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Increasing global accessibility to high-level treatments for cervical cancers

Chargari C^{1,2}, Arbyn M³, Leary A⁴, Abu-Rustum NR^{5,6}, Basu P⁷, Bray F⁸, Chopra S⁹, Nout R¹⁰, Tanderup K¹¹, Viswanathan AN¹², Zacharopoulou C¹³, Soria JC^{14,15}, Deutsch E^{1,2,15}, Gouy S^{2,15,16}, Morice P^{2,6,15,16}

1. *Radiation Oncology, Gustave Roussy Cancer Campus, Villejuif, France*
2. *Inserm U-1030, Université Paris-Saclay, Le Kremlin-Bicêtre, France*
3. *Unit Cancer Epidemiology – Belgian Cancer Centre, Brussels, Belgium*
4. *Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France*
5. *Surgical Oncology, Memorial Sloan Kettering Cancer Center, New York, United States*
6. *European Society of Gynecological Oncology; Geneva, Switzerland*
7. *Early Detection, Prevention & Infection Branch, International Agency for Research on Cancer, World Health Organization, Lyon, France*
8. *Cancer Surveillance Branch, International Agency for Research on Cancer*
9. *Radiation Oncology, Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai, Homi Bhabha National Institute, Maharashtra, India.*
10. *Radiotherapy, Erasmus MC Cancer Institute, University Medical Center Rotterdam, The Netherlands*
11. *Department of Oncology, Aarhus University Hospital, Aarhus, Denmark*
12. *Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins Medicine, Baltimore, MD, United States*
13. *European Parliament, Committee on the Environment, Public Health and Food Safety*
14. *Governance, Gustave Roussy Cancer Campus, Villejuif*
15. *Université Paris-Saclay, Le Kremlin-Bicêtre, France*
16. *Surgical Oncology, Gustave Roussy Cancer Campus, Villejuif, France*

Corresponding author:

Pr Cyrus CHARGARI, MD, PhD
Radiation Oncology Department
Gustave Roussy Cancer Campus
cyrus.chargari@gustaveroussy.fr

ABSTRACT

Human papillomaviruses (HPV)-related gynecological cancers are a major health care issue, and a leading cause of cancer death in low- and middle-income countries (LMIC). In 2020, the World Health Organization launched a program aimed at cervical cancer elimination, by screening and vaccination strategies. Offering the best possible care to women diagnosed with invasive cancer is a complementary objective. Treatment of cervical cancer as per modern standards is complex and multimodal, mainly relying on surgery, external-beam radiotherapy (+/-chemotherapy) and brachytherapy. In parallel with the pivotal role of multidisciplinary discussion, international societies provide guidance to define the most effective and least toxic anti-cancer strategy, homogenize treatment protocols and provide benchmark quality indicators as a basis for accreditation processes. The challenge is to offer the appropriate diagnostic workup and treatment upfront and to avoid non-evidence-based treatment that consumes resources, impairs quality of life (QoL), and compromises oncological outcome. Various strategies may be applied for improving treatment quality: development of surgical mentorship, companion-training programs and international cooperation. The lack of radiotherapy/brachytherapy facilities is a major concern in LMIC. Reinforcing international support in terms of education, training, research and development and technical cooperation with national projects is required to increase access to minimum requirements but also introduce modern techniques, upgrade radiotherapy/brachytherapy services, and expand access to modern systemic treatments. In countries with robust economies, compliance to standards should also be increased. Integrative cancer care and multidisciplinary approaches are needed to tackle the dual challenge of increasing cure rates while minimizing QoL impairment. Appropriate dimensioning of the resources to avoid harmful treatment delays and access to expert referral centers is also a priority.

Keywords: Human Papillomaviruses (HPV); cervical cancer; cervix; radiotherapy; surgery; brachytherapy

Human papillomavirus (HPV) induced cancers are a major health care issue. It is estimated that each year 570,000 cancer cases in women (8.6% of all cancer cases) are attributable to HPV-related oncogenesis worldwide.¹ Among HPV-related malignancies, cervical cancer is a leading cause of cancer death, especially in low- and middle-income countries (LMICs), where screening programs are either non-available or of suboptimal quality. Major disparities in health care access contribute to treatment heterogeneity and compromise patient outcome, while the vast majority of locally advanced cases cannot be treated in a curative intent.³

In 2020, the World Health Organization (WHO) launched the ambitious cervical cancer (CC) elimination initiative, aiming to reduce the incidence of CC below 4/100,000 women by the end of the century in all countries of the world by vaccinating girls by the age of 15 years against HPV (target 90%), by screening women at least twice by the age of 45 years (target 70%) and by treating cervical pre-invasive and invasive lesions appropriately (target 90%).^{2,3} Besides vaccination against and testing for the etiologic agent (HPV), offering the best possible curative and palliative care to women diagnosed with invasive cancer is a complementary priority of the WHO elimination initiative.⁴

We review the state of the art regarding current therapeutic procedures for cervical cancer and highlight strategies for increasing accessibility to high-level treatments around the globe.

1. Burden of HPV-related gynaecological cancers

Nearly all cervical cancers and a substantial fraction of vulvar (25%) and primary vaginal cancer (PVC) (78%) are caused by persistent infection with high-risk (hr) human papillomavirus (HPV) types^{1,5}. HPV16/18 is associated with 71%, 73% and 64% of cervical, vulvar and PVC, respectively; whereas the seven most frequent oncogenic HPV types (HPV16/18/31/33/45/52/58) are associated with 90% of cervical cancer^{1,6} (**Table 1**). According to the GLOBOCAN estimates of the International Agency for Research on Cancer for 2020, approximately 604,000 women were diagnosed with a cervical cancer⁷. The average world age-standardized incidence (ASIR) is estimated to be 13/100,000/year but varies widely between countries, from less than 2/100,000 up to 75/100,000.³ Clear patterns in the geographical distribution of cervical cancer can be discerned. Eighty four percent of cervical cancers occur in lower resourced countries (human development index<0.80) and it is the leading female cancer in sub-Saharan Africa (ASIR > 27/100,000).⁸ With 311,000 women dying from the disease world-wide in 2018, cervical cancer is the fourth most common cause of cancer death among women. The global estimated age-standardized mortality rate for 2018 was 7/100,000, which varies geographically in a similar way as the incidence rates. Cervical cancer occurs at a relatively young age (average at diagnosis 53 years).⁸ Trends of cervical cancer incidence and mortality demonstrate strong cohort effects with increases occurring in successive cohorts born circa 1920-1930 and ≥1945, probably due to changing sexual behaviour and increased exposure to HPV. In North America, the Nordic countries and West-European countries, Australia and New Zealand incidence and mortality trends have decreased substantially since the 1970s as a consequence of massive screening of pre-

invasive lesions by Pap smears.⁹⁻¹⁰ However, where screening coverage has been low or of poor quality as observed in several East European countries, Asia and Africa, cervical cancer incidence and mortality trends decreased only slightly or even increased.¹¹⁻¹⁵ Women living with human immunodeficiency virus (HIV) have a significantly increased risk of cervical cancer. The most affected regions are southern Africa and eastern Africa. It was recently shown that 5.8% (95% CI 4.6–7.3) of new cervical cancer cases in 2018 were diagnosed in women living with HIV, and 4.9% (95% CI 3.6–6.4) were attributable to HIV infection. Age-standardized incidence rates of HIV-attributable cervical cancer were more than 20 per 100 000 in six countries, all in southern Africa and eastern Africa.¹⁶ The clinical trials of HPV vaccination demonstrated a significant reduction in HPV infection and cervical precancer.¹⁴ More recently large correlation and linkage studies in the USA and in Sweden have confirmed that vaccination also significantly decreased the risk of invasive cervical cancer among young women.^{17,18} Similar evolutions are expected to become evident in the next decade in countries that have introduced vaccination against HPV. HPV infection is also a major cause of cancer in men, accounting now for 70% of oropharyngeal carcinoma in the United States and being implicated in approximately one third of penile glans carcinoma worldwide.^{19,20} Modeling exercises have shown that under the current conditions of screening and vaccination, the global number of HPV-related cancers would continue to rise over the coming decades, causing major societal and economic impact.²¹ Therapeutics will be needed for at least for another 70-80 years until elimination as a public health problems becomes a reality .

2. Staging of cervical cancers

Staging of cervical tumors is crucial to guide further treatment (**Figure 1**). It is based on the local characteristics of the tumor (size and spread to adjacent structures), as well as presence or absence of nodal and distant metastasis. Staging requires a meticulous and detailed clinical and radiological evaluation in order to accurately evaluate the extent of local and loco-regional disease. It is important to carefully search for factors that could contra-indicate primary surgery because of local tumor extension (extension to the urethra, the bladder, the ano-rectum, or the pelvic wall) or lymph node metastasis or distant disease. The recommended radiological evaluation of loco-regional disease is abdomino-pelvic magnetic resonance imaging (MRI), to thoroughly assess primary tumor size and extent, but also detect pelvic lymph node (LN) spread. MRI has a crucial role in distinguishing early stage tumors that can be treated with upfront surgery from locally advanced disease that should be referred to combination of chemoradiation and brachytherapy.²² Identification of nodal status and extra-pelvic disease is pivotal to determine the eligibility for and nature of surgery. Nodal spread could be pelvic nodes, para-aortic, inguinal (if tumor extends to the lower third of the vagina or to the vulva), and/or distant. For patients with locally advanced disease (definition in **Table 2**), extra-pelvic imaging is recommended to evaluate distant LN and/or metastases. In locally advanced cervical cancer (LACC), PET-CT (positrons emission tomography/computed tomography) imaging has the best sensitivity and specificity (>95%) to screen for nodal metastasis (≥ 5 mm) and to ensure the absence of distant/extra abdominal metastasis. It has however a low sensitivity to detect pelvic LN in tumors <4cm

confined to the cervix and is not indicated in patients with early stage disease.²² PET-CT is now also used for other locally advanced gynecological tumors. The availability of MRI and PET/CT in LMICs is however highly limited. In 2018, a survey of MRI availability in West Africa reported an increase in the number of available MRI units in the last decade, but still a very low number of infrastructures, with for example 0.30 units/million population in Nigeria.²³ There are several barriers for the use of modern imaging in LMICs: lack of investment plans and prioritization, equipment costs, difficulties for maintenance and safety. Strategies for increasing access to modern imaging modalities were recently reviewed. Those include technical solutions (e.g. development of digitization), regulatory perspectives in terms of quality assurance processes, and organizational solutions (e.g. regional management of imaging in centers of reference).²⁴ Abdominal and pelvic contrast enhanced computed tomography provides a comprehensive evaluation of nodal and distant disease, though soft-tissue contrast resolution is inferior to that of MRI.²⁵ Staging using abdomino-pelvic ultrasounds is inexpensive and has shown high accuracy for local tumor assessment, as compared to the gold-standard MRI.²⁶ It is however highly operator dependent and requires adequately trained and experienced radiologists to avoid understaging. In addition, assessment of nodal disease remains a major concern in patients with cervical cancer and therefore PET/CT (or CT if not available) are still necessary to rule out lymph node and/or distant tumor extension. The most accurate LN staging procedure is surgical. Para-aortic LN dissection (PALND) may be considered in patients with LACC and positive pelvic nodes to guide the extent of radiotherapy volumes.²⁷ However, two phase III randomized trials (the last one reported in 2020) failed to demonstrate an improvement in survival with surgical versus radiological LN staging.^{28,29} In addition, experienced surgeons able to perform complex laparoscopic PALND are however often unavailable in LMICs. After this clinical and radiological work-up, cervical cancers are staged according to the *Fédération Internationale de Gynécologie Obstétrique* (FIGO) and/or the TNM (Tumor, Node, Metastasis) staging systems.³⁰ The latest provides the most accurate definition of both primary tumor extent and nodal extent.³¹ There is ongoing research to integrate genomic and molecular characterization in HPV-related malignancies, in order to identify potential targets but also to refine patients prognosis.³²

3. Surgery

Many trials during the 3 last decades improved the indications or modalities of surgical procedure (staging or tumor resections) in cervical cancer (**Figure 2**). The purpose of surgery is the complete removal of the tumor and regional nodes (details in **Table 2**). In order to be oncologically adequate, surgery of cervical cancer and PVC should follow two major principles: 1/ To adapt the radicality of the tumor resection to the local spread assuring the key issue of having free surgical margins in all directions; 2/ To limit surgery to patients whose preoperative staging suggests that an exclusive surgery should be the sole treatment. In cervical cancer, radical hysterectomy is therefore proposed only to patients with a tumor limited to the cervix, ideally <4cm. For more advanced cases, upfront surgery is contra-indicated, as presence of these poor prognostic factors at histological examination will justify post-operative radiation therapy (RT).^{33,34} The combination of surgery and RT increases the

risk of major post-operative morbidities, without improving overall survival (OS) as compared to exclusive RT.³⁵ The question of surgical approach is challenging. The minimally invasive approach (robotic or laparoscopic) was historically considered as oncologically safe, with a decrease in surgery-related morbidities. However, a recent large randomized trial comparing conservative laparoscopic excision (widely considered as “safe” in many retrospective and prospective cohorts) and radical laparotomy-based hysterectomy in early stage cervical cancer showed an unexpected deleterious impact on OS of the laparoscopic procedure. Minimally invasive surgery was associated with a lower rate of disease-free survival than open surgery (3-year rate: 91.2% vs 97.1%), and the difference remained after adjustment on co-factors. In post-hoc analysis, the deleterious effect was shown independent of tumor size.³⁶ In a large retrospective European study (SUCCOR), the difference in relapse probability between mini-invasive surgery and laparotomy-based hysterectomy was significant only in the subgroup of patients with tumors > 2 cm (HR, 2.31;95% CI, 1.37 to 3.90; P=0.002).³⁷ While there are conflicting results in the literature, recent large multicenter series of patients treated with laparoscopic surgery suggested that a combined laparoscopic-vaginal technique for radical hysterectomy with avoidance of spillage and manipulation of tumor cells could provide excellent oncological outcome in these patients with early stage cancer.³⁸ Prospective studies are awaited to better guide the optimal surgical approach. Patients should therefore be carefully counseled about the oncologic risk of minimally invasive procedures, especially in tumors >2cm. In the LACC trial, quality of life was similar between treatment groups, and the potential benefit of a mini-invasive approach was compensated by a higher risk of relapse. In addition, the use of minimally invasive resulted in a similar overall incidence of intraoperative or postoperative adverse events, as compared with open radical hysterectomy.^{39,40} The standard pelvic node dissection (including external iliac, internal iliac, obturator and common iliac nodes) was established more than 8 decades ago in cervical cancer treatment. In order to decrease morbidities related to full pelvic lymphadenectomy, several prospective studies confirmed the value of sentinel node dissection (SND), which is now considered as one acceptable method of LN staging to decrease lymphatic related complications in patients with early stage disease.⁴¹⁻⁴² Training and experience of the surgeon and of the pathologist have however an important impact on detection and sensitivity rates. Technical aspects should therefore be carefully considered and a quality control process is required to ensure successful implementation of the procedure.⁴³ Ongoing trials are comparing on a larger scale full pelvic lymphadenectomy to selective surgical strategies.

Three major points to increase quality of surgery and to avoid non-oncological surgeries should be highlighted: 1/ The pivotal issue of the need of multidisciplinary discussion among treatment staff to define the best strategy prior to any treatment, each time a cervical cancer is suspected; 2/ The need of international guidelines to homogenize treatment strategy according to objective and reproducible prognostic criteria and 3/ The importance of providing surgical quality indicators (QI).³⁴ Fulfillment of benchmark QIs may be used for certification of referent centers. Such process is ongoing in Europe under the umbrella of European Society of Gynecological Oncology and may be finalized in 2021.

For LMICs, where the cervical cancer incidence is highest and availability of radiation therapy is very limited, various approaches are considered. One is to adjust guidelines for low resource countries to the modalities available with the purpose to maximize survival and decrease iatrogenic sequelae as far as possible. Currently, this approach is limited by the fact that world regions that have poor access to radiation facilities also have poor access to good quality oncological surgery. In addition, 70-80% patients in LMICs present in locally advanced setting where surgery is usually not an option, and therefore increasing access to external radiotherapy is a priority (see below).³ Another path is to develop mentorship and companion-training programs with experienced surgeons that will teach the best surgical practice to local surgeons in their own setting. This cooperation could be extended to twinning programs with expert centers from countries with developed economy to improve concretely the quality of the overall management of patients and not exclusively surgical aspects.

4. External beam radiotherapy

The standard upfront treatment of LACC is based on radiotherapy potentiated by concomitant chemotherapy (**Table 2, Figure 1**). The entire treatment should be carried out in as short an interval of time as possible.⁴⁴ Two recent randomized trials in LACC have shown an increased probability of relapse when LACC patients are treated with neoadjuvant chemotherapy followed with surgery.^{45,46} There is no room for induction chemotherapy, which is associated with a higher probability of tumor progression, death and toxicity.⁴⁷ Radiation therapy (including external radiation and brachytherapy +/- concurrent chemotherapy) is also indicated as adjuvant treatment in case of adverse histological factors. One major advancement in gynecological cancers is the implementation of intensity-modulated radiotherapy (IMRT) and image-guidance, which minimize the doses delivered to organs at risk and decrease the probability of radiotherapy-associated digestive and/or urinary late side effects in randomized phase III trials, without impacting on survival.⁴⁸⁻⁴⁹ The limited access to radiotherapy often leading to patient undertreatment is a multi-faceted problem in the LMICs (where 85-90% of cervical cancer deaths occur).⁵⁰ Those include distance from radiotherapy centers, lack of facilities and practitioners, as well logistic and cultural barriers to treatment.^{51,52} An analysis published in 2017 showed that actual coverage of the need for radiotherapy ranged from 34% in Africa to over 92% in Europe to about the double the needs in North America, with only 140 radiotherapy centers in Africa, including approximately 30% of Cobalt machines. For comparison, there were 2787 centers in North America, including 3.6% of Cobalt machines. It was estimated that proportional additional investments and operation costs were as high as more than 200% in Africa.⁵⁰ This insufficient coverage of the needs has a major impact on patients cure probability, but also limits access to high-quality palliative treatments, as the role of RT for symptoms palliation is major. The International Atomic Energy Agency and international academic societies are supporting these countries in terms of education, training, research and development activities and technical cooperation with national projects, not only to increase access to minimum requirements (access to 2D radiotherapy and concurrent chemotherapy use), but also to introduce modern techniques, upgrade radiotherapy services and facilitate local training of professionals. Technological developments and requirements for high-tech

RT are potential barriers, and the importance of staff expertise and implementation of a specific workflow must be appraised. The improvement in quality will be achieved by additional health care resources, but also by a better organization of existing ones.⁵²

The question of improving quality of care is also crucial in countries with robust economies. The misconception of a disappearance of the disease should be avoided and maintaining high level of expertise is problematic. A survey assessing practice patterns for LACC patients from 2005 to 2007 showed that patients treated in nonacademic facilities treating <3 patients per year were more likely to receive incomplete or protracted treatment, and less likely to receive concurrent chemotherapy compared to academic centers.⁵³ This encourages a close collaborative network between nonacademic and academic centers to provide the highest quality of care to all patients.⁵⁴ The development of international guidelines may facilitate decision making and homogenize practice to provide the highest possible quality.^{20,55-57}

5. Brachytherapy

Brachytherapy consists of placing sealed radioactive sources directly in or next to the tumor, and used for delivering a high dose boost to the tumor while sparing organs at risk.⁵⁸ Brachytherapy is not optional in LACC. An analysis from the Surveillance, Epidemiology, and End Results (SEER) database has shown that brachytherapy use for LACC decreased from 83% in 1988 to 58% in 2009. Brachytherapy treatment was independently associated with better cancer-specific survival (hazard ratio [HR], 0.64), and OS (HR 0.66).⁵⁹ Based on clinical evidence, national health authorities should recognize brachytherapy as a major priority in the treatment of HPV-related gynecological cancers. Implementation of 3D-image guided adaptive brachytherapy (IGABT) enables dose escalation in advanced cases or in poorly responding tumors, while decreasing the probability of normal tissue complication.⁵⁸ The ability to deliver high doses to the tumor is a major contributor of the therapeutic efficacy in locally advanced cervical cancers and local relapses are, in most of the cases, not curable even through mutilating surgeries (anterior, posterior, or total pelvic exenteration).⁶⁰ The utilization of advanced applicators allowing combined intracavitary-interstitial procedures to increase focally the dose is needed for excellent local control in cervix. The cost-effectiveness of IGABT supports its routine use compared with 2D brachytherapy in cervical cancer.⁶¹ As with all complex techniques, adequate training is required, with a correlation between increased experience, ability to fulfill planning aims, and patient outcome.⁶² Promoting education in brachytherapy should therefore be strongly considered. The transition from low dose-rate brachytherapy to high dose-rate brachytherapy may increase access to brachytherapy, increasing the maximum number of patients being treated on an outpatient basis. In parallel, guidelines have been written to homogenize target volumes definition on MRI and/or on computed tomography (if MRI is not available) in LACC. Multinational prospective studies have accompanied the development of IGABT in many countries worldwide prompting physicians to improve their practice.⁶³ The impact of brachytherapy on survival should incite health care policies and insurance providers to optimize patients care organization, promoting referral to

expert centers familiar with modern brachytherapy concepts and investing in advanced brachytherapy applicators (which are major technological tools for dose-escalation strategies but are quite expensive presently for LMICs). Expanding the engagement of patient navigators may be seen as a tool to reduce treatment care disparities.⁶⁴ External RT and brachytherapy may be delivered at many locations, provided that careful care coordination is provided, giving all patients the opportunity to receive the best treatment available, while keeping overall treatment time <50-55 days (+0.5% probability local relapse per additional day for IGABT treatments).⁴⁴ Radiotherapy treatment scale-up remains crucial by producing health benefits as well as a major return on investment to countries at different levels of development.^{65,66} A recent analysis of National Cancer Control Plans shows that approximately 50% of the countries do not project needs for investments into radiotherapy and brachytherapy.⁶⁶

6. Medical treatments: current standards and future trends

Loco-regional treatment is the cornerstone of HPV-related gynecological cancer management. The contribution of systemic therapies to cure and long-term survival has been modest. The one and notable exception is the use of concurrent chemotherapy with the aim of potentiating the efficacy of external beam radiotherapy. The most common regimen is weekly cisplatin (40mg/m²) and a number of studies have established that chemoradiation improves local control as well as PFS and OS in patients with LACC.⁶⁷ The role of additional chemotherapy delivered after completion of chemoradiation was tested in a phase III randomized trial (NCT01414608). Data were recently presented at ASCO 2021, showing no survival benefit with adjuvant chemotherapy after standard chemoradiation for LACC.⁶⁸

In relapsed or metastatic disease not eligible to loco-regional treatment, palliative chemotherapy can be proposed, to improve symptoms and prolong survival. In patients who have not previously received cisplatin concomitant to RT, a standard is a combination of cisplatin and paclitaxel.⁶⁹ In those previously exposed to cisplatin, carboplatin is equally effective and less toxic.⁷⁰ In the case of contraindications or concerns over toxicity, alternatives include topotecan and paclitaxel or platinum combined with gemcitabine or vinorelbine. Unfortunately, cervical cancer remains a fairly chemo-resistant disease and median PFS and OS with 1st platinum based chemotherapy remain disappointing at 6 and 12 months, respectively.⁷¹ The 1st biological agent that was approved against HPV-related gynecological malignancies was the anti-angiogenic bevacizumab. Its addition to 1st line combination chemotherapy in patients with metastatic cervical cancer resulted in an improvement in both PFS and OS.⁷² However while standard platinum based cytotoxics are a therapeutic option available around the globe, the access to bevacizumab is much more limited, even in countries with robust economies.

Patients will inevitably progress during or after 1st line treatment for metastatic disease. Therapeutic options are very limited and 2nd line chemotherapy results in an overall response rate of 5-15% with a

median PFS of 3 to 4 months.²² New strategies are needed to improve outcomes for women with incurable cervical cancers. In highly selected situations of inoperable local relapses, salvage reirradiation strategies have been proposed but salvage probability remains low, while significant morbidities are associated with reirradiation.⁷³

A greater understanding of the biology of these malignancies has led to the investigation of novel systemic therapies.⁷⁴ Boosting the host immune system could promote an anti-tumor immune surveillance. One promising approach in these HPV-related cancers has been immunotherapy. Inhibitors of the immune checkpoint PD1 and its ligand PDL1 have been investigated, importantly some of these trials included patients with relapsed cervical cancer as well as vaginal and vulvar cancer. Anti-PD1 and PDL1 antibodies have resulted in significant tumor shrinkage in 15-20% of patients.⁷⁵⁻⁷⁷ While these rates remain modest, responses can be long-lasting and these data led to the FDA approval of the anti-PD1 pembrolizumab in patients with metastatic PDL1+ cervical cancer progressing after 1st line chemotherapy. Due to high drug cost and benefit in a relatively small proportion of patients, this approach is not widely available and few countries outside the United States have access to an immune checkpoint inhibitor (ICI) for their patients. Interestingly a recent publication has shown that anti-PD1 efficacy is increased in cervical cancer patients with high tumor mutational burden.⁷⁷

A number of strategies are currently under investigation to harness more effectively the anti-tumor immune response and improve benefit for patients. Trials testing the combination of PD1/PDL1 inhibitors with VEGF inhibition or CTLA4 blockade have resulted in intriguing response rates of 30% to 50% in small studies of relapsed cervical cancer.⁷⁸ Another approach to re-direct the host immune system against the tumor is the use of adoptive T cell therapy (ATCT). ATCT is a form of 'personalized' immune strategy whereby autologous tumor-specific T cells are harvested from a patient's fresh tumor specimen, selected, activated and expanded. These cytotoxic HPV-directed T cells are then re-infused into the patient. Early data suggest that response rate to ATCT is around 30%, and there have even been reports of prolonged complete remissions lasting years in a small number of patients.⁷⁸ Larger trials are required to confirm the true benefit of ICI combinations or ATCT with a special attention to tolerance.

The high costs and small incremental benefit in the palliative setting will likely limit the applicability of immunomodulatory approaches to the world-wide population of patients. The true potential benefit of immune-oncology agents may be in the management of primary disease where the intent is to increase cure rates. Trials are evaluating the benefit of adding an ICI to standard chemoradiotherapy for high risk LACC (NCT02921269; NCT04221945). If these trials demonstrate an improvement in OS, these could pave the way for a broader acceptance and reimbursement of ICIs for our patients.

In addition to immune-oncology, a greater understanding of the genomics of HPV-related gynecological malignancies has started to uncover potential actionable drivers (e.g. pathogenic

PIK3CA mutations, activating mutations in the *HER2* oncogene), with promising results from targeted approaches.^{79,80}

7. Management of symptoms

Early stage cervical cancers are frequently asymptomatic and diagnosed by systematic gynecological examination. When symptoms occur, those frequently include vaginal bleeding, possibly revealed by sexual intercourse, vaginal discharge. In advanced cases, moderate to severe pelvic pain is reported in up to 84% of patients and urinary or digestive symptoms may occur. It has been shown that patients' general quality of life and functioning were impaired before any treatment and that cancer was associated with high prevalence of physical and psychological suffering.⁸¹ Symptoms related to tumor resolve after treatment, but several treatment-related symptoms may persist in cancer survivors, including vaginal, gastro-intestinal and urinary symptoms.⁸² Patient quality of life may also be impaired by treatment-related menopause, as well as potential surgical sequelae (e.g. fistula). As highlighted prior, combination of surgery and radiotherapy is a major factor for long-term sequelae and functional impairment. Access to best supportive care and management of treatment sequelae is an important objective to improve quality of care. This includes sexual rehabilitation. However, in most of the cases cervical cancers occur in LMIC, where such resources are not available. In parallel, the symptomatic management of tumors-related symptoms is a priority objective. For patients who cannot be cured from their disease, local tumor progression is frequently associated with major complications, and quality of life is drastically impaired. Access to palliative treatments is therefore a priority, especially in the context of very advanced tumors that cannot be cured, either because of the stage, or because of unavailability of resources for providing efficient curative treatments (e.g. radiotherapy facilities). Access to high-level supportive care is unfortunately limited in LMICs.⁸³ A group of experts recently published a set of prerequisites for palliative management of cervical cancer, adapted to countries with minimal technological and human resources to improve palliative management in LMIC.⁸⁴ A common barrier to optimal care in many countries worldwide is the lack of universal health care (UHC) or UHC programs which exclude cancer care. Out-of-pocket expenses preclude many women from receiving curative or even palliative treatment for cervical cancer and drive other women and their families to financial destitution. It was shown that cervical cancer led to very high prevalence of moderate to severe financial distress among decedents, nondecedents, and family caregivers.⁸⁴

8. What are we learning from the COVID-19 crisis?

The current COVID-19 crisis pushes to classify the best option strategies and to balance the risk of spread of the tumor, the potential infectious risk and also the availability of some of these resources (operative room, intensive care units or respiratory system, anesthesiologist or nurse-anesthetists) particularly at the peak of the outbreaks (top of the waves). With the COVID-19 crisis, disruption of elective health services related to systematic cervical screening and delays in early stage lesions diagnosis may lead to a higher incidence of LACC and increase health care disparities worldwide.⁸⁵

Treatment delays also have a strong impact. In addition, patients with LACC are at higher risk for severe events related to COVID-19 infection. Different societies have finalized recommendations for overall management or specific requirement for RT or brachytherapy in gynecological cancers at the time of COVID-19 crisis.⁸⁶⁻⁸⁹ The key message is to prioritize according to the overall prognosis of the tumor and then to delay the surgery of early stage cervical cancer in a less acute period without affecting the overall prognosis (risk of progression of the disease extending the delays) and to promote chemoradiation in more advanced diseases, decreasing the number of fractions to less expose patients to hospital visits. The deleterious impact of surgical delays was established and is linked to patient age and disease stage.⁸⁹ In this context, the best option could be to consider treating actively the patient with an optional treatment (for example, preferring upfront RT combined with brachytherapy in early stage tumors) instead waiting a too long delay before accessing to a radical surgery. In a large retrospective study, excellent oncological outcome was reported after non-surgical treatment of stage IB cervical cancer, based on radiotherapy plus image-guided brachytherapy.⁹⁰ This is why the current COVID-19 situation had also a direct impact on the current topic. There is slight porosity between standard and optional treatments detailed in **Table 2** according to the geographical availability of the different treatment and local expertise.

8. Conclusion

Promoting access to high-level treatment requires that national health researchers and policymakers have access to information about the global investment needed to ensure adequate cervix cancer therapeutics (**Figure 3**). The development of health data systems linking treatment information to cancer registries and death registries may be an important step to better recognize the impact of quality of care on patient outcome. Large database generated from such registries are particularly relevant to monitor the impact of health care policies, the benefit of therapeutic innovation, and the beneficial consequences of increasing compliance to modern standards. Medico-economic evaluations are also required to sensitize decision makers to the real benefit of increasing quality of cervical cancer care (e.g. implementation of image-guided brachytherapy), for patients but also for society. In addition to vaccination and early screening, increasing accessibility to high-quality treatments should be a complementary priority. This implies strengthening investments into imaging modalities, surgery, radiotherapy, brachytherapy and best supportive care to achieve this objective.

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FIGURE LEGENDS

Figure 1. General principles of treatments in cervical cancers

* *see table 2 for more details*

CC: cervical cancer; EBRT: external beam radiotherapy; MRI: magnetic resonance imaging; IMRT/ intensity modulated radiotherapy; IGRT: image-guided adaptive radiotherapy; LVI: lymphovascular involvement; MTD: multidisciplinary team discussion; PALND: para-aortic lymph node dissection; PET/CT: positons emission tomography/computed tomography; pN+: histopathologically proven lymph node extension; PVC: primary vaginal cancer; VC: vulver cancer

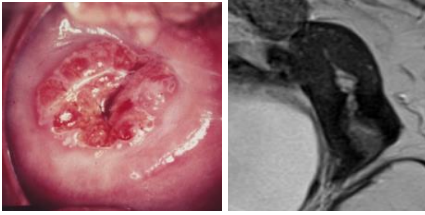
Figure 2. Three decades of phase III trials involving surgery (staging or tumor resection) and including overall survival as primary end-point.

Figure 3. Strategies to increase accessibility to high-level treatments over the globe for cervical cancers

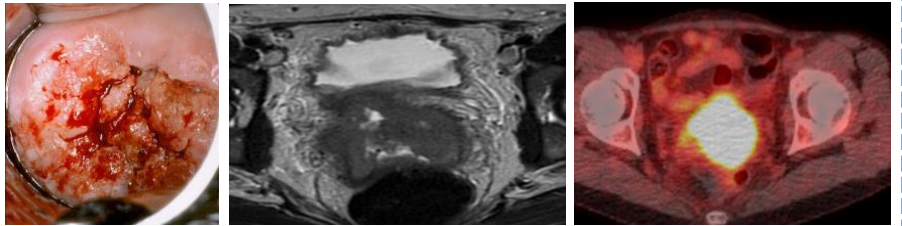
BT: brachytherapy; IMRT: intensity modulated radiotherapy; LMIC: low middle income countries; RT: radiotherapy

STAGING: Clinical examination, MRI +/- PET/CT +/- PALND

Early stage disease



Locally advanced disease



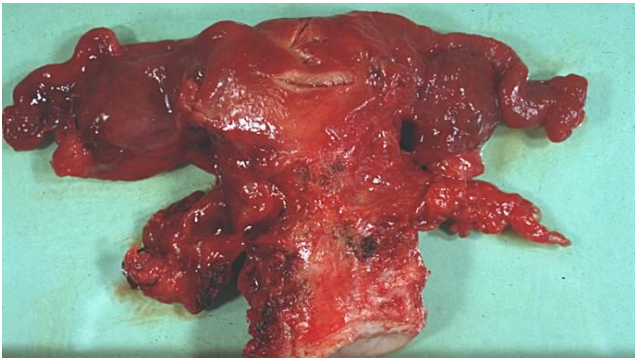
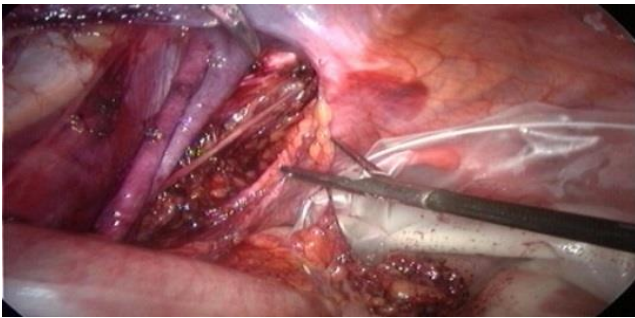
Locally advanced disease and/or adjuvant treatment expected

No ↓

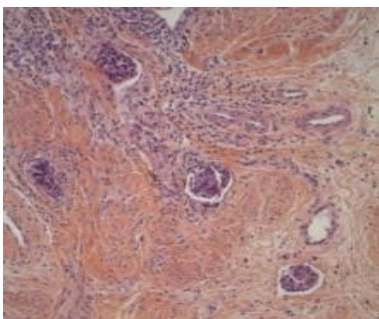
MTD

↓ Yes

Surgery (LN and primary T)



Defavourable histopathological factors*
(e.g. pN+, LVI, margins, stroma/parametrial invasion, tumor size)

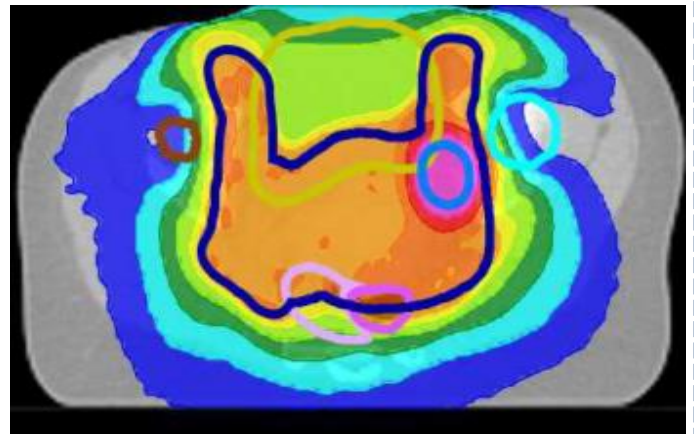


MTD

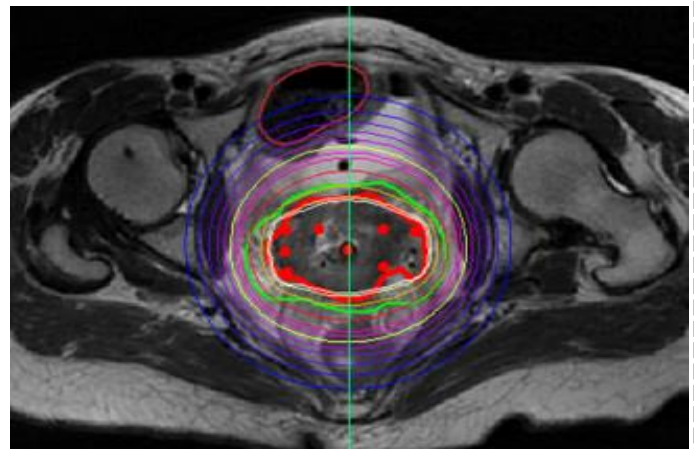


(Chemo)radiation

EBRT
+/- concurrent chemo
(tumor in place, high risk features)
Ideal technique: IMRT/IGRT



BRACHYTHERAPY BOOST (not optional)
Ideal technique: MRI-guidance



Chang 2000

NACT + RS versus RT; (bulky IB-IIA)
 No significant difference
 PMID: 10764435

Benedetti-Panici 2002

NACT + RS vs exclusive RT; (IB2-III)
 NACT+RS > conventional RT
 PMID: 11773168

Morice 2012

RS vs no RS after complete response after CRT (IB2-II) *
 No benefice of completion
 HT PMID: 22234626

Gupta 2018

NACT + RS vs CRT (IB2- IIB)
 CRT> NACT+RS
 PMID: 29432076

Landoni 2001

Class II vs class III RS (IB-IIA)
 Equivally effective approaches
 PMID: 11136561

Lai 2003

Surgical vs clinical staging (LACC) *
 Detrimental effects of surgical staging
 PMID: 12694671

Yang 2016

NACT + RS vs RS (IB2-IIB)
 NACT did not improve OS
 PMID: 26115978

Kenter 2020

NACT + RS vs CRT (Ib2-IIB)
 No difference in 5-year OS

Landoni 1997

RS vs RT (IB-IIA)
 Both treatments equivalent
 PMID: 9284774

Kays 2003

RT with and without extrafascial TAH (Bulky IB);
 No clinically important benefit with the use of extrafascial hysterectomy.
 PMID: 12798694

Katsumata 2013

NACT + RS vs RS (IB2-IIB)*
 Less adjuvant RT with NACT
 PMID: 23640393

Marnitz 2020

Surgical versus CT-staging prior to CRT (IIB-IVA)
 No difference in DFS
 PMID: 33293284

Cetina 2013

BT versus RS after CRT (IB2-IIB)
 RH after EBRT-CT not superior to standard BT
 PMID: 23609186

Ramirez 2018

Minimally Invasive versus Abdominal RH (IA1-IB1)
 Minimally invasive RH associated with poorer DFS/OS
 PMID: 30380365

Trials testing strategies

Trials testing technique

Trials testing staging

* Prematurely closed

OBJECTIVES	STRATEGIES
Access to minimum requirements in LMICs	Low-cost imaging modalities: CT scan, ultrasound Additional cobalt teletherapy or high energy linear accelerators Brachytherapy Concurrent chemotherapy Supportive care (palliative RT – analgesics– cytotoxic)
Rationalisation	Better organization of existing resources Technical cooperation programs Mapping of available resources Referral to expert centers (e.g. high-tech brachytherapy, salvage treatments) Avoidance of additional treatments
Promoting high-quality treatments	Improving staging modalities (MRI, PET-CT) Upgrading RT facilities (MRI, PET-CT, IMRT/IGRT) Image-guided adaptive RT Sexual rehabilitation – psychological support Access to molecular targeted agents
Accompanying innovation	Introduce modern RT techniques, adaptive RT, artificial intelligence Drug combination trials, immunotherapy trials, molecular profiling Surgical research (e.g. fertility sparing approaches)
Increasing compliance to standard	Collaborative network and twinning programs Surgical mentorship, companion-training programs International guidelines Adjust guidelines for LMIC to modalities available Promote multidisciplinary discussion Quality indicators Accreditation processes Involvement of international and national societies

Table 1. Burden of cervical cancers (all, and associated with HPV types).

Proportion of **cervical** cancers attributable to HPV infection (a, top); fraction of hrHPV+ cancers positive for HPV16/18 (b, top); fraction of hrHPV+ cancers that is associated with the 7 most oncogenic types (HPV16/18/31/33/45/52/58) (c, top); proportion of all cancer cases (d, top); proportion of all cancer deaths (e, top); world-age-standardised incidence rate (cases per 100,000 women-years (f, top); world-age-standardised mortality rate (deaths per 100,000 women-years (g, top); total number cases (a, bottom); number of cases associated with hrHPV (b, bottom); number of cases associated with HPV16/18 (c, bottom); number of cases associated with the 7 most oncogenic HPV types (d, bottom); number of deaths (f, bottom).

(a)	(b)	(c)	(d)	(e)	(f)	(g)
Attributable to hrHPV¹	Fraction + for HPV16/18¹	Fraction + for 7 hrHPV types¹	Proportion of all cancers	Proportion of all deaths	ASIR	ASMR
					/100,000 WY	
100%	70.8%	89.5%	6.9%	7.5%	13.1	6.9
Cases all	Number of cancer cases associated with			Deaths all		
	hrHPV	HPV16/18	7 hrHPV types			
570,000 ⁴	570,000	403,560	510,150	311,400 ⁴		

Table 2. Upfront indications of primary treatment in cervical cancers

STAGE	STANDARD TREATMENT	OPTION
Early stage Tumor limited to the cervix, and or tumor ≤4cm without LN extension)	Radical hysterectomy tailored to tumor size* + full PLND or SNB Adjuvant radiotherapy indicated according to histopathological findings (tumor size, lymphovascular invasion, deep stroma infiltration)	Pelvic radiotherapy followed with a brachytherapy boost
Locally advanced stage Tumor extending outside the cervix and/or > 4 cm and/or with LN involvement	Pelvic radiation and concomitant chemotherapy followed with a brachytherapy boost +/- para-aortic irradiation according to radiological and pathological findings	Type C2 radical hysterectomy** + full PLND is an option in selected patients with tumor limited to the cervix (or with minimal vaginal involvement) without LN involvement. Adjuvant radiotherapy indicated according to histopathological findings (tumor size, lymphovascular invasion, deep stroma infiltration) +/- concurrent chemotherapy (standard if pN+) Para-aortic lymph node staging in patients having pelvic lymph node spread ***

*: Radicality of the parametrial dissection tailored to the tumor size, local risk factors (lymphovascular involvement if known and depth of stromal invasion) and the results of current ongoing trial (SHAPE trial)

** : According to the Querleu-Morrow Classification. Such upfront surgery could be an alternative option in patients without negative prognostic factors and/or suspicious pelvic node on preoperative workup

*** Many teams consider PALND in patients with pelvic LN involvement on PET/CT and no FDG uptake in para-aortic LN to avoid unnecessary and potentially toxic prophylactic para-aortic irradiation. If performed, para-aortic surgical staging should be carried out using a laparoscopic approach and should not delay treatment initiation.

LN: lymph node; PLND: pelvic lymph node dissection; PALND: para-aortic lymph node dissection; SNB: sentinel node biopsy