Original Article

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Treatment Outcome of Cervical Cancer Patients in the Elderly Population Aged 80 Years and Above: A Single Institution Study

Oncology Section

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ABSTRACT

Introduction: Age-related deficits such as malnutrition, functional reliance, and cognitive decline also occur in older women, as they are typically weaker and have many co-morbid conditions like diabetes or cardiac illness. These prognostic factors might predict overall survival and progression-free survival.

Aim: To analyse the management outcomes of elderly patients with cervical carcinoma treated with radiotherapy and brachytherapy.

Materials and Methods: A retrospective observational study was conducted in the Department of Radiation Oncology at Himalayan Institute of Medical Sciences, Dehradun, Uttarakhand, India. Medical records were collected from 876 patients with cervical cancer who had been treated with radiotherapy or combined radiotherapy and chemotherapy from January 2009 to December 2021. A total of 876 patients presented with cervical cancer in the Outpatient Department (OPD), and 20 patients meeting the inclusion criteria were selected. Patients diagnosed with cervical cancer, Federation International Federation of Gynaecology and Obstetrics (FIGO) stage IB to IVA, aged equal to or greater than 80 years old, and Eastern Cooperative Oncology Group (ECOG) performance status I to III were considered for inclusion. Categorical variables were expressed as counts and percentages. The following clinicopathological characteristics of the study population were examined: FIGO staging, including stage IB to stage IVA, histopathological features of adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma, doses of radiotherapy and brachytherapy, overall survival, disease-free survival, and the patient's current status (alive or dead) was determined. If death occurred, the cause of death was determined. The Kaplan-Meier approach was used to analyse overall survival and disease-free survival in the study population using XLSTAT statistical software.

Results: The study population was age standardised, with 18 patients (90%) falling between the ages of 80 and 85, and 2 patients (10%) falling between the ages of 86 and 90. A total of 12 patients (60%) belonged to ECOG PS II. A total of 19 (95%) patients had histologically confirmed squamous cell carcinoma. 75% of the population was in a locally advanced stage (stage III-IVA). The overall survival (in months) was 65.58 months, which was statistically significant ($p<0.0083$). Similarly, the average disease-free interval was 38.73 months, which was also significant ($p<0.0062$).

Conclusion: According to the findings of the study, age may not be an independent risk factor for determining the outcome of cervical cancer patients in the Indian scenario. Even though elderly females may present with multiple co-morbidities, the standard treatment protocol must be radical.

Keywords: Carcinoma, Conventional external beam radiation therapy, Radiation oncology

INTRODUCTION

Cervical cancer is the fourth most prevalent cancer in women worldwide [1]. With approximately 570,000 new cases identified each year and 310,000 deaths due to the disease, cervical cancer is one of the most common malignancies in women around the world [2]. While there has been no change in the prevalence of cervical cancer in elderly females, the global incidence has decreased as a result of various screening programs. It has been noted that older age groups account for 25% of cervical cancer incidences [3]. According to a previous study, the prevalence of cervical cancer was lower in women under the age of 50 and increased by 2% for every additional year of age in those over 50 years of age [4]. Women over the age of 50 are often in the perimenopausal or postmenopausal stages, exhibiting physiological and pathological traits that are very different from those of women who are still in their reproductive years.

As a result, an increasing trend of awareness for older individuals with cervical cancer has been noted over time. Treatment options for cervical cancer, depending on the established FIGO staging, include surgery, brachytherapy, and concurrent chemo-radiotherapy [5]. Age-related deficits such as malnutrition, functional reliance, and cognitive decline also occur in older women, who are typically weaker and have many co-morbid conditions like diabetes or cardiac illness. These individuals are more likely to experience treatment toxicities [6]. Due to all of these characteristics, the treatment of cervical cancer in the elderly population varies, and prognostic factors that might predict whether or not a patient will survive cervical cancer in old age have not been thoroughly studied. The aim of the present study was to analyse the management outcome of elderly patients with cervical carcinoma treated with radiotherapy and brachytherapy.

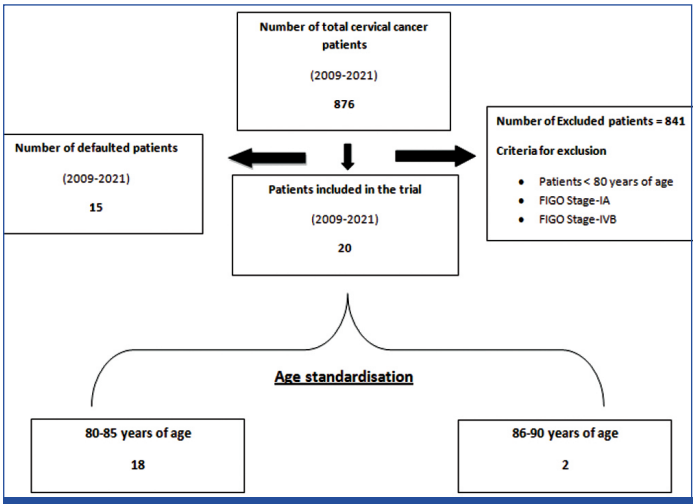
MATERIALS AND METHODS

A retrospective observational study was conducted in the Department of Radiation Oncology at Himalayan Institute of Medical Sciences, Dehradun, Uttarakhand, India. Medical records were collected from January 2009 to December 2021 for 876 patients with cervical cancer who had been treated with radiotherapy or combined radiotherapy and chemotherapy. Out of the 876 patients presenting with cervical cancer in the OPD, 20 patients who met the inclusion criteria were selected [Table/Fig-1].

Inclusion criteria: Patients diagnosed with cervical cancer, FIGO stage IB to IVA, aged 80 years or older, and with ECOG Performance status I to III were included in the study.

Study Procedure

The ECOG Performance Scale (PS) is a widely used to assess the functional status of a patient, compare treatment effectiveness, and



[Table/Fig-1]: Patient selection flowchart.

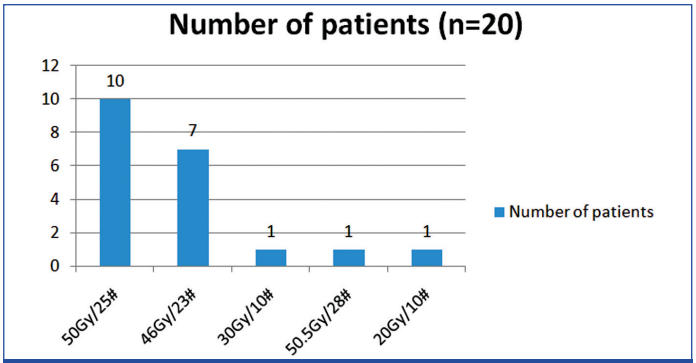
evaluate prognosis [7]. The scale classifies patients based on their functional impairment. The classifications are as follows:

- ECOG PS 0: Fully active, able to perform all pre-disease activities without restriction.
- ECOG PS 1: Restricted in physically strenuous activity but ambulatory and able to perform light or sedentary work, such as light housework or office work.
- ECOG PS 2: Ambulatory and capable of self-care, but unable to work; spends more than 50% of waking hours up and about.
- ECOG PS 3: Capable of only limited self-care; mostly confined to bed or chair, spending more than 50% of waking hours in this state.
- ECOG PS 4: Completely disabled; unable to perform any self-care; totally confined to bed or chair.
- ECOG PS 5: Deceased.

The demographic and clinicopathological characteristics of the patients were examined, including FIGO staging (stage IB to stage IVA), histopathological features (adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma), doses of radiotherapy and brachytherapy, overall survival, disease-free survival, and the current status (alive or deceased) of the patients. Overall survival is defined as the time elapsed between diagnosis and the last follow-up or death from any cause [8]. Disease-free survival refers to the time between treatment completion and either disease recurrence or death due to the disease [9].

Radiation therapy: The patients were treated with a conventional fractionation schedule for external beam radiation therapy using a 6 MV photon beam from a linear accelerator at various doses. This was followed by intracavitary brachytherapy to point A (the paracervical triangle on the medial edge of the broad ligament where the uterine vessels cross the ureter). External beam radiation therapy was interrupted if the patient's general condition deteriorated, the absolute neutrophil count fell below 1500, or the platelet count fell below 100,000/mm^3. It was resumed once counts rose above these levels or the patient's general condition improved [Table/Fig-2]. Five patients did not receive brachytherapy due to poor general condition and poor tolerance.

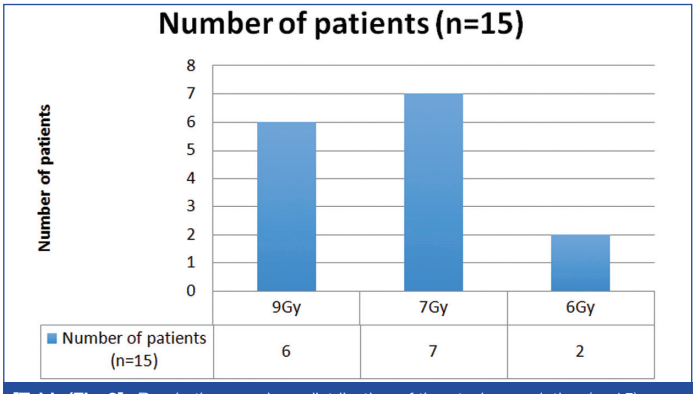
Brachytherapy: Out of 20 patients, 15 patients (75%) received brachytherapy. The doses of brachytherapy were modified based on the general condition of the patient. 6 (30%) patients received two sessions of intracavitary brachytherapy with a dose of 9.5 Gy per session, 7 (35%) patients received three sessions of intracavitary brachytherapy with a dose of 7 Gy per session, and 2 (10%) patients received four sessions of intracavitary brachytherapy with a dose of 6 Gy per session. Five patients did not receive brachytherapy due to their poor general condition and multiple co-morbidities.



[Table/Fig-2]: External beam radiotherapy dose distribution of the study population (n=20).

After three months of completing treatment with chemoradiotherapy followed by brachytherapy, a response assessment was performed. RECIST 1.1 criteria were used to evaluate the response [Table/Fig-3]. The standard Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1 are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non target) must have a reduction in short axis to <10 mm.
- Partial Response (PR): Atleast a 30% decrease in the sum of diameters of target lesions, taking the baseline sum diameters as reference.
- Progressive Disease (PD): Atleast a 20% increase in the sum of diameters of target lesions, taking the smallest sum on the study as reference (this includes the baseline sum if that is the smallest on the study). Additionally, the sum must demonstrate an absolute increase of atleast 5 mm. Note: the appearance of one or more new lesions is also considered progression.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking the smallest sum diameters while on the study as reference [10].



[Table/Fig-3]: Brachytherapy dose distribution of the study population (n=15).

STATISTICAL ANALYSIS

Categorical variables were expressed as counts and percentages. The Kaplan-Meier approach was used to analyse overall survival and disease-free survival in the study population using XLSTAT statistical software. A p-value of less than 0.05 was considered significant for all statistical analyses.

RESULTS

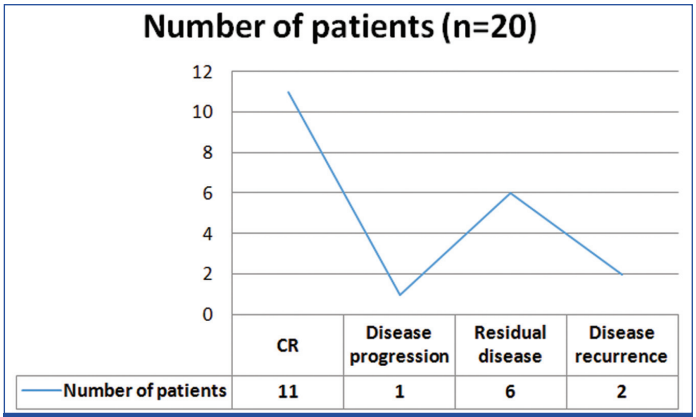
A total of 876 patients diagnosed with cervical cancer, who had been treated with radiotherapy or combined radiotherapy and chemotherapy from January 2009 to December 2021, were analysed. Twenty patients who met the inclusion criteria were selected. The clinicopathological characteristics of the patients included FIGO staging (stage Ib to stage IVa), histopathological features of adenocarcinoma, squamous carcinoma, or adenosquamous carcinoma, doses of radiotherapy and brachytherapy, overall survival, disease-free survival, and the patients' current status (alive

or dead). If death occurred, the cause of death was determined. The study population was age-standardised, with 18 patients (90%) falling between the ages of 80 and 85, and 2 patients (10%) falling between the ages of 86 and 90. The patients' ECOG performance status was examined according to the standard performance scale criteria, and 12 patients (60% of the study population) belonged to ECOG PS II. A total of 19 (95%) out of the 20 patients had histologically confirmed squamous cell carcinoma. The histopathological features included adenocarcinoma and adenosquamous carcinoma. Fifteen patients (75% of the study population) were in a locally advanced stage (stage III-IVA) [Table/Fig-4].

Characteristics	Frequency (n)	Percentage (%)
ECOG PS (n=20)		
I	0	0
II	12	60
III	8	40
Age group (n=20)		
80-85 years	18	90
86-90 years	2	10
Histopathological diagnosis (n=20)		
Squamous cell	19	95
Adenocarcinoma	0	0
Adenosquamous	1	5
FIGO stage (n=20)		
IB	0	0
IIA	1	5
IIB	4	20
IIIA	1	5
IIIB	7	35
IIIC	1	5
IVA	6	30
Radiotherapy dose (n=20)		
46 Gy/23	7	35
50 Gy/25	10	50
50.5 Gy/28	1	5
30 Gy/10	1	5
20 Gy/10	1	5
Brachytherapy dose (n=20)		
9 Gy	6	30
7 Gy	7	35
6 Gy	2	10
Not received (in view of poor tolerance and poor general condition)	5	25
Response assessment (n=20)		
Complete Response (CR)	11	55
Disease recurrence	2	10
Residual disease	6	30
Disease progression	1	5
Current status (n=20)		
Alive	11	55
Death	9	45
Cause of death (n=9)		
Disease	3	33
Other causes • Age • COVID-19 • Cardiac co-morbidity	6	67

[Table/Fig-4]: Clinicopathological characteristics of patients with cervical cancer between 2009 and 2021 in the study population (n=20).
Coronavirus disease-2019

Response assessment: After three months of treatment with chemoradiotherapy followed by brachytherapy, a response assessment was performed using RECIST 1.1 criteria. The standard RECIST criteria 1.1 are as follows: CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non target) must have a reduction in short axis to <10 mm. PR: Atleast a 30% decrease in the sum of diameters of target lesions, taking the baseline sum diameters as the reference. PD: Atleast a 20% increase in the sum of diameters of target lesions, taking the smallest sum on the study as the reference (this includes the baseline sum if it is the smallest on the study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of atleast 5 mm. (Note: the appearance of one or more new lesions is also considered progression). SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking the smallest sum diameters while on the study as the reference [10]. Out of 20 patients, 11 patients had CR, one patient had disease progression, six patients had residual disease, and two patients had disease recurrence [Table/Fig-5].



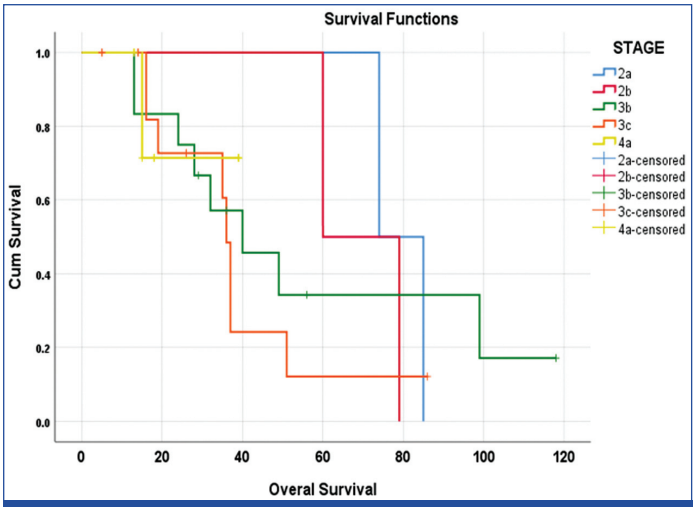
[Table/Fig-5]: Response assessment of the study population (n=20).

Survival analysis: The Kaplan-Meier approach was used to analyse overall survival and disease-free survival in the study population using XLSTAT statistical software. A significance level of $p<0.05$ was considered for all statistical analyses. The Kaplan-Meier survival analysis of overall survival and disease-free survival for different clinicopathological characteristics of patients with cervical cancer in the study population is shown in [Table/Fig-6]. It was observed that the maximum survival was 74.50 months in FIGO stage IIA, compared to other stages. The overall survival (in months) was 65.58 months, which was statistically significant with a 95% confidence interval of 36.23 (lower bound) and 65.58 (upper bound) in the present study ($p<0.0083$). Similarly, the maximum disease-free interval was 69.28 months observed in FIGO stage IIA, compared to other stages. The average disease-free interval was 38.73 months, which was significant with a 95% confidence interval of 33.38 (lower bound) and 52.08 (upper bound) in the present study ($p<0.0062$) [Table/Fig-6-9].

FIGO stage	Average survival time (in months)			p-value
	Average	95% confidence interval		
		Lower bound	Upper bound	
II A	74.50	68.72	90.28	0.0083
II B	59.50	50.88	88.12	
III B	46.91	32.93	80.90	
III C	38.81	25.56	52.06	
IV A	26.14	22.11	40.17	
Overall	42.91	36.23	65.58	

[Table/Fig-6]: Overall survival time in months of the study population (n=20).

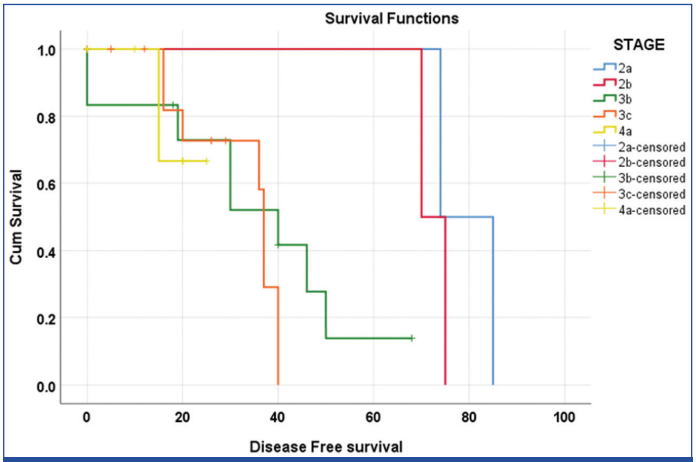
[Table/Fig-6] shows the overall average survival time in months of cervical cancer patients in the study population (n=20). It is illustrated



[Table/Fig-7]: Shows Kaplan-Meier graph illustrating that the horizontal axis (x-axis) represents survival time in months and the vertical axis (y-axis) shows the probability of surviving of patient.

FIGO stage	Average survival time (in months) (disease free)			p-value
	Average	95% confidence interval		
		Lower bound	Upper bound	
II A	69.50	68.72	90.28	0.0062
II B	62.50	57.60	77.40	
III B	35.17	22.50	47.84	
III C	32.36	26.41	38.32	
IV A	21.67	17.89	25.44	
Overall	38.73	33.38	52.08	

[Table/Fig-8]: Disease free survival time of the study population (n=20).



[Table/Fig-9]: Shows Kaplan-Meier graph wherein the horizontal axis (x-axis) represents disease free interval in Month and the vertical axis (y-axis) shows the probability of surviving of patient.

that the majority of survival was found to be 74.50 months in stage 2A, compared to other stages. The overall average survival time was found to be statistically significant at 42.91 months, with a 95% confidence interval of 36.23 (lower bound) and 65.58 (upper bound) in the present study. [Table/Fig-8] displays the disease-free interval of the study population in months. It is illustrated that the maximum disease-free interval was found to be 79.5 months in stage 2A, compared to other stages, and it was found to be significant with a 95% confidence interval of 33.38 (lower bound) and 52.08 (upper bound) in the present study.

DISCUSSION

Cervical cancer is one of the most common malignancies in women worldwide, with approximately 570,000 new cases diagnosed each year and around 310,000 deaths attributed to the disease annually [2]. In the present study, 12 patients (60%) had ECOG PS I, and 8 patients (40%) had ECOG PS II. Current study aligns with the research conducted by Hou PY et al., which also included 97.6% of the population with ECOG PS 0-2 [11]. Age standardisation was performed, and 18 patients (90%) fell within the age group of 80-85 years, while 2 patients (10%) were in the age group >85 years. The study conducted by Yu P et al., also categorised the study group into two age groups: those above 70 years and those below 70 years [11]. Out of the population, 95% (19 patients) were histopathologically diagnosed with squamous cell carcinoma, and one patient was diagnosed with adenosquamous carcinoma. In this study, 15 patients (75%) out of 20 had stage III-IV disease, which is consistent with the findings of Monk BJ et al., who reported that the estimated median proportion of locally advanced disease among all cervical cancer cases was 37.0%, with a range of 5.6%-97.5% [12].

Consequently, the present study revealed that the majority of elderly patients (75%) in the study were diagnosed with advanced-stage disease. Although the global incidence of cervical cancer is decreasing due to various screening programs, the incidence among elderly females remains unchanged. Multiple studies have shown that older women often present with advanced-stage disease at the time of diagnosis. Gao Y et al., reported that older women in France present with more advanced disease [13]. Similarly, Ioka A et al., reported that older women in Japan present with a later stages at diagnosis and have a poorer outcomes, likely due to underutilisation of pap smears [14]. The number of elderly patients diagnosed with cervical cancer is increasing worldwide, and elderly women account for more than 40% of cervical cancer deaths. However, the impact of age on cervical cancer survival remains unknown. A study conducted by Lindegaard JC et al., found that age was not a significant variable for any of the investigated endpoints when reviewing radiotherapy treatment in 114 women with a median age of 75.5 years [15].

According to the literature, cervical cancer has a similar prognosis in both older and younger women [16]. Others have suggested that being younger is an unfavourable prognostic factor, particularly in later stages [17]. On the other hand, Galic V et al., demonstrated that age is a poor prognostic factor for cervical cancer [18]. Furthermore, it has been shown that younger patients may have a better outcomes than older patients, and advanced age is associated with decreased survival in a various cancers [18]. Despite large population-based studies showing that survival for cervical cancer is inversely related to stage, older women have been reported to have worse survival rates compared to women in their 40s and 50s, regardless of stage [6]. The patients in the present study were treated with chemoradiotherapy followed by brachytherapy. The concurrent chemoradiotherapy schedules were modified according to the general condition of the patients and their co-morbidities.

Out of the 20 patients in the study population, five patients did not receive brachytherapy due to poor tolerance and general condition. Response assessment was conducted three months after completion chemoradiotherapy, using MRI pelvis. The analysis was performed using RECIST criteria 1.1. A total of 11 patients (55%) showed CR, two patients experienced disease recurrence, six patients had residual disease, and one patient had disease recurrence. The Kaplan-Meier approach was used to analyse overall survival and disease-free survival in the study population, employing XLSTAT statistical software. A significance level of $p<0.05$ was considered for all statistical analyses. It was observed that the maximum survival was 74.50 months in FIGO stage IIA, compared to other stages. In the present study, the overall survival was 65.58 months, which showed statistical significance with a 95% Confidence Interval (CI) ranging from 36.23 to 65.58, $p<0.0083$. Similarly, the maximum disease-free interval was 69.28 months, seen in FIGO stage IIA, compared to other stages. The average disease-free interval was 38.73 months, which

was significant with a 95% CI ranging from 33.38 to 52.08 in the present study, p<0.0062.

This is consistent with the findings of a study by Lindegaard JC et al., who discovered that age was not a significant variable in any of the investigated endpoints when standard treatment protocols were followed. They reviewed radiotherapy treatment in 114 women with a median age of 75.5 years [15]. Elderly cervical cancer patients are usually treated with less aggressive treatments than their younger counterparts due to considerations concerning patient safety. The author's findings suggest that outcomes in older women may not be correlated with age alone.

Limitation(s)

The first limitation is that the study was conducted retrospectively. The second limitation is that the data analysis was limited to a single Institution.

CONCLUSION(S)

According to the findings of the study, age may not be an independent risk factor for determining the outcome of cervical cancer patients in the Indian scenario. Even though elderly females may present with multiple co-morbidities, the standard treatment protocol may need to be modified. However, regardless of the patient's age, the treatment of cervical cancer must be radical.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Apr 14, 2023
- Manual Googling: May 06, 2023
- iThenticate Software: May 19, 2023 (24%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:

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- For any images presented appropriate consent has been obtained from the subjects. NA

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