REVIEW ARTICLE

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History of radiotherapy in the treatment of uterine cervix cancer: an overview

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INTRODUCTION

Since the very first beginning of the use of radiation in cancer treatment, cervical cancer has been one of the most suitable diseases for this application because it has a topography that is easy to assess for both diagnosis and the new emergent technology.

This manuscript will present a brief overview of the evolution of radiotherapy in the treatment of cervical cancer, with the main achievements and perspectives in the field.

HISTORICAL NOTES

The first treatment of cervical cancer using radium alone was performed by Robert Abbe, an American surgeon, in 1904[1]. In 1912, Forsell reported clinical healing in several cases of inoperable cervical carcinoma with radium application in Stockholm[2]. However, most part of the method was developed in France, where in 1913, Dominici, Cheron, and Rubens-Duval reported 158 cases[1]. Soon, there was a worldwide recognition of the value of the new element, and its use was adopted in most countries[1]. Those implants paved the way to what is now described as brachytherapy.

After 1916, roentgen rays started to be more efficient for the treatment of deeper parts of the body with the possibility of delivering large doses to the uterus. Roentgen rays alone or in combination with radium implants were then used for the treatment of cervical cancer[1]. In the early 1930s, the reported cure rate for all stages of cervical cancer was around 22% using this strategy[1].

In the decade of 1950–1960, randomized trials founded many principles of radiotherapy for cervical cancer. It was established that for stages I and II, two insertions of radium alone within a period of 10 days would be the treatment of choice. For stage III (or II, with infiltration of the parametrium), x-ray therapy should be combined with the radium implants for an overall treatment course of 5–6 weeks. For stage IV, megavoltage x-ray therapy of the pelvis with an additional low-dose radium contribution or a single palliative radium insertion was recommended[3].

As an outstanding treatment for cervical cancer, irradiation presented increasing rates of cure and long-term survival for those patients. Radiotherapy was used either in association with surgery, or alone, in locally advanced disease. Standard treatment consisted of external beam irradiation and intracavitary/interstitial brachytherapy, as it is used until today.

ASSOCIATION OF RADIOTHERAPY WITH SURGERY

Historically, the association of irradiation with surgery has always been attempted. Results varied according to disease stage and treatment indications. Since the association could elevate the complication rates, better patient selection and treatment strategy definitions were warranted.

For stages I and IIA tumors, the results of surgery or radiotherapy alone are equivalent with survival rates of 70–90%. The modalities, however, differ in the associated morbidity and types of complications. Several prospective, randomized studies reported comparable survival outcomes with radiotherapy or radical hysterectomy for stages IB and IIA. The most remarkable one was from Landoni et al.[4] who observed no significant differences in overall 5-year survival (83%), disease-free interval (74%), or relapses (25%), with twice the morbidity in the surgery arm. Even for bulky tumors (4 cm or more), the Gynecologic Oncology Group (GOG) trial 71[5] demonstrated the lack of benefit of the association of adjuvant surgery after irradiation in these patients with a 60–65% 5-year survival rate.

In the adjuvant scenario, postoperative radiotherapy is currently indicated based on the criteria defined by GOG 92 study ("Sedlis criteria") for the definition of high- and intermediate-risk

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disease. Lymph node involvement, parametrial invasion, and positive/close margins (3–5 mm) are considered high-risk factors with an indication for post-operative pelvic irradiation. Lymphovascular invasion, depth of stromal invasion, tumor size, and histological type are considered intermediate- or low-risk factors and should be evaluated individually for an indication of postoperative irradiation[6,7].

Currently, it is wise to choose the treatment strategy based on an evaluation of the risk factors. If an indication of adjuvant irradiation is a possibility, then radiotherapy should be the preferred treatment, as historically proposed by Landoni, a surgeon, in his landmark publication.

RADIOTHERAPY ALONE OR COMBINED WITH CHEMOTHERAPY?

After the establishment of radiotherapy as the standard of care for locally advanced cervical cancer (LACC), the expected overall 5-year survival remained stable, around 40–60%, including all stages. Thus, new treatment strategies emerged over the years.

In 1999–2000, the publication of five randomized trials[8-12] that evaluated radiation alone versus chemoradiation made the National Cancer Institute of the United States of America release an announcement: all patients with high-risk invasive cervical cancer should be treated with the combination of radiotherapy and chemotherapy. The combined treatment presented an absolute benefit of 10–13% with an improvement in overall and progression-free survival and a reduction of local and systemic relapses[13].

Later (2008), a more consistent 6% benefit in survival (from 60 to 66%) favoring the chemotherapy groups was demonstrated[14] with an increase in acute toxicity. Of note, platinum-based chemotherapy should be used.

In most of those studies, patients with stage III tumors were underrepresented. A phase III Brazilian study[15,16], including only patients with stage IIIB squamous cell carcinoma, demonstrated a significant benefit in disease-free and overall survival in favor of the combined regimen. Thus, concomitant chemoradiation proved to be beneficial for all patients with LACC.

Studies evaluating neoadjuvant chemotherapy, with different drug combinations, followed by irradiation alone or concomitant with chemotherapy, failed to demonstrate any benefit, with even a detrimental effect of the neoadjuvant strategy in some[17,18].

The same occurred with adjuvant chemotherapy after chemoradiation, where the evidence of the use of this strategy is not yet encouraging[19].

Therefore, the current standard of care for LACC is concomitant radiochemotherapy. Whenever chemotherapy is not possible to deliver, the historical regimen of radiotherapy alone remains the standard of care.

TECHNOLOGICAL DEVELOPMENTS AND ACHIEVEMENTS

Technological developments in radiotherapy, allied with the computing sciences and imaging evolution, diversification, and availability, allowed the improvement of treatment delivery. From an era of bidimensional (2D) techniques based only on surface anatomy and radiographs, generation of tridimensional (3D) image reconstructions of patient's and tumor's anatomy from computed tomography scans became possible. A range of possibilities emerged with the increased use of 3D conformal radiotherapy, followed by intensity-modulated radiotherapy and more advanced techniques that are available nowadays (volumetric modulated arc therapy [VMAT], image-guided radiotherapy [IGRT], radiosurgery, and stereotactic radiotherapy, among others). A better definition of tumor anatomy and topography could improve results by preventing eventual geographic misses[20], and intensity-modulated techniques that have the property of better conform the target have been demonstrated to be less toxic[21-23] (Figure 1).

Brachytherapy followed the same path, evolving from a simple insertion of radium capsules in the uterine cavity by visual and hand-guidance only to 2D treatments using radiographs and 3D image-guided techniques, based on volumetric images of magnetic resonance imaging and/or computed tomography scans. The development of different radioactive sources (Cesium-136, Cobalt-60, and Iridium-192), applicators, afterloading systems, and high dose-rate brachytherapy made the treatment safer for both the patient and the staff. The simple fact of better defining the tumor volume and dose delivery with the image-guided approach increased local control and survival, with lower toxicity[24-27] (Figure 2).

Approaches with proton therapy and stereotactic body therapy may present dosimetric advantages over the other techniques. For cervical cancer, attempts have been made to replace brachytherapy by these techniques or to use them as a boost for patients where brachytherapy is not feasible. However, neither technique has yet proven to be superior[28,29].

The historical and basic concepts of cervical cancer treatment are keeping the same over the years, but the technologies are still evolving and are promising in the oncological treatment scenario. New drug combinations, associations with immune and targeted therapies, and more precise radiation delivery possibilities are on the way[30].

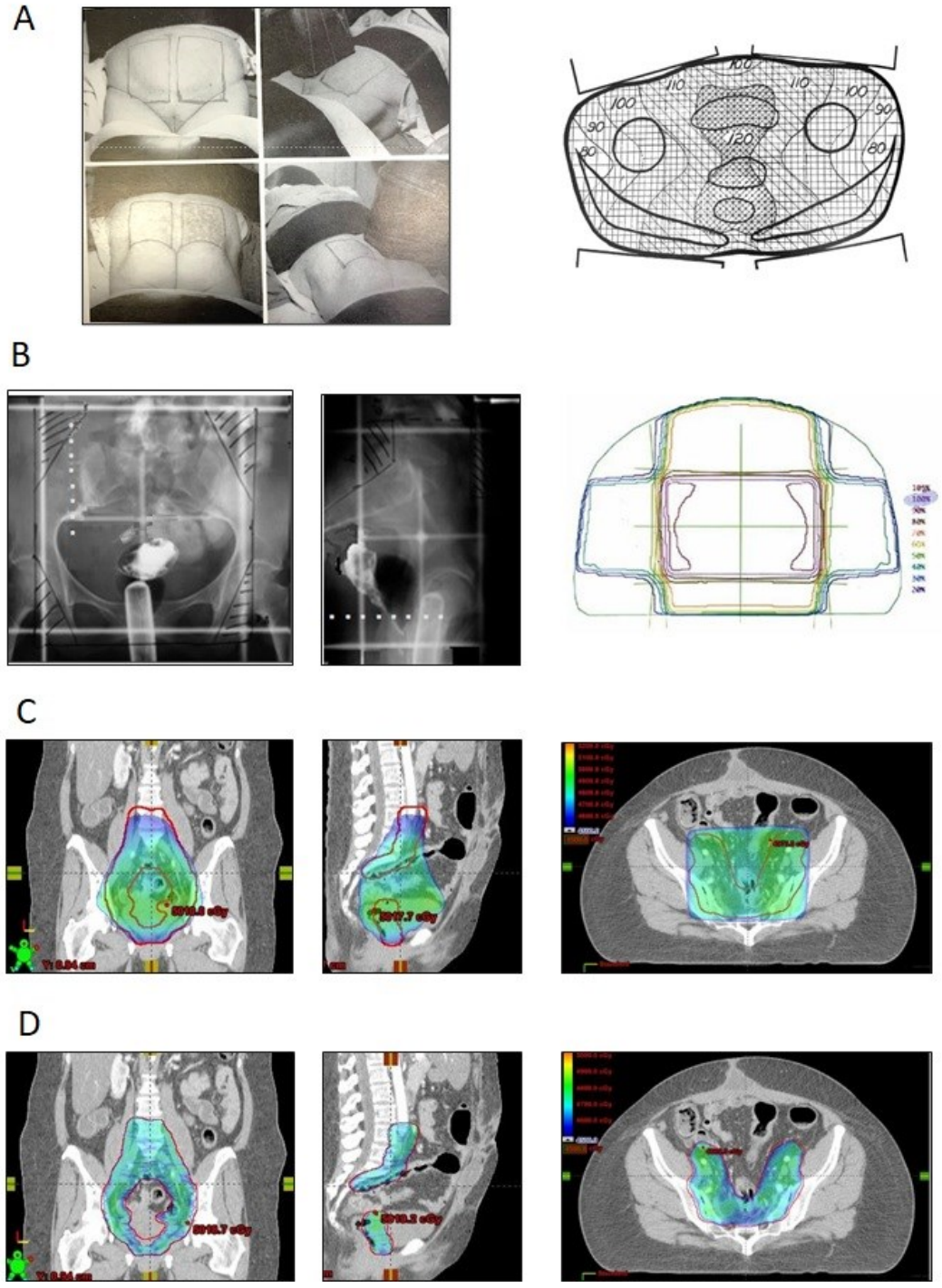

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Figure 1. Evolution of radiotherapy for cervical cancer over the years. External beam irradiation. (A) Bidimensional (2D) technology, beginning with surface anatomy only and roentgen therapy, followed by panel (B) orthogonal x-rays for fields definition, and the correspondent dose distribution below. (C) Three-dimensional (3D) technology based on computed tomography scans with volumetric image reconstruction and the respective dose distribution. (D) Intensity-modulated radiotherapy (IMRT) dose distribution. Comparing panel (C) with panel (D), target coverage is the same, but IMRT provides better normal tissue sparing.

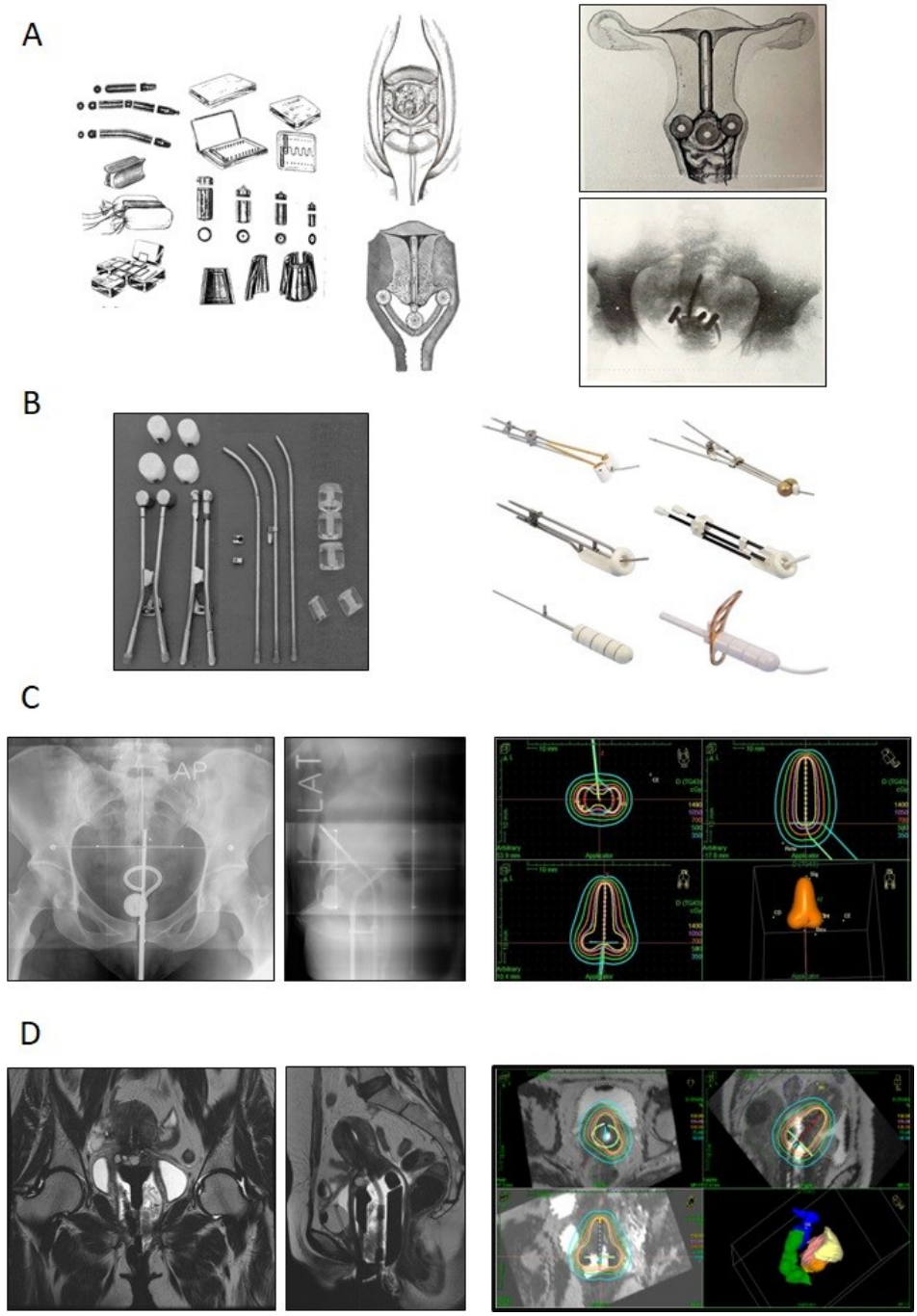

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Figure 2. Evolution of radiotherapy for cervical cancer over the years. (Brachytherapy). (A) Diagrams of among the first brachytherapy pre-loaded applicators and their positioning with available imaging in the right. (B) Low dose-rate (left) and high dose-rate (right) brachytherapy gynecological applicators, both for afterloading systems. (C) Radiographs and dose distribution of high dose-rate intracavitary brachytherapy based on dose points (bidimensional). (D) Magnetic resonance images of image-guided gynecological brachytherapy, with the applicator in place and the correspondent volumetric dose distribution.

REMARKS AND CONCLUSION

Cervical cancer is the fourth-most frequently diagnosed and the fourth-leading cause of cancer death in women worldwide. In low- and middle-income countries, it occupies the first place, both in incidence and mortality[31,32]. It affects mainly young women with a higher number of childbirth, and the most important risk factor is the herpes papilloma virus (HPV) infection[31]. Therefore, it is imperative to study and understand the disease for better prevention, treatment, and control.

Since the beginning of the 20th century until today, the combined treatment of external beam irradiation with brachytherapy has become the standard of care for advanced cervical cancer. The irradiation techniques have evolved, combined treatments have improved the results, and complications are being reduced and better controlled over time. Nevertheless, the cure for invasive cervical cancer still relies on the combination of treatment with radiotherapy.

In 2018, the World Health Organization (WHO) launched a global call for action toward the elimination of cervical cancer in the world[33]. "Each country should meet the 90-70-90 targets by 2030 to get on the path to eliminate cervical cancer within the next century.

- Vaccination: 90% of girls fully vaccinated with the HPV vaccine by the age of 15;
- Screening: 70% of women screened using a high-performance test by the age of 35, and again by the age of 45;
- Treatment: 90% of women with pre-cancer treated and 90% of women with invasive cancer managed."

The management of invasive cervical cancer was addressed[34], and several other linked initiatives around the world were taken.

We hope that, not so far in the future, this disease will no longer exist. Until then, radiation will remain as one of the cornerstones in the treatment of this disease.

AUTHORS' CONTRIBUTIONS

HAC: Conceptualization, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing. **GPM:** Conceptualization, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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