

CERVICAL CANCER IN THE CURRENT AGE: QUO VADIS?

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ABSTRACT

The recognition of human papillomavirus (HPV) as the main cause for cervical cancer transformed prevention and management, leading to widespread HPV vaccination and a change from Pap smear to HPV-based screening. Therapeutic progress includes advances in image-guided radiotherapy, concurrent chemoradiation, and the integration of targeted biologic agents such as anti-angiogenics and immune checkpoint inhibitors. Emerging technologies, including digital pathology, artificial intelligence-assisted diagnostics, and immunohistochemistry-based profiling, are improving accuracy and enabling personalized treatment. New immunotherapeutic approaches, including tumor-infiltrating lymphocyte therapy, offer new options for advanced or recurrent disease. Despite these advances, global disparities persist in access to vaccination, early detection, and comprehensive care. Achieving the World Health Organization's elimination targets will require coordinated efforts to expand preventive strategies and ensure timely, equitable treatment.

Keywords: cervical cancer; innovative treatment; digital pathology.

Introduction

Cervical cancer currently is the fourth most common cancer in women worldwide, with the greatest burden in low- and middle-income countries where access to screening and vaccination is limited (1).

The history of cancer is as old as the history of mankind, but the first discovered official report of this disease was in 3000 B.C in the Edwin-Smith papyrus – a partial copy of an Egyptian textbook about trauma surgery. Although the term used at that time was not „cancer”. In that text, 8 cases of breast tumors or ulcers were described and were excised by using a device called a „fire

drill”. Also, the text mentions that for this type of disease „No cure exists” (2).

The etymology of the word cancer comes from the Greek language and Hippocrates was the first to use the term „carcinos” and „carcinoma” in order to describe ulcerative or non-ulcerative tumors. Several centuries later, the Roman doctor Celsius translated the term in Latin as „cancer” (2).

During the 18th century several other observations were made regarding tumors that were mostly discovered after autopsies. Some physicians suggested that those tumors could be removed if were „movabeale”, but lack of anesthesia (substances and techniques) made that

endeavour impossible (2).

The first report about cervical cancer was made in the 19th century in Italy and mentioned the different frequency of this pathology in the female population. In 1842 Rigoni-Stern reports that this type of tumor is more frequent in married and widowed women compared to female nuns (3).

After investigation of several infectious agents, Harald zur Hausen was the one that demonstrated with outmost certainty the viral origin of cervical cancer (4). He was awarded the Noble Prize for Physiology/Medicine in 2008 for the discovery that humanpapilloma virus (HPV) are the triggering factor for cervical cancer.

Presently, cervical pathology is dominated by HPV infection and its neoplastic consequences and HPV infection is considered necessary for the development of cervical dysplasia that can evolve to cervicl cancer (5). However it is worth mentioning that a significant proportion of cervical cancer is not associated with HPV infection, especially cervical adenocarcinoma. Additionally, similar to other anatomical regions like the oropharynx or vulva, HPV independent cervical carcinoma are more aggressive compared to the HPV dependent ones.

Cervical cancer is a disease that can affect women at any age, but is more frequently diagnosed in women aged 35-44 years (6). While efforts and progress were made regarding early detection and identifying the optimal treatment to ammeliorate survival , there are still many cases in which the dedicated management doesn't have the best outcome. Estimation prediction. It is estimated that, in the absence of adequate measures, between 2018 and 2030 the annual number of new cases of cervical cancer will increase from 570,000 to 700,000, and the annual number of deaths will rise from 311,000 to 400,000 (7).

Constant research is needed to identify new therapeutical targets that may lead to a prolonged survival and better quality of life.

Early and Con temporary Milestones

Cervical cancer management matured through sequential publichealth and therapeutic innovations that set the stage for later

modalityspecific advances. Key turning points were the introduction of cytologic screening, the identification of HPV as the causal agent, and the development of prophylactic HPV vaccines, each reshaping prevention and treatment priorities.

The major key turning points are as follows:

- Pap-smear cytology was introduced as a screening test in the 1940s-1950s. Romanian physician Aurel Babeş presented in the French medical press an article about diagnostic of cervical cancer by using a smear in the 1920s (8), but the one that was credited for introducing this procedure was Greek physician Georgios Nikoulaou Papanicolaous (9).
- HPV is established without a doubt as the causative agent for cervical carcinoma in then1980s-1990s. This discovery shifted the focus to viral etiology and vaccine development (10).
- Radical surgery and lymphadenectomy become more refined during the 1990s-2000s, hence standardized radical hysterectomy for invasive disease and later fertility-sparing options are explored (11)
- Evolution of radiotherapy – both radiotherapy and brachytherapy become image guided during the 1990s-2010s which offers improvement in dose delivery and organ sparing techniques for locally advanced disease (12). This process is ongoing as professionals in the medical field try to find the best solutions for radiation treatment in oncological patients.
- Platinum-based chemoradiation becomes standard in locally advanced cervical cancer during the 2000-2010s as it was proven that concurrent cisplatin improved disease control versus radiotherapy alone (13).
- Treatment with the anti-angiogenic agent named Bevacizumab (anti-VEGF) demonstrated survival benefits in advanced disease in 2014. This represented the beginning of a new era in cervical cancer treatment as both anti-agiogenic therapy and monoclonal antibodies where introduced into systemic care in cervical cancer (14).
- Therapy welcomes other newer options

as immune checkpoints inhibitors and antibody drug-conjugates enter clinical trials and subsequent approvals starting from 2016 – these therapeutical agents reshape option treatment for metastatic or recurrent disease (15,16,17).

- Prophylactic HPV vaccines are implemented widely and WHO proposes and urges for elimination targets – this action shifts the standard of care as primary prevention becomes the main focus and long term eradication strategies are developed (18)
- FIGO revised its staging guideline for cervical cancer in 2018 proposing a slightly different staging system that offered better stratification of patients (19).
- Clinical guidelines emphasize the central role of HPV infection in cervical cancer and recommend shifting screening test from routine Pap-smear to mandatory HPV testing (20).

Regarding treatment options, clinical guidelines emphasize choosing the treatment plan according to stage, patient comorbidity and fertility goals (13,20).

Meanwhile surgery progressed from ablative local procedures to a range of tailored interventions balancing oncologic control and fertility preservation. Early excisional therapies like conization, treated precancerous lesions; radical hysterectomy with pelvic lymphadenectomy became the standard for invasive early disease, while fertility sparing trachelectomy and less radical procedures have been validated for selected cases in early stages of the disease (11).

Evidence supports conservative surgery (cone, simple hysterectomy, radical trachelectomy) in carefully selected early stage patients to preserve fertility without compromising oncologic outcomes (11).

Lymph node management changed as sentinel lymphnode techniques and selective nodal dissection reduced morbidity compared with routine extensive pelvic/paraortic dissection (11).

Pelvic exenteration maintains its salvage potential, but is indicated in rare, rigorously selected cases and requires multidisciplinary

expertise. The procedure also carries important mortality and morbidity risk (11).

Radiotherapy advanced from 2D external beams and fixed brachytherapy prescriptions to imageguided, adaptive techniques that improve local control while reducing toxicity. This transition to 3D conformal planning, intensity modulated and image guided external beam radiotherapy (IGIMRT) and 3D image guided adaptive brachytherapy (3DIGABT) represents the major technological shift in the last two decades (12).

Also, concurrent platinumbased chemotherapy with radiotherapy became the standard for locally advanced cervical cancer (LACC), driven by randomized data demonstrating improved survival when chemotherapy is administered with definitive radiotherapy (13).

Past and ongoing trials are evaluating the integration of immunotherapy with chemoradiation and testing whether systemic immune modulation can enhance definitive local therapies (21,22).

Systemic therapy evolved from singleagent cytotoxics to combination platinum regimens, to targeted antiangiogenics and now immunotherapies and antibody–drug conjugates in advanced disease. Platinumbased doublets (cisplatin or carboplatin with paclitaxel) formed the backbone for metastatic and recurrent disease before targeted agents were added (23).

Combinations that pair cytotoxic chemotherapy with antiangiogenic agents and immunotherapy are a major focus of contemporary trials aiming to prolong survival beyond historical chemotherapyonly expectations (24).

Prevention can be obtain through HPV vaccination and improved screening (HPV nucleic acid testing and molecular triage). These measures are central in reducing cervical cancer incidence, while new systemic and immune therapies are redefining care for advanced disease. The widespread adoption of prophylactic HPV vaccines, that evolved from bivalent to quadrivalent and currently nonavalent vaccines, targets highrisk strains and is the primary global prevention tool promoted by WHO elimination targets (18).

Although prophylactic vaccines prevent

incident infection with vaccine-targeted HPV types and reduce future cancer burden, HPV vaccination has certain limits. HPV vaccination does not clear established infections or treat lesions that are ongoing at vaccination time (18,25).

Achieving WHO targets (vaccinate, screen, treat) requires infrastructure and medical access improvements while mortality remains concentrated in low and middle-income countries. Countries in this category lack programs that easily offer routine vaccination, screening availability, delayed management of preinvasive lesions and/or face difficulties for the patients to access the full therapeutic sequence (19).

So far, medical literature and institutions failed to provide a quantification for the population-level timeline for global vaccination coverage or to predict exact eradication timelines.

Innovative Options

Innovative options are included in the diagnosis of preinvasive or invasive lesions, but also management of invasive lesions.

Digital pathology and the aid of AI are the newest options for diagnosis. Digital pathology represents the sum of all activities for acquiring, managing, sharing and interpreting pathological information – slides and data – in a digital environment. Digital slides are manufactured by capturing glass microscope slides with a dedicated scanner, resulting in a high-resolution image that can be viewed on the computer screen or other mobile devices. This type of examination offers several benefits such as: better analysis of the examined slide, reduced error rate, increased collaboration among medical specialists, possibility of remote work, education and training of medical personnel and improved opportunities for scientific research and development (26,27).

AI-based methods, through algorithmic and statistical models, identify patterns in the examined slide and make predictions that aid the decision-making process. By using AI methods, the decision-making process becomes more efficient and accurate and subsequently a more precise diagnosis is obtained (28,29). Also AI methods add several advantages to the examination of abnormal cells like increased cost-effectiveness

and speed, reduced workload intensity, time consumption and interobserver variability (30).

Immunohistochemistry (IHC) represents the evaluation of the tissue specimen using immunohistochemical biomarkers that are antibodies that detect specific antigens in the examined tissue. This method allows the pathologist to visualize and assess certain cells or proteins and contributes to the diagnosis and classification of diseases, especially malignant pathologies.

The use of IHC has progressively expanded and in present times it is used to evaluate predictive and prognostic markers in several malignant diseases (31,32). Although there are guidelines for the standardized analytical validation of IHC tests, the number of available markers continues to grow, and for some of them, reporting and interpretation may vary (32,33). The integration of AI-based methods with immunohistochemical testing enhances the performance of the pathologist ensuring a faster, less time-consuming and more precise diagnosis (34-38).

IHC contributes to a better understanding of the biological complexity of cervical carcinoma and potential usefulness of the IHC biomarkers for personalized therapeutic sequences and post-treatment monitoring.

An innovative treatment option in cervical cancer is represented by TIL therapy, this type of therapy consists of extracting tumor-infiltrating lymphocytes (TILs) from the tumor, which originate from the patient's own immune system and consists of the host's specific immune response against malignant cells (39). The principle of this type of therapy is to harness the patient's own immune cells to fight against cancer. This type of therapy was first used in cervical cancer in 2015 in nine patients diagnosed with advanced recurrent disease and metastases, resulting in complete remission in 2 patients and partial remission in one (40). Other clinical trials published in 2015 (41) and 2019 (42) showed promising results. Ongoing trials on TIL therapy are being conducted by different biotechnology companies (43-46). Future therapeutic opportunities include the use of genetically modified TILs (47) and combinations with traditional therapies such as chemotherapy

and radiotherapy (48,49), as well as combinations with other therapeutic approaches, such as immune checkpoint inhibitors (50,51) and other targeted therapies like anti-angiogenic agents.

Since 2014 an anti-angiogenic agent – Bevacizumab, anti-VEGF agent - has been approved for the treatment of cervical carcinoma. In the last decade though, another therapeutical anti-angiogenic agent is being tested: carotuximab, a monoclonal antibody targeted against endoglin, is showing promising results in several clinical trials (52-56).

Immunotherapy with pembrolizumab – an immune checkpoint inhibitor monoclonal antibody – has been approved by the FDA in 2024 for the treatment of persistent, recurrent or metastatic cervical cancer resistant to chemotherapy. Clinical trials have showed that this drug significantly improved survival of cervical cancer patients (56-59).

Life After Cancer Diagnosis

Cancer treatment and post-treatment management haven't undergone major changes in the last 20 years. Extensive surgery (where it is indicated), radiotherapy, brachytherapy and chemotherapy are still the central part of the therapeutical plan.

With the help of clinical features such as stage, pathological features such as histological grade and invasion of the lymphovascular space and immunohistochemical analysis that can ascertain different biomarkers, pannels that offer better risk strtification can and must be developed. These pannels could be useful in personalising therapeutical strategies and post-treatment management that in turn could offer a longer survival period and better quality of life.

Traditional cancer treatment has several disadvantages – one of which being important changes in the pelvic cavity induced either by extensive surgery or radiation treatment. These changes are generally associated with the onset of induced menopause (surgically or otherwise). Urinary disturbances, vaginal dryness or a combination of those two can be managed in a cost-effective and simple way by Kegel exercises or combined Kegel exercises with intravaginal estriol therapy for patients in which estriol

therapy is permitted (60,61).

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