN cervical cancer clinical trials continue to be supported by the GCIG, International Gynecologic Cancer Society (IGCS), nonprofit organizations, and industry sponsors and provide important avenues for improving care in Latin America.

5. Conclusion

Cervical cancer remains one of the leading causes of cancer death among women worldwide with large disparities in incidence and mortality rates between developed and underdeveloped regions (International Agency for Research on Cancer WHO, 2018). Many challenges exist in managing cervical cancer in developing regions, including the need for widespread implementation of screening and vaccination programs and for improving accessibility to radiotherapy and medical treatments (Small Jr. et al., 2017). CCRN aims to reduce global disparities in cervical cancer by promoting access to high-quality, low-cost clinical trials across Latin America and other less-developed regions. Participation in clinical trials can improve quality assurance and raise the level of care for all patients in cancer centers and hospitals. In creating enthusiasm for a culture of good clinical practice and clinical trials, we hope to continue to improve care standards and outcomes for all women with cervical cancer around the globe.

Conflicts of interest and disclosures

A. Poveda is an advisor for AstraZeneca, TESARO, Roche, PharmaMar, and ClovisOncology.

All other authors declare no conflicts of interest.

Acknowledgements

The authors would like to acknowledge the following sponsors for

their continued support of the CCRN mission and its clinical trials: Varian, Elekta-Nucletron, Zeria, Advaxis, GICOM, Roche Mex, and AZ Mex.

References

- Atun, R., Jaffray, D.A., Barton, M.B., Bray, F., Baumann, M., Vikram, B., et al., 2015. Expanding global access to radiotherapy. *Lancet Oncol.* 16, 1153–1186.
- Campbell, O.B., Akinlade, I.B., Arowojolu, A., Babarinsa, I.A., Agwimah, R.I., Adewole, I.F., 2000. Comparative evaluation of hypofractionated radiotherapy and conventional fractionated radiotherapy in the management of carcinoma of the cervix in Ibadan, Nigeria. *Afr. J. Med. Med. Sci.* 29, 253–258.
- Chemoradiotherapy for Cervical Cancer Meta-Analysis C, 2008. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J. Clin. Oncol.* 26, 5802–5812.
- Gaffney, D.K., Suneja, G., Ryu, S.Y., McCormick, M., Plante, M., Mileskin, L., et al., 2015. The cervix Cancer research network: a global outreach effort on behalf of the gynecologic cancer intergroup. *Int. J. Radiat. Oncol. Biol. Phys.* 92, 506–508.
- Gaffney, D., Small, B., Kitchener, H., Young Ryu, S., Viswanathan, A., Trimble, T., et al., 2016. Cervix Cancer research network (CCRN): improving access to cervix Cancer trials on a global scale. *Int. J. Gynecol. Cancer* 26, 1690–1693.
- Haviland, J.S., Owen, J.R., Dewar, J.A., Agrawal, R.K., Barrett, J., Barrett-Lee, P.J., et al., 2018. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.* 14, 1086–1094.
- Huh, W.K., Dizon, D.S., Powell, M.A., Leath, C.A., Landrum, L.M., Tanner, E., et al., 2016. ADXS11-001 immunotherapy in squamous or non-squamous persistent/recurrent metastatic cervical cancer: Results from stage I of the phase II GOG/NRG0265 study. *J. Clin. Oncol.* 34, 5516.
- International Agency for Research on Cancer WHO, 2018. Cervical Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012.
- Mishra, S.K., Laskar, S., Muckaden, M.A., Mohindra, P., Shrivastava, S.K., Dinshaw, K.A., 2005. Monthly palliative pelvic radiotherapy in advanced carcinoma of uterine cervix. *J. Cancer Res. Ther.* 1, 208–212.
- Pinillos, L., Pinto, J.A., Sarria, G., 2017. History of the development of radiotherapy in Latin America. *Ecancelmedscience* 11, 784.
- Rosenblatt, E., Zubizarreta, E., Izewska, J., Binia, S., Garcia-Yip, F., Jimenez, P., 2015. Quality audits of radiotherapy centres in Latin America: a pilot experience of the International Atomic Energy Agency. *Radiat. Oncol.* 10 (169).
- Ryu, S.Y., Lee, W.M., Kim, K., Park, S.I., Kim, B.J., Kim, M.H., et al., 2011. Randomized clinical trial of weekly vs. triweekly cisplatin-based chemotherapy concurrent with radiotherapy in the treatment of locally advanced cervical cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 81, e577–e581.
- Small Jr., W., Bacon, M.A., Bajaj, A., Chuang, L.T., Fisher, B.J., Harkenrider, M.M., et al., 2017. Cervical cancer: a global health crisis. *Cancer* 123, 2404–2412.