IJFANS INTERNATIONAL JOURNAL OF FOOD AND NUTRITIONAL SCIENCES

ISSN PRINT 2319 1775 Online 2320 7876

 Journal Volume 11, S.Iss 06, 2022

Recent Developments in Radiation Oncology for Cervical Cancer Therapy

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Abstract.

Background: Over the past two decades, there has been significant advancement in the management of cervical cancer, particularly in the domain of definitive chemoradiotherapy for locally advanced cervical cancer (LACC). Indeed, radiation treatment paradigms have shifted from a two-dimensional (2D) approach solely based on anatomical bony landmarks, to an image-guided three-dimensional (3D) approach, with the goal of delivering doses more precisely to clinical targets with an increased sparing of organs-at-risk. Methods: This is a narrative review on the advances in radiation technologies for the treatment of cervical cancer. Using the PubMed database, we identified articles published in English up until November 18, 2021 on the treatment of LACC with external beam radiotherapy (EBRT) and brachytherapy. A search of the Clinicaltrials.gov and Clinicaltrialsregister.eu retrieved information on ongoing clinical trials on the topic of combined immunotherapy and radiotherapy in cervical cancer. we discuss other advances in the field, notably the use of stereotactic body radiotherapy (SBRT) as a substitute to brachytherapy, and the addition of immunotherapy to chemoradiation. Conclusions: The use of IG-IMRT and 3D-IGABT have considerably improved treatment outcomes and toxicity profiles for patients with LACC, and are now considered the gold standard in many countries. The use of SBRT boost as a replacement for brachytherapy has been associated with increased toxicity and decreased efficacy and should be used with caution in the context of clinical trials. New experimental approaches include the addition of immunotherapy to chemoradiation regimens.

1. Introduction

Cervical cancer is the fourth most common cancer in women worldwide [**1**,**2**]. The majority of cervical cancers in developed countries are diagnosed early at stage I and 5-year overall survival (OS) for all stages remains above 73% [**3**,**4**]. However, outcomes for those with locally advanced cervical cancer remain quite poor. The 5-year OS for patients with regional disease is around 55% [**3**,**5**]. The addition of concurrent chemotherapy to radiotherapy (RT) has improved the prognosis of these patients; however treatment-related toxicity and distant recurrence remain a challenge [**6**]. Thus, there is much room for improvement in the treatment of locally advanced cervical cancer and new strategies are needed to further improve outcomes. Standard treatment

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of locally advanced cervical cancer (LACC) consists of concurrent chemoradiotherapy (CCRT) with external beam radiotherapy (EBRT), followed by brachytherapy (BT) [7]. CCRT has been the standard of care for LACC since 1999, based on the results of five Phase III randomized controlled trials (RCT) showing a 30% to 50% survival advantage by adding cisplatin-based chemotherapy to radiation (GOG 85, GOG 120, GOG 123, SWOG 8797/Intergroup 0107, RTOG 9001) [**8**,**9**,**10**,**11**,**12**]. In the past two decades, radiation treatment paradigms have shifted from a two-dimensional (2D) approach, solely based on anatomical bony landmarks, to an image-guided three-dimensional (3D) approach, taking into account variations in tumour size and position, with the goal of delivering doses more precisely to clinical targets with an increased sparing of organs-at-risk (OARs).

2. Material and Methods

A literature search was performed in the PubMed database for articles on radiotherapy for the treatment of LACC. The following keywords were used in various search algorithms: "cervical cancer", "radiotherapy," "radiation therapy," "chemoradiation", "IMRT", "brachytherapy", "SBRT", "immunotherapy," and "immune checkpoint inhibitors". Original research, review papers, or meeting abstracts published on the topic up to 18 November 2021 were considered. Articles published in languages other than English were excluded. Further references found within the articles and relevant to the subject were also used. A search query was also performed in Clinicaltrials.gov and Clinicaltrialsregister.eu to retrieve information on ongoing clinical trials on combined immunotherapy and RT in cervical cancer.

2.1. From 2D Radiotherapy to 3D-Conformal Radiotherapy (3DCRT)

Historically, the treatment of LACC with RT has been performed with 2D external beam radiotherapy, solely based on empirically defined anatomical landmarks. These anatomical bony landmarks were defined based on X-rays to be able to largely cover the primary disease as well as any potential extent of the tumour to the adjacent soft tissues and draining lymph nodes. The most rudimentary technique of EBRT consists of two parallel opposed fields (AP-PA). This was followed by the use of Biaxial Telecobalt pendular irradiation of the pelvic lymph nodes combined with ^{226}Radium-BT to treat cervical cancer in the 1960s, especially in the recurrent setting [**13**]. Later, the "four-field box" technique was introduced and achieved better OARs sparing. It consists of four large treatment fields, with the anterior border placed anteriorly to the pubic symphysis, posterior border covering the sacrum at the S3/S4 level, superior border at the level of the aortic bifurcation around the L3-L5 vertebral body levels, or at the level of T12 in the case of extended fields, when the para-aortic lymph nodes are involved. The inferior border is defined as the bottom of the obturator foramen and finally the lateral borders are placed 1.5 to 2 cm lateral to the pelvic brim. Although easily applicable, the use of standardized fields based only on bony landmarks has the caveat of not being adaptable to variations in individual patients' anatomy and has been associated with geographical misses leading to decreased LC [**14**,**15**].The

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computerized tomography (CT) scanner was invented in 1971 by Hounsfield and Cormack, but it was not until the 1990s that it was used in the planning and delivery of RT [**16**], marking the evolution from 2D-RT to 3DCRT. Indeed, 3DCRT takes advantage of the soft tissue and anatomical information obtained from a CT scan of the patient in a reproducible treatment position, to delineate the target disease and the neighboring OARs. Based on this information, gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV) are delineated as defined by the ICRU 50 and 62 reports [**17**,**18**]. This allowed for the use of the "four field box" technique based on anatomical rather than empirical bony landmarks, and the use of field blocks or multileaf collimators (MLCs) to better shape the dose distribution to the PTV while limiting the dose delivered to the OARs [**19**,**20**]. Compared to a 2D technique, 3DCRT also provides the advantage of recording volumetric dosimetry, correlating it with treatment outcomes and toxicities.

2.2. Adaptive External Beam Radiotherapy

The uterus and cervix are highly susceptible to changes in position during RT delivery, mainly due to variations in bladder and rectal filling and tumour regression during RT [**35**]. The reported mean interfractional cervical motion varies between 2.3 and 16 mm in the anterior-posterior direction, 2.7 and 8 mm in the superior-inferior direction and between 0.3 and 10 mm in the lateral direction [**36**]. Thus, the concept of internal target volume (ITV) has been introduced to account for such variations in position [**37**]. The ITV is generated by doing simulation CT scans on a full and empty bladder and combining the CTV drawn on each of these scans to account for every position change between these two bladder-filling extremes. A PTV margin of 5–7 mm is then added to this ITV to account for setup and position in errors. However, cone beam CT (CBCT) is recommended so as to ensure adequate coverage of the CTV and PTV daily prior to RT delivery. Moreover, this approach has the benefit of decreasing the volume of OARs exposed to higher doses of RT and the use of image-guided IMRT has been associated with a decrease in GI and hematological toxicities compared with IMRT alone [**38**]. Other adaptive RT technologies have emerged over the past few years to further improve image guidance during EBRT delivery,

2.3.X-ray rotation therapy

The simplest form of dynamic therapy is rotation therapy, otherwise described as arc therapy or proportional arc therapy. The principle underlying rotation therapy is that a high dose can be delivered

at the intersection of multiple beams in the target volume while lower doses are delivered to tissues outside the target, where the beams do not intersect.

In the case of two intersecting beams (or two orthogonal opposing pairs of beams) the dose outside the target volume will be approximately 50% of the dose in the target and for three fields it will be approximately 33%. Increasing the number of fields reduces the dose outside by spreading the

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energy deposited over a larger volume of the patient. As far as the linear accelerator is concerned rotation therapy requires that the gantry should rotate in a highly controllable way during irradiation. In proportional arc therapy the gantry rotation speed is proportional to the dose rate. This

can be achieved by treating either the dose rate or the gantry speed as the independent variable. In the first case the dose rate is used to control the gantry speed; in the second the gantry is rotated at a constant speed and the dose rate controlled as the dependent variable.

2.4. Conformal therapy

The term conformal therapy has been applied to techniques where particular attention is paid to 'conforming' the dose distribution to the target volume. All such techniques depend on three-dimensional identification of the target volume requiring state of the art imaging, three-dimensional treatment planning taking into account the properties of the radiation beams and the individual anatomy of each patient and in some cases assessment of the expected biological effects of the proposed treatment in addition to the dose distribution. The inclusion of biological modelling in the treatment planning process is, at the time of writing, subject to considerable uncertainty. However as the responses of different tissues are known to vary it seems logical that the introduction of biological modelling should be pursued and when the models are proved and data established it will be possible to optimize treatment plans on the basis of predicted biological effects rather than on the basis of dose distribution.

3. Advances in Brachytherapy for the Treatment of Locally Advanced Cervical Cancer.

Brachytherapy (BT) is a type of RT in which small, sealed radioactive sources are placed in or near a tumour volume to deliver a therapeutic dose. It is an integral part of the treatment algorithm for LACC as it helps in boosting the RT dose to the local disease to a curative level. The addition of BT to the treatment of LACC is independently associated with a significantly higher survival rate, with up to a 12% absolute improvement in 4-year OS (from 46% to 58%, $p < 0.001$) with hazard ratios (HR) of 0.66 (95% CI, 0.60–0.74) [5]. In this SEER database analysis, BT was also associated with significantly improved cancer-specific survival (CSS) with a 4-year CSS of 64.3% vs. 51.5% for those who did not receive BT ($p < 0.001$) and HR of 0.64 (95% CI, 0.57–0.71).

4. From 2D-Brachytherapy (2D-BT) to 3D Image Guided Adaptive Brachytherapy (3D-IGABT)

Historically, BT for LACC was delivered through a 2D technique, whereby a 2 Gy equivalent cumulative dose (EQD2) of 80 to 85 Gy was delivered according to the Manchester system, to point A defined on X-ray. First introduced in 1938, the Manchester system defined point A as a point 2 cm superior to the external OS and 2 cm lateral and perpendicular to the applicator tandem, anatomically representing where the uterine vessels cross the ureter [**40**,**41**]. Thus, 2D-BT delivers a known dose to point A bilaterally, generating a pear-shaped distribution,

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but without factoring in patient-specific factors such as tumour size, anatomy, or doses to OARs, as these cannot be readily identified on an X-ray. However, with the advent of CT and MRI imaging during the procedure, the delivery of BT has evolved to a volume-based approach, taking into account variations in tumour size and position over the treatment course. This allows for conformal treatment of a high-risk clinical target volume (HR-CTV) while simultaneously sparing OARs.

4.1. Immunotherapy as an Adjunct to Chemoradiation

Advances in chemoradiation for the treatment of LACC, notably the use of MRI-based IGABT, have translated into improved LC and toxicity profile. However, the OS for patients with advanced disease remains dismal, and this is thought to be mainly driven by distant failures rather than local recurrences. Thus, new systemic treatments are needed to improve OS for patients with LACC. One of such treatment adjuncts is immunotherapy. Indeed, cervical cancers are thought to be highly immunogenic, as a virus-driven type of cancer (HPV), thus amenable to respond to immunotherapy. Cervical cancer ranks amongst the tumours with the most somatic mutations, neoantigen formation and immune cell infiltrates [**63**,**64**]. Furthermore, a landmark Cancer Genome Atlas study on invasive cervical cancer identified several targetable mutations in this type of cancer, notably amplifications in the immune checkpoint regulators programmed death ligand (PD-L1 and PD-L2 [**65**]. Finally, several studies have shown that HPV positivity is associated with increased PD-L1 expression [**66**,**67**]. Taken together, all these factors argue for the rationale that cervical cancer tumours would respond to checkpoint-inhibitor targeted therapy.

To date, a few studies have investigated the role of targeted anti PD1/PD-L1 therapy in cervical cancer. The Keynote-28 (NCT02054806) was a single-arm, phase IB basket trial of 477 patients from 20 different cohorts with advanced or metastatic PD-L1-expressing solid tumours, including 24 cervical cancer patients. Patients received pembrolizumab every two weeks for up to 24 months. The primary endpoint was overall response rate as per RECIST v1.1 criteria and secondary endpoint was safety. With a median follow-up of 11 months, the objective response rate (ORR) in the cervical cancer cohort was 17% (95% CI, 5% to 37%) with four patients achieving a partial response and median duration of response was 5.4 months (4.1 to 7.5 months) [**68**]. The 6-month PFS was 13% and 6-month OS was 66.7%. Treatment-related adverse events (AEs) were reported in 18 patients (75%) with five patients experiencing grade 3 treatment-related AEs. There were no grade 4 treatment-related AEs or deaths

Furthermore, KEYNOTE-158 (NCT02628067) is an ongoing phase II trial including 1595 patients with advanced (unresectable and/or metastatic) solid tumours who have progressed to standard of care therapy and treated with pembrolizumab [**69**]. This included a total of 98 patients with previously treated advanced cervical cancer, of which 82 patients (83.7%) had PD-L1-positive tumours. Pembrolizumab monotherapy was administered every 3 weeks for 2 years until progression. The primary endpoint was ORR as per RECIST v1.1 criteria and secondary

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endpoints included PFS and OS. With a median follow-up of 10.2 months, ORR was 12.2% (95% CI, 6.5–20.4), with three complete and nine partial responses. All 12 responses were observed in patients with PD-L1-positive tumours. Median duration of response was not reached (range, ≥ 3.7 to ≥ 18.6 months) at time of interim analysis. Median OS was 9.4 months for the entire cohort and 11.0 months for the PD-L1-positive patients. Treatment-related AEs occurred in 65.3% of patients with grade 3 and 4 treatment-related AEs occurring in 12.2% of patients. The most common AEs were hypothyroidism (10.2%), decreased appetite (9.2%), and fatigue (9.2%) [**69**]. These two trials showed that pembrolizumab had durable anti-tumour activity in cervical cancer with acceptable toxicity. Based on this, the Food and Drug Administration (FDA) approved, in June 2018, the use of pembrolizumab for the second-line treatment of PD-L1-positive metastatic or recurrent cervical cancer.

In the definitive setting, ENGOT-cx11/KEYNOTE-A18 (NCT04221945) is a phase III, randomized trial evaluating the combination of pembrolizumab with concurrent CRT for the treatment of locally advanced cervical cancer [**72**]. It is still ongoing and aims to recruit 980 patients with high-risk LACC (FIGO 2014 stage IB2-IIB with node-positive disease or stage III-IVA) who have not received prior treatments, randomized 1:1 to receive either 5 cycles of pembrolizumab vs. placebo every 3 weeks plus CRT followed by 15 cycles of pembrolizumab vs. placebo every 6 weeks. The CRT regimen is as per the standard practice, including 5–6 cycles of cisplatin 40 mg/m^2 weekly + EBRT followed by brachytherapy (IGABT). Randomization will be stratified based on the EBRT technique (IMRT or VMAT vs. non-IMRT), cancer stage at screening (stage IB2-IIB vs. III-IVA) and planned total RT dose. The primary endpoints are PFS as per RECIST v1.1 and OS. The secondary endpoints are 2-year PFS, 3-year OS, complete response at 12 weeks, ORR, PFS and OS in PD-L1–positive patients, EORTC QLQ-C30 and QLQ-CX24, and safety. Results of this trial are highly anticipated and will further elucidate whether immunotherapy combined with definitive CRT can improve LC, PC and survival in patients with LACC. Currently, there are ten clinical trials assessing the combination of immunotherapy and definitive chemoradiation in the treatment of cervical cancer (**Table 1**). Results from all these trials are eagerly awaited to assess whether immunotherapy could improve distant control as well as survival rates in LACC without significantly increasing toxicitie

Table 1. Clinical trials combining immunotherapy with definitive radiotherapy in the treatment of locally advanced cervical cancer.

Trial ID	Design	Eligibility	Intervention	Details	Outcome Measures	Status
NCT04221945 (KEYNOTE-A18/ENGOT-	Randomized Phase III	FIGO 2014 Stage	**Pembrolizumab** + CRT + BT vs. Placebo + CRT +	Pembrolizumab 200 mg IV vs. placebo q3	Primary: PFS (RECIST	Recruiting

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cx11/GOG-3047)		IB2–IIB (with N+ disease) or FIGO 2014 Stages III–IVA cervical cance	BT	weeks × 5 cycles, followed by Pembrolizumab 400 mg IV vs. placebo q6 weeks × 15 cycles + Cisplatin qweek during EBRT + BT (to a total RT dose of 80 Gy for volume directed and 75 Gy for point directed	1.1), OS Secondary: 2-year PFS, 3-year OS, CR at 12 weeks, ORR, PFS and OS in PD-L1+ patients, PFS after next line treatment, EORTC QLQ-C30, QLQ-CX24, and safety	
NCT03738228	Multi-arm Phase I	Stage IB2, II, IIIB, or IVA cervical cancer	**Atezolizumab** + CRT + BT	Arm A: Atezolizumab IV on **days -21, 0, and 21** + Cisplatin qweek concurrent with EBRT (Monday–Friday) × 5 weeks + IGBT at week 4 or 5 Arm B: Atezolizumab IV on **days -21, 0, and 42** + Cisplatin qweek concurrent with EBRT	Primary: T cell receptor beta (TCRB) clonal expansion in peripheral blood Secondary: Incidence of DLTs, Frequency and severity of AEs as per CTCAE v5, TCR clonality,	Active, not recruiting

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				(Monday-Friday) × 5 weeks + IGBT at week 4 or 5	diversity, and frequency in peripheral blood and tissue, PD-L1 expression in tissue	
NCT03612791 (ATEZOLACC)	Randomized Phase II	FIGO 2009 stage IB1–IIA (N+) or stage IIB–IVA cervical cancer	**Atezolizumab** + SoC CRT + BT vs. SoC CRT + BT	tezolizumab 1200 mg IV q3 week starting on week1 and continued as adjuvant treatment for a max of 20 cycles + Cisplatin qweek concurrent with pelvic +/– para-aortic EBRT by IMRT (45Gy/25Fx) + BT starting at week 7 (85 Gy EQD2 to HR-CTV) vs concurrent CRT +BT alone as above	Primary: PFS (RECIST 1.1)	Recruiting
NCT03830866 (CALLA)	Phase III RCT	FIGO (2009) Stages IB2 to IIB N+ or	**Durvalumab** + SoC CRT + BT followed by Durvalumab monotherapy up to	Durvalumab IV q4 weeks + Cisplatin (or Carboplatin) qweek	Primary: PFS (RECIST 1.1) Secondary:	Active, not recruiting

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		FIGO (2009) IIIA–IVA any node cervical adenoCa or SCC	24 months or until progression of disease, vs. Placebo + SoC CRT + BT	concurrent with EBRT + BT	OS, CR (RECIST 1.1), duration of response, QoL (EORTC QLQ-C30, EORTC CX24), 3-year PFS, PFS and OS in PD-L1+ patients	

5. Conclusions and Perspectives

RT plays a primordial role in the treatment of LACC. Radiation oncology technologies have progressed rapidly in the past two decades. Notably, the use of IG-IMRT and 3D-IGABT have considerably improved treatment outcomes and toxicity profiles for patients with LACC and are now considered the gold standard in many countries. However, there is still room for improvement, and new experimental perspectives include the addition of immunotherapy to chemoradiation regimens, or a move towards an even more personalized approach to treatment with the identification of risk factors and biomarkers that can be used to de-escalate or intensify treatments according to individual patients' risk group (EMBRACE III). Other technological innovations such as the use of the SBRT boost to replace BT boost have been associated with increased toxicity and decreased efficacy and so should be used with caution and only in the context of clinical trials.

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