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Radiotherapy alone in locally advanced cervical cancer: a palliative treatment? Real-world data

Radioterapia isolada no câncer cervical localmente avançado: um tratamento paliativo? Dados do mundo real

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ABSTRACT

Objective: To investigate the benefit of radiotherapy alone in patients diagnosed with locally advanced cervical cancer when the addition of chemotherapy was contraindicated. **Methods:** A single-center cohort study of patients diagnosed with locally advanced cervical cancer as defined by the FIGO 2009 (stage IB2 to IVA) and contraindication for concomitant chemotherapy was retrospectively evaluated. Patients included were treated with radiotherapy in a curative intent and those patients who completed the external beam radiotherapy were considered for brachytherapy. Patient's demographics, reasons for not receiving concomitant chemotherapy and treatment responses were analyzed. Disease-free survival (DFS) and overall survival (OS) were calculated. **Results:** With a median follow-up of 13.9 months (range 0.10-81.8), the median DFS was 11.6 months (95% CI: 10.2-13.1), and the median OS was 15.9 months (95% CI: 11.5-20.3). **Conclusion:** This real-world study provides descriptive information confirming that radiotherapy with curative intent should be offered to patients with locally advanced cervical cancer even when chemotherapy is not an option due to clinical or laboratory contraindications.

Keywords: Uterine cervical neoplasms; Radiotherapy; Brachytherapy; Antineoplastic agents.

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RESUMO

Objetivo: Investigar o benefício da radioterapia isolada em pacientes com diagnóstico de câncer cervical localmente avançado quando a adição de quimioterapia foi contraindicada. **Métodos:** Um estudo de coorte unicêntrico de pacientes com diagnóstico de câncer cervical localmente avançado, conforme definido pela FIGO 2009 (estágio IB2 a IVA) e contraindicação para quimioterapia concomitante foi retrospectivamente avaliada. Os pacientes incluídos foram tratados com radioterapia com intenção curativa e os pacientes que completaram a radioterapia com feixe externo foram considerados para braquiterapia. Dados demográficos do paciente, razões para não receber quimioterapia concomitante e respostas ao tratamento foram analisados. Sobrevida livre de doença (SLD) e sobrevida global (SG) foram calculadas. **Resultados:** Com um acompanhamento médio de 13,9 meses (intervalo de 0,10-81,8), a SLD mediana foi de 11,6 meses (IC 95%: 10,2-13,1) e a SG mediana foi de 15,9 meses (IC 95%: 11,5-20,3). **Conclusão:** Este estudo do mundo real fornece informações descritivas que confirmam que a radioterapia com intenção curativa deve ser oferecida a pacientes com câncer cervical localmente avançado, mesmo quando a quimioterapia não é uma opção devido a contraindicações clínicas ou laboratoriais.

Descritores: Neoplasias do colo uterino; Radioterapia; Braquiterapia; Agentes antineoplásicos.

INTRODUCTION

Cervical cancer (CC) is a public health problem. It is the fourth most common cancer and the fourth leading cause of cancer death among females around the world,[1] with 410,000 deaths expected for 2030.[2] Approximately 85% of cases and deaths occur in low- and middle-income countries (LMIC).[3-5] According to the Brazilian National Cancer Institute (INCA), 16,590 new cases are estimated for 2021 in Brazil, representing the third most commonly diagnosed cancer in women in this country.[6] Human papillomavirus (HPV) infection is the most important risk factor and can be detected in 99.7% of cases.[7,8]

In 2018, the International Federation of Gynecology and Obstetrics (FIGO) revised the staging and treatment recommendations. Patients with locally advanced disease (stages IB3 to IVA) have worse prognosis, with increased risk of recurrence and shorter overall survival (OS) than patients diagnosed at earlier stages. Five-year OS for stages III and IV varies from 40% to 15%, respectively.[9]

The recommended treatment for locally advanced disease is external beam radiotherapy (EBRT) concomitant with weekly cisplatin followed by high dose (HDR) or low dose (LDR) brachytherapy. Since the early 2000s, increasing utilization of HDR has been adopted, in opposition to LDR.[10] Five phase 3 studies,[11-15] including patients with FIGO 2009 stages IB2 to IVA, showed a 30 to 50% reduction in the risk of death in patients receiving chemoradiation. The improved efficacy of the combined modality is due to the direct cytotoxicity effect of the platin compound, its radiosensitization action in tumor cells, and the control of subclinical metastases.[16] However, the benefit of concurrent chemotherapy with radiotherapy in patients with FIGO stage IIIB disease was not substantially proven until 2018, when a randomized phase 3 trial demonstrated a significant improvement of disease-free survival (DFS) and OS in favor of the combination therapy with an absolute benefit of 8.5% and 8%, respectively.[17]

Moreover, it is important to note that all trials comparing the benefits of the association of chemotherapy and radiotherapy included patients suitable for the combination approach, excluding patients considered not fit for chemoradiotherapy. Cisplatin, the drug of choice for concurrent therapy, is well known to be nephrotoxic, and patients with moderate to severe renal insufficiency are not eligible to receive this medication. Moreover, patients with compromised performance status; comorbidities such as severe heart or liver disease, neuropathy, and hearing deficiency are ineligible for this combined treatment.

Although the benefits of combined chemotherapy and radiation therapy in CC treatment have been evident since 1999, when papers showing survival gains were published, the radiotherapy and brachytherapy techniques used at that time were the standard treatment. Currently, the population chosen for combined treatment is always the one with the best clinical and prognostic conditions. Thus, radiotherapy alone and brachytherapy are reserved for those with the worst clinical condition and poor prognostic factors.

The objective of this study was to evaluate the results of radiotherapy alone in patients diagnosed with locally advanced CC when the addition of chemotherapy was contraindicated such as those with renal insufficiency, performance status >2, severe baseline neuropathy, advanced comorbidities, and advanced age. This group considered of inferior prognosis was evaluated

exploring the clinical outcomes proportioned by this single-modality therapy.

METHODS

The current study was approved by the Ethics in Human Research Committee of INCA (CEP-INCA), Rio de Janeiro, Brazil, under the number CAAE 48092415.3.0000.5274 and conducted in accordance with the good clinical practice guidelines.

This was a retrospective single-center cohort study of consecutive patients with locally advanced CC, as defined by the FIGO 2009 (stages IB2 to IVA) and contraindication for concomitant chemotherapy and treated between January 2010 and December 2012. Patients were submitted to physical examination and imaging according to the physicians' discretion. Data collected included patients' demographics, the reason for contraindication to concomitant chemotherapy, clinical and response data and dates of the last follow-up or death. All data was anonymized after collection and before the analysis.

Patients included in this study were treated with radiotherapy in a curative manner and were not eligible for concomitant approach due to, among many reasons, cisplatin contraindication, including renal insufficiency defined as creatinine clearance lower than 50mL/min (as per institutional guidelines), performance status >2, hearing loss grade ≥2, and severe baseline neuropathy. Patients with metastatic CC (FIGO stage IVB), except those with affected paraaortic lymph nodes, other histology than squamous cell carcinoma or adenocarcinoma were not included.

Patients who completed the EBRT were considered for brachytherapy. The median value of total dose of radiotherapy (EBRT + brachytherapy) was assumed as cutoff point. Adverse events (AEs) were graded according to the common terminology criteria for adverse events (CTCAE v.4.03). The responses were discriminated clinically and using imaging tests when considered indicated. Clinical benefit (CB) was defined as best response of complete response (CR), partial response (PR) or stable disease (SD) by RECIST 1.1, when a radiological assessment was undertaken, as well as a clinical response through physical examination and categorized according to the WHO criteria as follows: complete response with complete resolution of tumor as judged clinically, partial clinical response with more than 50% regression of initial tumor volume, and no responders were patients with a minimal response (less than 50% regression of the initial tumor volume), no change or local/distant progression.

Disease-free survival (DFS) was defined from the date of radiotherapy onset until the date of tumor recurrence or death by any cause and was censored at the date of the last follow-up. OS was calculated from the date of first treatment to the date of death and was censored at the date of the last follow-up. Survival rates were calculated by Kaplan- Meier curves and were compared by the log-rank test. A Cox regression analysis was fitted to analyze the association between clinical characteristics and OS. With the purpose of adjusting for confounding factors variables with $p<0.15$ in the univariate analysis were included in a forward stepwise manner in the multivariate model. In all analysis a *p*-value lower than 0.05 was considered statistically significant. For the statistical analysis, Statistical Package for Social Sciences (SPSS) software, version 24, was used.

RESULTS

From January 2010 to December 2012, 2,224 were diagnosed with locally advanced CC at Brazilian National Cancer Institute, whereas 182 patients from this cohort were diagnosed with locally advanced CC at INCA and were treated with radiotherapy alone due to contraindication to the concomitant chemotherapy and enrolled in this study. Baseline characteristics are presented in Table 1. The median age at the time of initial diagnosis was 60 years (range 26.4-101.4), and the most frequent histology was squamous cell carcinoma (88.5%). The majority of patients were white (52.7%), with performance status 1 (58.6%) at diagnosis, and 109 patients (59.9%) were diagnosed as FIGO stage III.

Table 1. Clinical and pathological characteristics of patients

Characteristics	N (%)
Median age (range)	60 (26.4 – 101.4)
Ethnicity*	
White	96 (52.7)
Non-white	86 (47.3)
Histological subtype	
Squamous cell carcinoma	161 (88.5)
Adenocarcinoma	20 (11.0)
Other	1 (0.5)
FIGO stage	
IB2	13 (7.1)
II	49 (26.9)
III	109 (59.9)
IVA	11 (6.0)
Performance status	
1	106 (58.3)
2	56 (30.8)
3	19 (10.4)
Unknown	1 (0.5)
Creatinine clearance (mL/min)	
< 50	120 (65.9)
≥ 50	62 (34.1)
Smoking	
Yes	76 (42)
No	106 (58)
Total	182 (100)

FIGO: International Federation of Gynecology and Obstetrics
*Self-reported

Contraindications for concomitant treatment with cisplatin use according to physicians' discretion were renal dysfunction in 65.9% (n=120), impaired performance status in 26.9% (n=49), and other reasons in 29.1% of the cases (n=53); some patients had more than one contraindication for cisplatin use.

Regarding radiotherapy, 153 patients (84.1%) received 25 to 30 fractions of EBRT, and 29 (15.9%) patients received less than 25 fractions due to treatment-related AEs, clinical deterioration or progression of disease during radiotherapy. A total of 105 patients (59%) received ≥5000cGy, and 94 patients did not receive brachytherapy. A complete description of treatment with EBRT and brachytherapy is shown in Table 2.

Table 2. Distribution of radiotherapy and brachytherapy

Radiotherapy/Brachytherapy	N (%)
Radiotherapy (cGy)	
< 700	2 (1.1)
700-1800	10 (5.6)
2000-3000	7 (3.9)
4000-4600	52 (29.2)
5000-5400	105 (59.0)
Missing	6
Brachytherapy (cGy)	
1400-1800	4 (4.7)
2000-3000	82 (95.3)
Missing	2
No brachytherapy	94
Total dose (cGy)*	
1st Quartile	6900
Median	7400
3rd Quartile	7440

Differences in total are due to missing data; percentages were calculated considering only patients with available data.
*Refers to 86 cases

The most common AEs reported were actinic colitis (14.9%), pelvic pain (11.6%), and bladder-vaginal fistula (7.2%). Other less frequent toxicities were constipation (3.9%), actinic cystitis (3.8%), rectovaginal fistula (3.8%), urinary incontinence (3.3%), and nausea (3.3%).

Response assessment was documented in 162 patients (89%), and 116 patients had clinical benefit (CR - 71 patients, PR - 43 patients, and SD - 2 patients) – Table 3. Of note, response assessment was done using gynecological physical examination in 82.6% of patients and only 17.4% had a radiological evaluation.

With a median follow-up of 13.9 months (range: 0.10-81.8), the median DFS was 11.6 months (95% CI: 10.2-13.1), and the median OS was 15.9 months (95% CI: 11.5-20.3) (Figure 1). Table 4 summarizes the differences in DFS and OS between the subgroups.

Table 3. Response to radiotherapy

Response	N (%)
CR	71 (43.8)
PR	43 (26.5)
PD	46 (28.4)
SD	2 (1.2)
Clinical benefit (CR + PR + SD)	116 (71.6)
Missing	20

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease

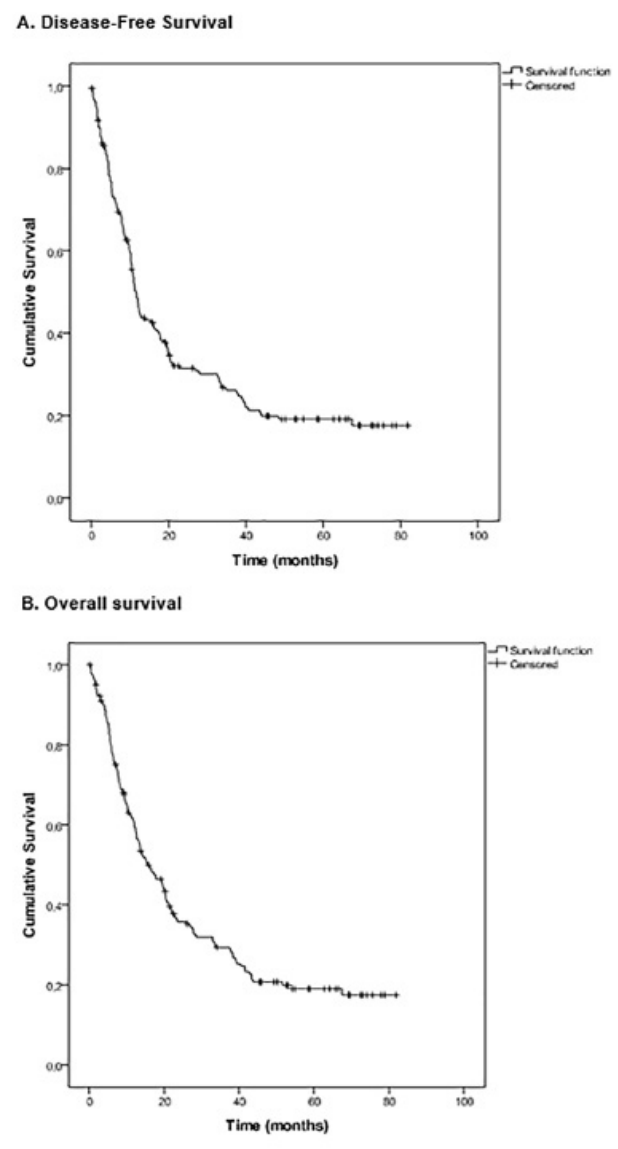

Figure 1. Kaplan–Meier estimates

There was a statistical difference in terms of DFS in the following subgroups: age ≥65 years (p=0.031), performance status (p= 0.037), and brachytherapy (p<0.001). Concerning OS a significant difference was observed in the following subgroups: age (p=0.017), smoking (p=0.029), and brachytherapy (p<0.001).

After controlling for potential confounding factors, the multivariable Cox proportional hazards model showed that only age ≥65 years was associated with the risk of recurrence or distant metastasis (Table 5). Similarly, age ≥65 years and performance status = 3 were independently associated with the risk of death (Table 6).

DISCUSSION

In this retrospective study, locally advanced CC patients not eligible for combined treatment due to their clinical or laboratory conditions were treated exclusively with radiotherapy. The main objective was to evaluate the outcomes of radiotherapy alone in this real-world practice population.

It is undeniable to mention that the dose and correct technique of radiotherapy are determinants for the success of local control and pelvic relapse[18] and the effect of curative radiotherapy for CC may be improved by the inclusion of brachytherapy.[14] The objective of irradiation is to achieve maximum tumor control with the lowest incidence of sequelae and with an acceptable

Table 4. Disease-Free Survival and overall survival according to the subgroups.

	DFS (months) Median (95% CI)	OS (months) Median (95% CI)
Age ≥ 65 years		
Yes	17.2 (9.8-24.6)	20.3 (15.7-25.0)
No	10.3 (9.2-11.5)	12.2 (8.8-15.7)
p-value	0.031	0.017
Histological subtype		
Squamous cell carcinoma	11.5 (10.4-12.6)	15.5 (11.0-20.1)
Adenocarcinoma	17.2 (3.2-31.2)	19.8 (10.6-29.1)
p-value	0.574	0.312
FIGO stages		
I/II	20.1 (6.2-34.2)	20.3 (13.1-27.6)
III/IV	11.2 (9.8-12.5)	15.2 (10.5-20.0)
p-value	0.457	0.493
Performance status		
1	12.1 (8.1-16.2)	17.2 (11.5-22.9)
2	10.8 (7.9-13.8)	17.8 (10.5-25.1)
3	9.7 (2.0-17.3)	11.8 (4.0-19.6)
p-value	0.037	0.058
Creatinine clearance (mL/min)		
< 50	11.1 (9.5-12.7)	15.5 (10.0-21.1)
≥ 50	12.0 (6.4-17.6)	17.2 (10.0-24.5)
p-value	0.794	0.666
Smoking		
Yes	9.7 (7.3-12.2)	12.6 (8.3-16.8)
No	12.6 (8.5 -16.6)	19.5 (13.8- 24.9)
p-value	0.064	0.029
Radiotherapy (cGy)		
< 5000	12.0 (5.1-18.8)	15.5 (7.4-23.7)
≥ 5000	11.6 (10.4-12.8)	17.2 (12.3-22.1)
p-value	0.786	0.994
Brachytherapy		
No	6.2 (3.6-8.8)	8.1 (5.6-10.5)
Yes	20.5 (6.5-34.4)	33.0 (17.8-48.2)
p-value	< 0.001	< 0.001
Total dose of radiotherapy (cGy)*		
< 7400	19.8 (17.4-22.2)	26.9 (7.1-46.8)
≥ 7400	33.0 (18.7-47.4)	37.9 (24.2-51.6)
p-value	0.625	0.583
Overall	11.6 (10.2-13.1)	15.9 (11.5-20.3)

DFS: Disease free survival; OS: Overall survival
Bold text indicates a statistically significant difference with a p-value < 0.05

Table 5. Risk of recurrence or distant metastasis

	HR (95%CI)	p-value	aHR* (95%CI)	p-value
Age				
< 65 years	Ref		Ref	
≥ 65 years	0.7 (0.5-0.95)	**0.025**	0.7 (0.5-0.95)	**0.025**
Histological subtype				
Adenocarcinoma				
Squamous cell carcinoma	1.2 (0.7-2.0)	0.571		
FIGO stages				
I/II	Ref			
III/IV	1.3 (0.7-2.6)	0.412		
Performance status				
1	Ref			
2	1.2 (0.8-1.7)	0.452		
3	1.9 (1.1-3.1)	0.018		
Creatinine clearance (mL/min)				
< 50	Ref			
≥ 50	0.9 (0.7-1.3)	0.728		
Smoking				
No	Ref			
Yes	1.3 (1.0-1.9)	0.082		
Total dose of radiotherapy (cGy)*				
≥ 7400	Ref			
< 7400		0.626		

Bold text indicates a statistically significant difference with a p-value < 0.05 Ref = Reference
* Only age was retained by the adjusted model.

Table 6. Risk of death

	HR (95%CI)	p-value	aHR (95%CI)	p-value
Age				
< 65 years	Ref		Ref	
≥ 65 years	0.7 (0.5-0.97)	**0.031**	**0.6 (0.5-0.9)**	**0.014**
Histological subtype				
Adenocarcinoma	Ref		Ref	
Squamous cell carcinoma	1.3 (0.8-2.3)	0.324		
FIGO stages				
I/II	Ref		Ref	
III/IV	1.3 (0.7-2.6)	0.449		
Performance status				
1	Ref		Ref	
2	1.3 (0.9-1.8)	0.251		
3	1.8 (1.1-3.0)	**0.027**	1.9 (1.1-3.2)	**0.015**
Creatinine clearance (mL/min)				
< 50	Ref		Ref	
≥ 50	0.9 (0.6-1.3)	0.571		
Smoking				
No	Ref		Ref	
Yes	1.5 (1.1-2.1)	**0.025**		
Total dose of radiotherapy (cGy)*				
≥ 7400	Ref		Ref	
< 7400	0.9 (0.5-1.5)	0.584		

Bold text indicates a statistically significant difference with a p-value < 0.05 Ref = Reference

quality of life. Tumor control is related to its extension and the dose of radiation given.[17] Whereas doses of 4500-5000cGy are adequate to control subclinical disease, doses in the range of 8500 to 9000cGy are required to eradicate larger tumors.[18] In the current study, only 45% of patients received more than 70Gy, mainly because there was a shortage of patients treated with brachytherapy. With a relatively short follow-up (13.9 months), the death rate was as high as 70.9% caused primarily by cancer, with only 24.7% of patients still alive. These findings contrast negatively when compared with other randomized trials and meta-analyses.[11-15] Such disproportionate mortality could be justified by underestimated staging.

However, in this study, 15.9% patients (29 cases) received less than 25 radiotherapy fractions, 51.6% patients (94 cases) did not receive brachytherapy. Such disparities can be attributed to reduced performance status and clinical deterioration during radiotherapy and delayed onset of brachytherapy. Moreover, social development in the city of Rio de Janeiro and peripheral cities is mostly precarious. Transportation problems to get to the hospital associated with poor food and housing conditions can contribute to the clinical worsening. During data collection, hospitalizations for clinical complications such as kidney failure and infectious conditions that evolved to severe sepsis and death were mentioned. Finally, the wait to perform brachytherapy is long and serves patients from institutions outside the Brazilian National Cancer Institute.

Cisplatin is nephrotoxic chemotherapy and has many contraindications. Because of that, several studies have emerged evaluating other drugs to be combined with radiotherapy for treatment of locally advanced CC. Therefore, when any contraindication to cisplatin is identified, other options could be considered, allowing patients to have treatment with the same extension of benefit when compared to the ones treated with concomitant cisplatin. Carboplatin is an effective radiosensitizer as seen in a prospective study that compared carboplatin 100mg/m² with cisplatin combined to radiotherapy. It was found a similar overall response rate and no difference in survival outcomes at three years.[19] The use of carboplatin, therefore, is supported by small phase 1 and 2 studies, and there is preclinical evidence of synergism of this drug with radiotherapy.[20-24] Ana Morais et al. carried out a retrospective study comparing radiotherapy plus cisplatin 40 mg/m² and radiotherapy plus carboplatin AUC2 in locally advanced CC stage IIB-IVA. That analysis did not find any difference in terms of side effects comparing cisplatin and carboplatin in combination with radiotherapy, response, PFS and OS.[25] Gemcitabine is another possibility to be considered for chemoradiotherapy. In a Mexican trial, gemcitabine was used with radiotherapy for patients with obstructive nephropathy and kidney dysfunction.[26] Nine patients were treated and completed the chemoradiotherapy regimen, 89% achieved CR, and one patient had persistent disease. At a median follow-up of 11 months, all patients were alive and two had evidence of recurrent disease. Paclitaxel and 5-fluorouracil were also trialed, with no consistent benefit observed.[27,28] Finally, combined radiotherapy and hyperthermia can be considered as another valid option for the first-line treatment of advanced-stage CC with benefits in terms of local control rate, improved survival, limited restrictions on its clinical application and low costs.[29]

In this study, smoking was a prominent factor since the median overall survival was 12.6 months for smokers versus 19.5 months for non-smokers. The mutagenic effect of cigarette smoking occurs in cervical cells and this leads to progression from squamous intraepithelial lesion to cervical cancer. Finally, smoking increases the frequency of chromosomal damage.[30]

The majority of patients in this analysis were stage III (59.9%). FIGO stage III CC patients have been a point of disagreement in many clinical trials. Because of this lack of more definitive information, a randomized phase 3 trial was developed to analyze stage III CC patients at the Tata Memorial Hospital, Mumbai, India. Between July 2003 and September 2011, 850 women were enrolled. With a median follow-up of 88 months, the 5-year DFS was 52.3% (95% CI: 52.2%-52.4%) in the chemoradiotherapy arm and 43.8% (95% CI: 43.7%-43.9%) in the radiotherapy arm, with an unadjusted hazard ratio (HR) for relapse or death of 0.81 (95% CI: 0.68-0.98; p=0.03). At 5 years, the OS was 54% (95% CI: 53.9%-54.1%) in the chemoradiotherapy arm and 46% (95% CI: 45.9%-46.1%) in the radiotherapy arm, with an unadjusted HR for death of 0.82 (95% CI: 0.68-0.98; p=0.03). Finally, it was showed that chemoradiotherapy using weekly cisplatin is significantly better in terms of DFS and OS compared with radiotherapy alone in women with stage IIIB squamous cell carcinoma.[17]

Therefore, chemoradiotherapy remains the preferred therapy for patients with locally advanced CC, with good performance status, adequate renal function, and no other debilitating comorbidities. In the current study, patients not eligible for concomitant approach achieved some clinical benefit (tumor control) with exclusive radiotherapy, showing that even when contraindication to chemotherapy exists, the dose/schedule of EBRT should be maintained at a curative approach.

The results of this study confirm once again the importance of HPV vaccination and screening for prevention and early diagnosis of CC. Moreover, the continuous investigation for alternative approaches to cisplatin, such as the use of immunotherapy or PARP inhibitors concomitant to radiotherapy should be pursued.

Real-world studies could be useful as a measure in understanding health care data collected under real-life practice circumstances,[31] and the results can help to define if a treatment is effective and safe also in a real-world setting and not only within a clinical trial.

As a real-world study, there are several limitations to this report, as there is a possible bias due to its retrospective nature. However, the aim to

characterize the benefits of EBRT in real-world practice, as the population studied is, in general, excluded from the clinical trials, was achieved.

Differences in characteristics among patients enrolled in clinical trials and those in real-world setting could highlight the limitations of generalizing clinical trial data.[32]

The key strength of the current study is the large number of patients identified using a single-institution register, where patients could have received a more homogeneous evaluation during the whole process, including documentation.

CONCLUSION

Our real-world data demonstrated that, despite the lower survival outcomes rates, radiotherapy alone with curative intent should be offered to patients with locally advanced cervical cancer not suitable for chemotherapy. However, for those with good performance status but kidney dysfunction, chemotherapy regimens with gemcitabine or carboplatin should be considered. Finally, the current study provides descriptive information confirming that radiotherapy with curative intent should be offered to patients with locally advanced CC even when chemotherapy is not an option due to clinical/laboratorial contraindications.

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