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The Cervical Cancer Research Network (Gynecologic Cancer InterGroup) roadmap to expand research in low- and middle-income countries

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ABSTRACT

Cervical cancer is a global health problem which disproportionately affects women in low- and middle-income countries. The World Health Organization recently launched its global strategy to eliminate this disease in the next two decades. For those women diagnosed today with cervical cancer better strategies are needed to improve outcome and reduce treatment-related morbidity. Clinical trials are critical to shaping future treatment, and much has been achieved already. However, such opportunities are limited in low resource settings, and the Cervical Cancer Research Network is dedicated to expanding access to new technologies in surgery, radiation, and medical oncology. In this article we review the status of the trials portfolio and outline future objectives, including the launch of a number of research grants for aspiring or established researchers in low- and middle-income settings

INTRODUCTION

Cervical cancer remains a global health problem, a fact acknowledged by the World Health Organization (WHO) with a call to action issued by its director general in May 2018. WHO works with a number of organizations globally to raise awareness of the disease, improve access to human papillomavirus vaccination and screening and access to the treatment of established disease. The global strategy to eliminate cervical cancer was launched on November 17, 2020. Women diagnosed with cervical cancer have many unmet needs. From the early stages where the radicality of surgery can impact fertility, morbidity, and quality of life to the more advanced stages where the focus is on extending survival. Clinical research is of the utmost importance in addressing these issues and delivering change. The concept for a Cervical Cancer Research Network (CCRN) evolved in 2012 to bring together researchers from low- and middle-income countries interested in cervical cancer management. It has long been recognized that the incidence and mortality from cervical cancer varies widely with geography, with the greatest incidence in low- and middle-income countries.¹ Even in the best

resourced settings up to 30% of women with locally advanced disease will relapse and die from cervical cancer. Consequently, there is an urgent need to improve outcomes for all women with cervical cancer. This underpins the need for research and importance of potentially practice changing phase III clinical trials. It is essential to include patients from a wide geographical and cultural background to ensure that new treatments can be safely implemented across many different healthcare settings. Of course, it is also imperative to complete such studies in as short a time as possible while the research question remains relevant.

The Gynecologic Cancer InterGroup (GCIG) is a non-profit organization established to promote cooperation in clinical trials with the specific aim of benefiting women with gynecologic cancers. Currently, it has representation from 33 research groups spread across 46 countries. However, Latin America, Africa, and the Indian subcontinent are among the regions under-represented in this forum. The CCRN provides a bridge to potential sites beyond the GCIG to participate in GCIG badged clinical trials. Within GCIG the Harmonization Committee has shared experiences in overcoming the unique challenges associated with trial set up especially in Latin America and India. This process has been helped enormously by the expertise of a dedicated CCRN clinical research associate.

The CCRN is run by members from across the GCIG cooperative groups and is managed by the GCIG executive. It has representation from radiation oncology, medical oncology, and gynecologic oncology. One of the first challenges was to identify and connect with potential researchers in low- and middle-income countries, and this has been facilitated by establishing regional symposia. The inaugural symposium was held in Bangkok² in 2016 and since then has become an annual event with subsequent meetings in Mexico City³ in 2017, Bucharest⁴ in 2018, and Johannesburg (manuscript in preparation) in 2019. The 2020 event was scheduled to take place on 22–23 February in Da Nang but was unfortunately canceled on orders of the Vietnamese government following the outbreak

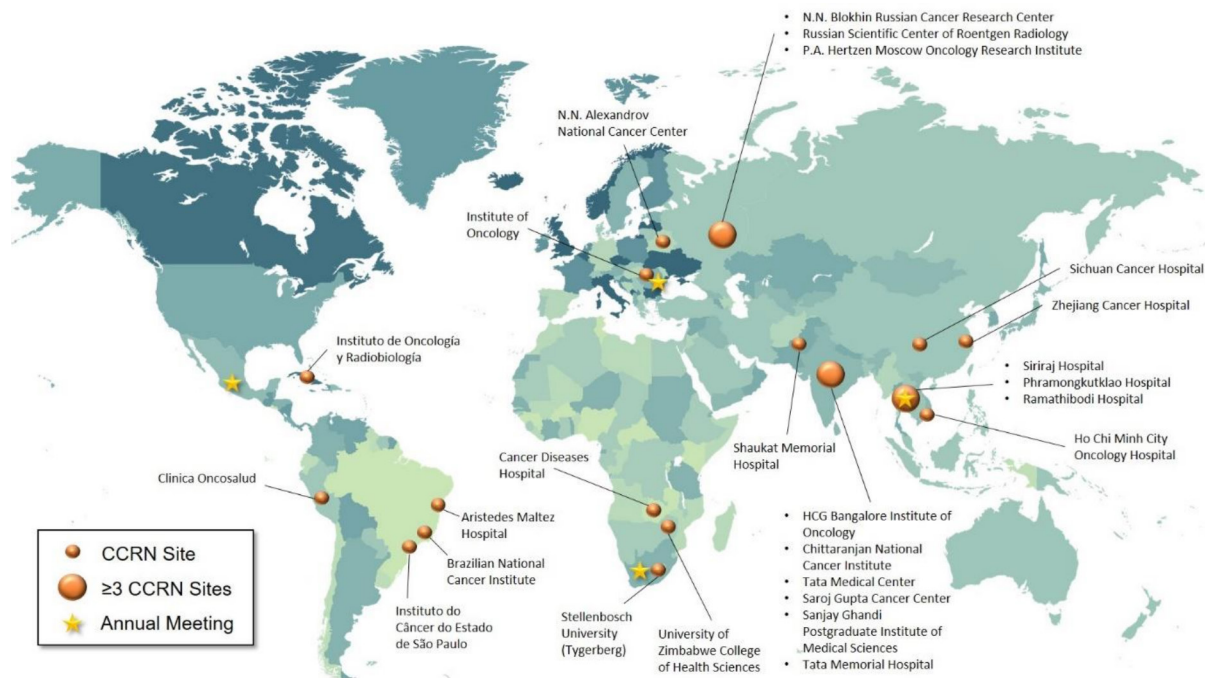


Figure 1 Map showing Cervical Cancer Research Network (CCRN) sites represented by circles and locations of previous annual symposia represented by stars.

of COVID-19. In view of the ongoing COVID-19 pandemic CCRN is exploring options for a virtual meeting with Vietnamese colleagues in 2021.

JOINING THE CCRN AND NEW RESEARCH INITIATIVES

Currently, 27 sites from 14 countries are registered with the network (Figure 1). We are keen to encourage new centers to join the network, irrespective of their current ability to participate in international trials. The basic requirements are access to radiation facilities, a radiation oncologist, a medical oncologist, and a surgeon with expertise in gynecologic cancer management. All sites are then asked to complete a pre-qualifying questionnaire, which is reviewed by the executive and approved subject to the basic requirements outlined above. Further information on the process can be obtained via email from CCRN operational support (cervixcancerresearchnetwork@gmail.com)

The CCRN is proud to announce its new grant initiative to support new or established researchers in low- and middle-income countries to undertake original research, including national audit/retrospective review pertaining to cervical cancer. Applications are welcome from all CCRN sites. Colleagues whose sites are not currently affiliated with CCRN may register to join the network and once accepted will become eligible to apply. Four grants up to US\$5000 each will be available for 2021–2022 on a competitive basis. Further information on the application process and the eligibility criteria can be obtained by emailing the operational support team (cervixcancerresearchnetwork@gmail.com)

CCRN TRIALS

Within the CCRN/GCIG trials portfolio there are three ongoing international clinical trials (SENTICOL III, CONTESSA/NEOCON-F, and INTERLACE), which are outlined below. The SHAPE study recently

completed accrual (December 2019). An additional 3-year of follow-up is required, thus results should be available in 2023, while the OUTBACK trial is expected to report later this year. The TACO study has also recently closed to recruitment and is currently in follow-up.

SENTICOL-III

Sentinel lymph node (SLN) mapping is now part of the lymph node evaluation process in several gynecologic tumors, such as uterine, cervical, and vulvar cancer. Data from SENTICOL-I and II studies showed excellent sensitivity, specificity, and predictive values of SLN mapping, and a reduction in lymphatic morbidity without compromising the 3-year recurrence-free survival.⁵ However, there are no prospective randomized trials confirming the long-term oncologic safety of SLN mapping alone compared with lymph node dissection. In addition, several issues remain unsettled, including standardization and quality assessment of the SLN processing.^{6,7} Moreover, the management of patients with low-volume metastasis, including micrometastasis or isolated tumor cells, is uncertain. Data from SENTICOL-I study suggests that the presence of micrometastasis or isolated tumor cells does not impact progression-free survival in untreated patients.⁸

Therefore, the SENTICOL-III protocol was developed by the French GINECO cooperative group under the GCIG leadership, and several CCRN sites are participating in the study. It is a prospective international randomized multicenter trial comparing SLN mapping alone with SLN followed by pelvic lymphadenectomy in patients with early-stage cervical cancer, up to 4 cm in size. Details of the trial design have been published.⁹ This is an ambitious trial with a planned accrual of 950 patients, thus requiring large international collaboration. The trial was activated in 2018 in France. Currently, 145 sites are open in France, 12 in China, 1 in Italy, and three in Japan. Several other GCIG groups are in the process of activating

the trial. Importantly, seven sites in Brazil and two sites in India are also in the process of opening the trial. As of January 2021, 208 patients have been screened and 161 randomized.

The SENTICOL-III trial is an important study, which will provide level 1 evidence and a definitive answer as to whether SLN mapping alone is oncologically safe and associated with a better quality of life. It will also provide important data on outcome of patients with low-volume metastasis. It is believed that contribution from countries such as Brazil, China, and India will be extremely important to help expedite accrual, considering the high rates of cervical cancers in those areas of the world. With their contribution, it is hoped that the trial will be completed in 2023.

CONTESSA/NEOCON-F

Radical trachelectomy is now a recognized and accepted treatment for the management of women with early-stage cervical cancer who wish to preserve fertility.¹⁰ However, the oncologic safety has mostly been validated for women with lesions <2 cm in size. For women with lesions measuring >2 cm and wishing to preserve fertility, there are no 'standard of care' treatment options. The two main strategies include upfront radical trachelectomy or neoadjuvant chemotherapy followed by fertility-preserving surgery.¹¹ This approach appears to offer equivalent oncologic results to those of upfront trachelectomy but with superior fertility and obstetrical outcome. Studies on neoadjuvant chemotherapy followed by fertility-preserving surgery are limited because they are all retrospective. The CONTESSA/NEOCON-F study was developed to address this treatment option in a standardized fashion. The detailed protocol has already been published elsewhere.¹²

It is hoped that the CONTESSA/NEOCON-F trial will provide robust data on the option of neoadjuvant chemotherapy followed by fertility-preserving surgery in young women with cervical cancer (2 to ≤4 cm). Data on oncologic outcomes, rates of fertility preservation, and obstetrical outcome will be collected. This trial will provide important quality of life information regarding the tolerability and 'acceptability' of chemotherapy in this young patient population as well as its impact on ovarian function. This is an important trial with a planned accrual of 90 patients. Since it is a very rare condition, international collaboration is essential. We also look forward to opening the trial in low- and middle-income countries where cervical cancer is highly prevalent.

INTERLACE

INTERLACE is a Cancer Research UK funded National Cancer Research Institute (NCRI)/GCIG badged multicenter international phase III trial in locally advanced cervical cancer (ClinicalTrials.gov identifier: NCT01566240). The study is open to recruitment in Mexico, Italy, and India, with a further site in set up in Brazil. While advances in radiation techniques have led to substantial improvements in local control and reduced morbidity, there has been little impact on overall survival. Many women still die from metastatic disease, prompting investigators to intensify systemic therapy. The INTERLACE trial is re-examining the subject of additional upfront or induction chemotherapy prior to standard of care chemoradiation but with some important differences. The induction chemotherapy is a combination of carboplatin and paclitaxel delivered in a dose-dense weekly schedule for 6 weeks followed immediately in week 7 by standard chemoradiation. The incorporation of

a taxane, the dose-dense schedule, and the elimination of the gap between chemotherapy and chemoradiation is novel and will, it is hoped, improve overall survival. A phase II study confirmed that this approach was feasible with manageable toxicity and did not compromise the chemoradiation.¹³ A positive trial would indeed be of immense interest to countries where there are long waiting times for radiation and where upfront chemotherapy is often used but without evidence. The main inclusion criteria are FIGO (2014) stage IB1 node positive to stage IVA histologically confirmed squamous, adeno, or adenosquamous cancer of the cervix in patients suitable and fit for standard chemoradiation with no active evidence of tuberculosis and who are human immunodeficiency virus negative. All participating sites complete a radiation therapy quality assurance exercise prior to site activation. All participants must give written informed consent and be able to comply with the trial follow-up schedule. To date, the trial has randomized 430 patients out of a target of 500. It is anticipated that it will complete accrual by the end of 2021.

New Horizons: Expanding the Portfolio

Cervical cancer is the second most common cancer among women in less developed countries.¹⁴ The Gynecologic Oncology Group 240 trial transformed the treatment of advanced cervical cancer by demonstrating improved survival with bevacizumab added to standard chemotherapy,¹⁵ and early-phase studies using pembrolizumab showing response rates of 14–17% have subsequently led to Food and Drug Administration approval for second-line immune checkpoint inhibitor therapy in cervical carcinomas expressing PD-L1.^{16,17} Unfortunately, patient access to targeted therapies like bevacizumab and pembrolizumab remains limited in many lower middle-income countries and further highlights the unmet need for better treatments and more equitable access to therapies in countries where the burden of cervical cancer is highest.

Over the years, the CCRN has actively been engaging with low- and middle-income countries to enable participation in multinational GCIG trials that have mainly been focused on surgical and radiation oncology-based therapeutic strategies. It is now well-recognized that many individual sites in low- and middle-income countries are centers-of-excellence equipped with world-class specialist capabilities and facilities to execute even more complex clinical studies, such as trials involving novel systemic therapeutic agents. Many of the current and future clinical trials in advanced cervical cancer will include anti-angiogenic and/or immunotherapy drugs as a backbone on which other novel agents may be tested in combination. With clinical equipoise firmly in mind, expanding the systemic therapy clinical trials portfolio of the CCRN would be an opportunity to provide improved access to potentially life-prolonging treatments for patients who are managed in these centers. Importantly, this will also provide greater diversity of safety and efficacy data for new drugs across a broad spectrum of ethnic groups, facilitate local expertise, and familiarity with new treatments and clinical research, and provide a global community of key opinion leaders for practice-changing clinical application in the real world if the investigational products are proved to be effective, and eventually obtain regulatory approval. There are clearly significant synergies to be wrought from these international collaborations, and we are already exploring this approach with several pharmaceutical companies that are keen to include low- and middle-income countries in their

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trials, as we persist in our efforts to reduce the worldwide mortality and morbidity of cervical cancer.

Partnership with the International Gynecologic Cancer Society
In association with the International Gynecologic Cancer Society (IGCS) the CCRN is working in collaboration with the GCIG Education Committee to offer high-quality education through the Young Investigator Program. It is a yearly 1 day educational symposium offered to young GCIG investigators and will be expanded to investigators from CCRN centers as well. A wide range of topics related to all aspects of clinical research are presented to teach key elements of trial design, methodology, and execution, such as scientific justification, design, statistics, quality of life and patient-reported outcomes endpoints, translational research, data integrity, and international cooperation. Virtual meetings now offer the opportunity for investigators from low- and middle-income countries to benefit from high-quality education at very low cost. GCIG/CCRN is also keen to collaborate with the IGCS gynecologic oncology global curriculum and mentorship program to offer this educational symposium to young fellows in training as part of their fellowship, again taking advantage of the virtual low-cost format. We believe this initiative will also provide networking opportunities for young fellows with GCIG/CCRN members and facilitate research connections once those fellows have established their practice in their respective centers. Lastly, the annual IGCS meeting will be an opportunity for researchers from low- and middle-income countries and young fellows to present their work through the GCIG/IGCS early career program.

CONCLUSION

With the plethora of new approaches under investigation for the management of cervical cancer the future looks promising for our patients. It is therefore imperative that the large numbers of patients in low- and middle-income countries have access, where possible, to these new technologies within clinical trials. We must ensure that the advances in care are not just for the few and will ultimately reach the many thousands of women in low- and middle-income countries diagnosed annually with this disease.

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